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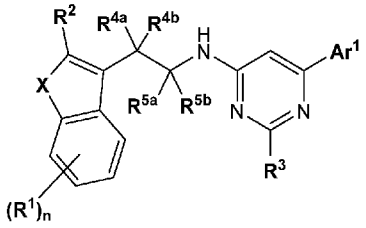
(54) Title: BENZOFURANE AND BENZOTHIOPHENE DERIVATIVES AS PGE2 RECEPTOR MODULATORS



(I)

(57) Abstract: The present invention relates to benzofurane and benzothiophene derivatives of formula (I) Formula (I) wherein $(R^1)_n$, R^2, R^3, R^{4a}, R^{4b}, R^{5a}, R^{5b} and Ar^1 are as described in the description and their use in the treatment of cancer by modulating an immune response comprising a reactivation of the immune system in the tumor. The invention further relates to novel benzofurane and benzothiophene derivatives of formula (II) and their use as pharmaceuticals, to their preparation, to pharmaceutically acceptable salts thereof, and to their use as pharmaceuticals, to pharmaceutical compositions containing one or more compounds of formula (I), and especially to their use as modulators of the prostaglandin 2 receptors EP2 and/or EP4.

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Benzofurane and benzothiophene derivatives as PGE2 receptor modulators

The present invention relates to benzofurane and benzothiophene 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 benzofurane and benzothiophene derivatives of formula (II) 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 (II), 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 (II) 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, PGF2α, 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)

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).

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).

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, OncoImmunology 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.

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

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-γ, TNF-α 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 responsivness, expansion and cytotoxicity of T-cells thereby contributing to local immunsuppresion (see for example Specht C et al, Int J Cancer 200191:705-712); (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 e 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 all, 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 and 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 PGE2, 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 all, 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-γ) 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-β) 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 PGI2 and TXA2 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 Phramacol 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 endometric 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 endometric cells in vitro (Banu SK et al, MOl 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(2) 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, Artherioscler 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 toxican (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 etal, 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).

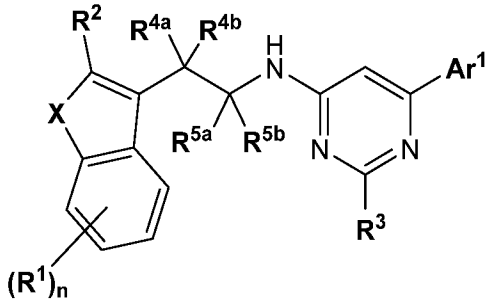
EP2 and/or dual EP2/EP4 antagonists may also be useful to treat autosomal dominant polycystic kidney disease (ADPKD): PGE2 via EP2 induces cystogenesis of human renal epithelial cells; and EP2 was found to be overexpressed in patient samples (Elberg G et al, Am J Physiol Renal Physiol 2007, 293(5):F1622-32).

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 all, 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 protaglandin 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. 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 novel benzofurane and benzothiophene derivatives of formula (I) / formula (II) 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)

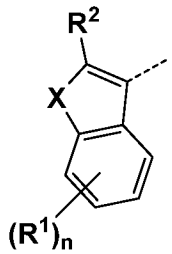
for use in the treatment of a cancer, wherein said cancer is treated by modulating an immune response comprising a reactivation of the immune system in the tumor;

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)

the fragment



is substituted with **R²**, wherein **R²** represents hydrogen, (C_{1-4})alkyl (especially methyl, ethyl), halogen (especially chloro, bromo), or cyano; and

is optionally substituted with **$(R^1)_n$**; wherein **$(R^1)_n$** represents one, two or three optional substituents (i.e. said fragment is, in addtition to **R²**, unsubstituted, or substituted with one, two or three **R¹**), wherein said substituents **R¹** are independently selected from (C_{1-3})alkyl (especially methyl), (C_{1-3})alkoxy (especially methoxy), halogen (especially fluoro, or chloro), (C_{1-3})fluoroalkyl (especially trifluoromethyl), (C_{1-3})fluoroalkoxy (especially trifluoromethoxy), or cyano; (for avoidance of any doubt: substituents **$(R^1)_n$** are in addition to the substituent **R²** as defined above);

X represents S or O;

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;

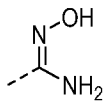
Ar^1 represents

- 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_{1-6})alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 1-methyl-propan-1-yl, tert.-butyl, 3-methyl-butyl);
  - (C_{1-4})alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy);
  - (C_{1-3})fluoroalkyl, wherein said (C_{1-3})fluoroalkyl is optionally substituted with hydroxy (especially trifluoromethyl, 2,2,2-trifluoro-1-hydroxy-ethyl);
  - (C_{1-3})fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
  - halogen (especially fluoro, chloro, bromo);
  - cyano;
  - (C_{3-6})cycloalkyl, wherein said (C_{3-6})cycloalkyl is unsubstituted or mono-substituted with amino (especially cyclopropyl, 1-amino-cyclopropyl);
  - (C_{4-6})cycloalkyl containing a ring oxygen atom, wherein said (C_{4-6})cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy (especially 3-hydroxy-oxetan-3-yl);
  - (C_{3-6})cycloalkyl-oxy (especially cyclobutyl-oxy, cyclopentyl-oxy);
  - hydroxy;
  - -X^1-CO-R^{O1}, wherein
    - X^1 represents a direct bond, (C_{1-3})alkylene (especially -CH_2-, -$CH(CH_3)$-,-$C(CH_3)_2$-,-CH_2-CH_2-), -O-(C_{1-3})alkylene-* (especially -O-CH_2-*, -O-$CH(CH_3)$-*, -O-$C(CH_3)_2$-*, -O-CH_2-CH_2-*), -NH-(C_{1-3})alkylene-* (especially -NH-CH_2-*, -NH-$CH(CH_3)$-*), -S-CH_2-*, -CF_2-, –CH=CH-, –CH≡CH-, -NH-CO-*, -CO-, or (C_{3-5})cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-R^{O1} group; and
    - R^{O1} represents
      - -OH;
      - -O-(C_{1-4})alkyl (especially ethoxy, methoxy);
      - -NH-SO_2-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})alkylene

wherein the (C_{3-6})cycloalkyl optionally contains a ring oxygen atom, (C_{1-3})fluoroalkyl, or -NH_2;

- -O-CH_2-CO-$\mathbf{R^{O4}}$, wherein $\mathbf{R^{O4}}$ repesents hydroxy, or (C_{1-4})alkoxy, or -N[(C_{1-4})alkyl]$_2$;
- -O-CH_2-O-CO-$\mathbf{R^{O5}}$, wherein $\mathbf{R^{O5}}$ repesents (C_{1-4})alkyl or (C_{1-4})alkoxy;
- -O-CH_2-CH_2-N[(C_{1-4})alkyl]$_2$ (especially -O-CH_2-CH_2-N(CH_3)$_2$); or
- (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyloxy-;

[wherein in particular such group -$\mathbf{X^1}$-CO-$\mathbf{R^{O1}}$ represents -COOH, -CO-O-CH_3, -CO-O-C_2H_5, -O-CH_2-COOH, -O-CH(CH_3)-COOH, -O-C(CH_3)$_2$-COOH, -O-CH_2-CH_2-COOH, -NH-CH_2-COOH, -NH-CH_2-CO-O-CH_3, -NH-CH(CH_3)-COOH, -CO-NH-SO_2-CH_3, -CO-NH-SO_2-C(CH_3)$_2$, -CO-NH-SO_2-cyclopropyl, -CO-NH-SO_2-C_2H_5, -CO-NH-SO_2-NH_2, -CO-O-CH_2-COOH, -CO-O-CH_2-CH_2-N(CH_3)$_2$, -CO-O-CH_2-CO-N(CH_3)$_2$, -CO-O-CH_2-O-CO-O-C_2H_5, -CO-O-CH_2-O-CO-propyl, (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyl-O-CO-, -CH_2-COOH, -CH_2-CO-O-CH_3, -CH_2-CO-O-C_2H_5, -CH_2-CH_2-COOH, -CH=CH-COOH, –CH≡CH-CO-O-C_2H_5, -CF_2-COOH, -NH-CO-COOH, -CO-COOH, 1-carboxy-cyclopropan-1-yl];

- -CO-CH_2-OH;
-  ;
- 2-hydroxy-3,4-dioxo-cyclobut-1-enyl;
- hydroxy-(C_{1-4})alkyl (especially hydroxymethyl, 1-hydroxy-ethyl);
- dihydroxy-(C_{2-4})alkyl (especially 1,2-dihydroxyethyl);
- hydroxy-(C_{2-4})alkoxy (especially 2-hydroxy-ethoxy);
- (C_{1-4})alkoxy-(C_{2-4})alkoxy (especially 2-methoxy-ethoxy);
- -(CH_2)$_r$-CO-N$\mathbf{R^{N3}R^{N4}}$ wherein **r** represents the integer 0 or 1; and wherein $\mathbf{R^{N3}}$ and $\mathbf{R^{N4}}$ independently represent hydrogen, (C_{1-4})alkyl, hydroxy-(C_{2-4})alkyl, (C_{1-3})alkoxy-(C_{2-4})alkyl, or hydroxy (wherein preferably at least one of $\mathbf{R^{N3}}$ and $\mathbf{R^{N4}}$ represents hydrogen; and wherein particular examples of such group -CO-N$\mathbf{R^{N3}R^{N4}}$ 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);
- -$\mathbf{X^2}$-N$\mathbf{R^{N1}R^{N2}}$, wherein $\mathbf{X^2}$ represents -(CH_2)$_m$-, wherein **m** represents the integer 0 or 1; or $\mathbf{X^2}$ represents -O-CH_2-CH_2-*,wherein the asterisk indicates the bond that is linked to the -N$\mathbf{R^{N1}R^{N2}}$ group; and wherein
  - $\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ independently represent hydrogen, (C_{1-4})alkyl, (C_{1-4})alkoxy-(C_{2-4})alkyl, (C_{3-6})cycloalkyl, or (C_{2-3})fluoroalkyl;
  - or $\mathbf{R^{N1}}$ independently represents hydrogen or (C_{1-4})alkyl, and $\mathbf{R^{N2}}$ independently represents –CO-H, –CO-(C_{1-3})alkyl, –CO-(C_{1-3})alkylene-OH, or –CO-O-(C_{1-3})alkyl;

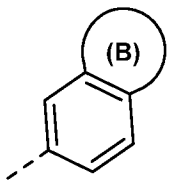
- or R^{N1} and R^{N2} together with the nitrogen to which they are attached form a 4-, 5- or 6-membered saturated ring optionally containing one ring oxygen or ring sulfur atom, wherein said ring is unsubstituted, or mono-substituted with oxo on a ring carbon atom, or disubstituted with oxo on a ring sulfur atom;

(especially such group $-X^2-NR^{N1}R^{N2}$ 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, $–N(C_2H_5)$-CO-H, –NH-CO-C_2H_5, -NH-CO-CH_2-CH_2-OH, –NH-CO-O-CH_3, $–N(CH_3)$-CO-O-CH_3; 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);

- -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 hydroxy, (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-OH, -SO_2-NH-CH_3);
- -S-R^{S2} wherein R^{S2} represents (C_{1-4})alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C_{3-6})cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);
- -$(CH_2)_q$-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- 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_{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)

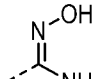
- or **Ar**^{1} represents 8- to 10-membered bicyclic heteroaryl (notably 9- or 10-membered bicyclic heteroaryl; especially indazolyl, benzoimidazolyl, indolyl, benzotriazolyl, benzofuranyl, benzooxazolyl, quinoxalinyl, isoquinolinyl, quinolinyl, pyrrolopyridinyl, or imidazopyridinyl); wherein said 8- to 10-membered bicyclic heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C_{1-4})alkyl (especially methyl); (C_{1-4})alkoxy (especially methoxy); (C_{1-3})fluoroalkyl (especially trifluoromethyl); (C_{1-3})fluoroalkoxy (especially trifluoromethoxy); halogen; cyano; hydroxy, or -(C_{0-3})alkylene-COO**R**^{O2} wherein **R**^{O2} repesents hydrogen or (C_{1-4})alkyl (especially such group -(C_{0-3})alkylene-COO**R**^{O2} 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**^{1} 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-isoindolyl, 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_{1-6})alkyl (especially methyl, ethyl, propyl, butyl, isobutyl) and -(C_{0-3})alkylene-COO**R**^{O3} wherein **R**^{O3} repesents hydrogen or (C_{1-3})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**^{1} 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_{4-6})cycloalkyl containing a ring oxygen atom, wherein said (C_{4-6})cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy; hydroxy;  ;-**X**^{1}-CO-**R**^{O1}; 2-hydroxy-3,4-dioxo-cyclobut-1-enyl; hydroxy-(C_{2-4})alkoxy; -$(CH_2)_r$-CO-N**R**^{N3}**R**^{N4}; -NH-CO-N**R**^{N5}**R**^{N6}; -SO_2-**R**^{S1}; -$(CH_2)_q$-**HET**^{1}; -$(CH_2)_p$-**HET;**
  - and the other of said substituents, if present, independently are selected from (C_{1-6})alkyl; (C_{1-4})alkoxy; (C_{1-3})fluoroalkyl; (C_{1-3})fluoroalkoxy; halogen; cyano; (C_{3-6})cycloalkyl, wherein said (C_{3-6})cycloalkyl is unsubstituted or mono-substituted with amino; (C_{3-6})cycloalkyl-oxy; hydroxy; hydroxy-(C_{1-4})alkyl; dihydroxy-(C_{2-4})alkyl; hydroxy-(C_{2-4})alkoxy; (C_{1-4})alkoxy-(C_{2-4})alkoxy; -**X**^{2}-N**R**^{N1}**R**^{N2}; -S-**R**^{S2};

  wherein the above groups and substituents are as defined in embodiment 1).

- or **Ar**^{1} 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_{1-4})alkyl; (C_{1-4})alkoxy; (C_{1-3})fluoroalkyl; (C_{1-3})fluoroalkoxy; halogen; cyano; hydroxy, or -(C_{0-3})alkylene-COO**R**^{O2} wherein **R**^{O2} repesents hydrogen or (C_{1-4})alkyl;
- or **Ar**^{1} represents a group of the structure (Ar-III) as defined in embodiment 1).

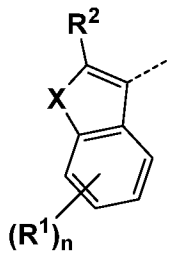
2) A second embodiment relates to compounds according to embodiment 1), wherein **R**^{3} represents hydrogen.

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

4) Another embodiment relates to compounds according to any one of embodiments 1) to 3), wherein **R**^{4a} and **R**^{4b} both represent hydrogen.

5) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein **R**^{5a} and **R**^{5b} both represent hydrogen. Particular compounds of formula (I) are compounds wherein **R**^{4a} and **R**^{4b} both represent hydrogen; and **R**^{5a} and **R**^{5b} both represent hydrogen.

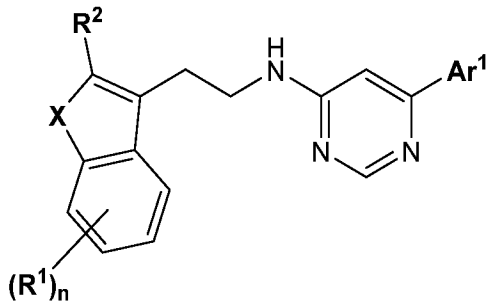
6) Another embodiment relates to compounds according to any one of embodiments 1) to 5), wherein the characteristics defined for the fragment



according to embodiments 8), and 15) to 25) below apply *mutatis mutandis*.

7) Another embodiment relates to compounds according to any one of embodiments 1) to 6), wherein the characteristics defined for the substituent **Ar**^{1} according to embodiments 8) to 14) below apply *mutatis mutandis*.

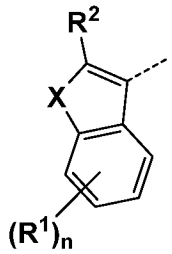
8) A second aspect of the invention relates to compounds of the formula (II)



Formula (II)

wherein in compounds of the formula (II)

the fragment



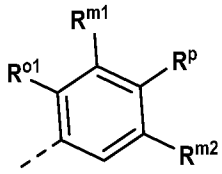
is substituted with **R**^{2}, wherein **R**^{2} represents hydrogen, (C_{1-4})alkyl (especially methyl, ethyl), halogen (especially chloro, bromo), or cyano; and

is optionally substituted with **(R**^{1}**)**$_n$; wherein **(R**^{1}**)**$_n$ represents one, two or three optional substituents (i.e. said fragment is, in addtition to **R**^{2}, unsubstituted, or substituted with one, two or three **R**^{1}), wherein said substituents **R**^{1} are independently selected from (C_{1-3})alkyl (especially methyl), (C_{1-3})alkoxy (especially methoxy), halogen (especially fluoro, or chloro), (C_{1-3})fluoroalkyl (especially trifluoromethyl), (C_{1-3})fluoroalkoxy (especially trifluoromethoxy), or cyano; (for avoidance of any doubt: substituents **(R**^{1}**)**$_n$ are in addition to the substituent **R**^{2} as defined above);

X represents S or O;

Ar^{1} represents

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



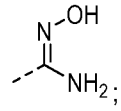
(Ar-I)

wherein

- **R**^{p} represents
  - (C_{4-6})cycloalkyl containing a ring oxygen atom, wherein said (C_{4-6})cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy (especially 3-hydroxy-oxetan-3-yl);
  - hydroxy;
  - -**X**^{1}-CO-**R**^{O1}, wherein
    - **X**^{1} represents a direct bond, (C_{1-3})alkylene (especially -CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -CH_2-CH_2-), -O-(C_{1-3})alkylene-* (especially -O-CH_2-*, -O-$CH(CH_3)$-*, -O-$C(CH_3)_2$-*, -O-CH_2-CH_2-*), -NH-(C_{1-3})alkylene-* (especially -NH-CH_2-*, -NH-$CH(CH_3)$-*), -S-CH_2-*, -CF_2-, –CH=CH-, –CH≡CH-, -NH-CO-*, -CO-, or (C_{3-5})cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-**R**^{O1} group; and
    - **R**^{O1} represents
      - -OH;
      - -O-(C_{1-4})alkyl (especially ethoxy, methoxy);
      - -NH-SO_2-**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})alkylene wherein the (C_{3-6})cycloalkyl optionally contains a ring oxygen atom, (C_{1-3})fluoroalkyl, or -NH_2;
      - -O-CH_2-CO-**R**^{O4}, wherein **R**^{O4} repesents hydroxy, or (C_{1-4})alkoxy, or -N[(C_{1-4})alkyl]$_2$;
      - -O-CH_2-O-CO-**R**^{O5}, wherein **R**^{O5} repesents (C_{1-4})alkyl or (C_{1-4})alkoxy;
      - -O-CH_2-CH_2-N[(C_{1-4})alkyl]$_2$ (especially -O-CH_2-CH_2-N(CH_3)$_2$); or
      - (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyloxy-;

[wherein in particular such group -**X**^{1}-CO-**R**^{O1} represents -COOH, -CO-O-CH_3, -CO-O-C_2H_5, -O-CH_2-COOH, -O-$CH(CH_3)$-COOH, -O-$C(CH_3)_2$-COOH, -O-CH_2-CH_2-COOH, -NH-CH_2-COOH, -NH-CH_2-CO-O-CH_3, -NH-$CH(CH_3)$-COOH, -CO-NH-SO_2-CH_3, -CO-NH-SO_2-$C(CH_3)_2$, -CO-NH-SO_2-cyclopropyl, -CO-NH-SO_2-C_2H_5, -CO-NH-SO_2-NH_2, -CO-O-CH_2-COOH, -CO-O-CH_2-CH_2-N(CH_3)$_2$, -CO-O-CH_2-CO-N(CH_3)$_2$, -CO-O-CH_2-O-CO-O-C_2H_5, -CO-O-CH_2-O-CO-propyl, (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyl-O-CO-, -CH_2-COOH, -CH_2-CO-O-CH_3, -CH_2-CO-O-C_2H_5, -

CH_2-CH_2-COOH, -CH=CH-COOH, –CH≡CH-CO-O-C_2H_5, -CF_2-COOH, -NH-CO-COOH, -CO-COOH, 1-carboxy-cyclopropan-1-yl];

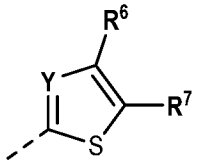
-  ;
- 2-hydroxy-3,4-dioxo-cyclobut-1-enyl;
- hydroxy-(C_{1-4})alkyl (especially hydroxymethyl, 1-hydroxy-ethyl);
- hydroxy-(C_{2-4})alkoxy (especially 2-hydroxy-ethoxy);
- -(CH_2)$_r$-CO-N$\mathbf{R^{N3}R^{N4}}$ wherein **r** represents the integer 0 or 1; and wherein $\mathbf{R^{N3}}$ and $\mathbf{R^{N4}}$ independently represent hydrogen, (C_{1-4})alkyl, hydroxy-(C_{2-4})alkyl, (C_{1-3})alkoxy-(C_{2-4})alkyl, or hydroxy (wherein preferably at least one of $\mathbf{R^{N3}}$ and $\mathbf{R^{N4}}$ represents hydrogen; and wherein particular examples of such group -CO-N$\mathbf{R^{N3}R^{N4}}$ 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);
- -N$\mathbf{R^{N1}R^{N2}}$, wherein $\mathbf{R^{N1}}$ independently represents hydrogen or (C_{1-4})alkyl, and $\mathbf{R^{N2}}$ independently represents –CO-H, –CO-(C_{1-3})alkyl, or –CO-(C_{1-3})alkylene-OH; (especially such group -(CH_2)$_m$-N$\mathbf{R^{N1}R^{N2}}$ 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-N$\mathbf{R^{N5}R^{N6}}$ wherein $\mathbf{R^{N5}}$ and $\mathbf{R^{N6}}$ independently represent hydrogen or (C_{1-4})alkyl (wherein preferably at least one of $\mathbf{R^{N5}}$ and $\mathbf{R^{N6}}$ represents hydrogen; and wherein particular examples of such group -NH-CO-N$\mathbf{R^{N5}R^{N6}}$ are –NH-CO-NH_2, –NH-CO-NH-C_2H_5);
- -SO_2-$\mathbf{R^{S1}}$ wherein $\mathbf{R^{S1}}$ represents (C_{1-4})alkyl (especially methyl), or -N$\mathbf{R^{N7}R^{N8}}$ wherein $\mathbf{R^{N7}}$ and $\mathbf{R^{N8}}$ independently represent hydrogen or (C_{1-3})alkyl (wherein preferably at least one of $\mathbf{R^{N7}}$ and $\mathbf{R^{N8}}$ represents hydrogen; and wherein particular examples of such group -SO_2-$\mathbf{R^{S1}}$ are -SO_2-CH_3, -SO_2-NH_2, -SO_2-NH-CH_3);
- -(CH_2)$_q$-$\mathbf{HET^1}$, wherein **q** represents the integer 0, 1 or 2 (especially **q** is 0, i.e. $\mathbf{HET^1}$ is linked to $\mathbf{Ar^1}$ by a direct bond); and wherein $\mathbf{HET^1}$ 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 $\mathbf{Ar^1}$ 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 -N$\mathbf{R^{N9}R^{N10}}$ wherein $\mathbf{R^{N9}}$ and $\mathbf{R^{N10}}$ 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^{m1} represents
  - hydrogen;
  - (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, isobutoxy);
  - (C_{1-3})fluoroalkyl (especially trifluoromethyl);
  - (C_{1-3})fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
  - halogen (especially fluoro or chloro);
  - (C_{3-6})cycloalkyl (especially cyclopropyl);
  - (C_{3-6})cycloalkyl-oxy (especially cyclopropyl-oxy, cyclobutyl-oxy, cyclopentyl-oxy);
  - hydroxy;
  - hydroxy-(C_{2-4})alkoxy (especially 2-hydroxy-ethoxy);
  - -X^2-N$R^{N1}R^{N2}$, wherein X^2 represents a direkt bond; or X^2 represents -O-CH_2-CH_2-*, wherein the asterisk indicates the bond that is linked to the -N$R^{N1}R^{N2}$ group; and wherein R^{N1} and R^{N2} independently represent hydrogen, (C_{1-4})alkyl (especially methyl), or (C_{3-6})cycloalkyl (especially cyclopropyl); (especially such group -X^2-N$R^{N1}R^{N2}$ represents amino, methylamino, ethylamino, propylamino; or 2-(dimethylamino)-ethoxy);
  - -S-R^{S2} wherein R^{S2} represents (C_{1-4})alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C_{3-6})cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);

  wherein in a sub-embodiment, R^{m1} especially is different from hydrogen;
- R^{m2} represents hydrogen, methyl, fluoro, or chloro; and
- R^{o1} represents hydrogen; or, in case R^{m2} represents hydrogen, R^{o1} represents hydrogen or fluoro;

- or Ar^1 represents a 5-membered heteroaryl group of the structure (Ar-II):

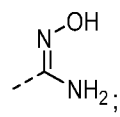


(Ar-II)

wherein

- **Y** represents C**R**^{8} wherein **R**^{8} represents especially hydrogen, or halogen (notably fluoro, chloro); or **Y** represents N;

- **R**^{7} represents
  - (C_{4-6})cycloalkyl containing a ring oxygen atom, wherein said (C_{4-6})cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy (especially 3-hydroxy-oxetan-3-yl);
  - -**X**^{1}-CO-**R**^{O1}, wherein
    - **X**^{1} represents a direct bond, (C_{1-3})alkylene (especially -CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -CH_2-CH_2-), -O-(C_{1-3})alkylene-* (especially -O-CH_2-*, -O-$CH(CH_3)$-*, -O-$C(CH_3)_2$-*, -O-CH_2-CH_2-*), -NH-(C_{1-3})alkylene-* (especially -NH-CH_2-*, -NH-$CH(CH_3)$-*), -S-CH_2-*, -CF_2-, –CH=CH-, –CH≡CH-, -NH-CO-*, -CO-, or (C_{3-5})cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-**R**^{O1} group; and
    - **R**^{O1} represents
      - -OH;
      - -O-(C_{1-4})alkyl (especially ethoxy, methoxy);
      - -NH-SO_2-**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})alkylene wherein the (C_{3-6})cycloalkyl optionally contains a ring oxygen atom, (C_{1-3})fluoroalkyl, or -NH_2;
      - -O-CH_2-CO-**R**^{O4}, wherein **R**^{O4} repesents hydroxy, or (C_{1-4})alkoxy, or -N[(C_{1-4})alkyl]$_2$;
      - -O-CH_2-O-CO-**R**^{O5}, wherein **R**^{O5} repesents (C_{1-4})alkyl or (C_{1-4})alkoxy; or
      - -O-CH_2-CH_2-N[(C_{1-4})alkyl]$_2$ (especially -O-CH_2-CH_2-N$(CH_3)_2$);
      - (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyloxy-;

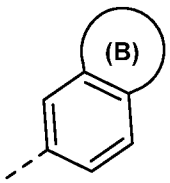
    [wherein in particular such group -**X**^{1}-CO-**R**^{O1} represents -COOH, -CO-O-CH_3, -CO-O-C_2H_5, -O-CH_2-COOH, -O-$CH(CH_3)$-COOH, -O-$C(CH_3)_2$-COOH, -O-CH_2-CH_2-COOH, -NH-CH_2-COOH, -NH-CH_2-CO-O-CH_3, -NH-$CH(CH_3)$-COOH, -CO-NH-SO_2-CH_3, -CO-NH-SO_2-$C(CH_3)_2$, -CO-NH-SO_2-cyclopropyl, -CO-NH-SO_2-C_2H_5, -CO-NH-SO_2-NH_2, -CO-O-CH_2-COOH, -CO-O-CH_2-CH_2-N$(CH_3)_2$, -CO-O-CH_2-CO-N$(CH_3)_2$, -CO-O-CH_2-O-CO-O-C_2H_5, -CO-O-CH_2-O-CO-propyl, (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyl-O-CO-, -CH_2-COOH, -CH_2-CO-O-CH_3, -CH_2-CO-O-C_2H_5, -CH_2-CH_2-COOH, -CH=CH-COOH, –CH≡CH-CO-O-C_2H_5, -CF_2-COOH, -NH-CO-COOH, -CO-COOH, 1-carboxy-cyclopropan-1-yl];
  -  ;
  - 2-hydroxy-3,4-dioxo-cyclobut-1-enyl;
  - hydroxy-(C_{1-4})alkyl (especially hydroxymethyl, 1-hydroxy-ethyl);
  - hydroxy-(C_{2-4})alkoxy (especially 2-hydroxy-ethoxy);

- $-(CH_2)_r-CO-NR^{N3}R^{N4}$ wherein **r** represents the integer 0 or 1; and wherein R^{N3} and R^{N4} independently represent hydrogen, (C_{1-4})alkyl, hydroxy-(C_{2-4})alkyl, (C_{1-3})alkoxy-(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_{1-3})fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
- halogen (especially fluoro or chloro);
- hydroxy;
- (C_{3-6})cycloalkyl (especially cyclopropyl);
- (C_{3-6})cycloalkyl-oxy (especially cyclopropyl-oxy, cyclobutyl-oxy, cyclopentyl-oxy);
- hydroxy-(C_{2-4})alkoxy (especially 2-hydroxy-ethoxy);
- -$\mathbf{X^2}$-N$\mathbf{R^{N1}R^{N2}}$, wherein $\mathbf{X^2}$ represents a direkt bond; or $\mathbf{X^2}$ represents -O-CH_2-CH_2-*, wherein the asterisk indicates the bond that is linked to the -N$\mathbf{R^{N1}R^{N2}}$ group; and wherein $\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ independently represent hydrogen, (C_{1-4})alkyl, or (C_{3-6})cycloalkyl; (especially such group -$\mathbf{X^2}$-N$\mathbf{R^{N1}R^{N2}}$ represents amino, methylamino, ethylamino, propylamino; or 2-(dimethylamino)-ethoxy);
- -S-$\mathbf{R^{S2}}$ wherein $\mathbf{R^{S2}}$ represents (C_{1-4})alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C_{3-6})cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);

- or $\mathbf{Ar^1}$ represents 8- to 10-membered bicyclic heteroaryl (notably 9- or 10-membered bicyclic heteroaryl; especially indazolyl, benzoimidazolyl, indolyl, benzofuranyl, benzooxazolyl, quinoxalinyl, isoquinolinyl, or quinolinyl); wherein said 8- to 10-membered bicyclic heteroaryl independently is mono-substituted with -(C_{0-3})alkylene-COO$\mathbf{R^{O2}}$ wherein $\mathbf{R^{O2}}$ repesents hydrogen or (C_{1-4})alkyl (especially methyl) (wherein especially such group -(C_{0-3})alkylene-COO$\mathbf{R^{O2}}$ 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 $\mathbf{Ar^1}$ 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.

The compounds of formula (I) / formula (II) 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 formula (I) / formula (II) may further encompass compounds with one or more double bonds which

are allowed to be present in Z- as well as E-configuration and/or compounds with substituents at a ring system which are allowed to be present, relative to each other, in cis- as well as trans-configuration. The compounds of formula (I) / formula (II) may thus be present as mixtures of stereoisomers or preferably as pure stereoisomers. Mixtures of stereoisomers may be separated in a manner known to a person skilled in the art.

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

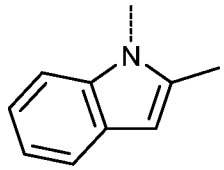
The term "enriched", when used in the context of stereoisomers, is to be understood in the context of the present invention to mean that the respective stereoisomer is present in a ratio of at least 70:30, especially of at least 90:10 (i.e., in a purity of at least 70% by weight, especially of at least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

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

The present invention also includes isotopically labelled, especially ^{2}H (deuterium) labelled compounds of formula (I) / formula (II) according to embodiments 1) to 34), which compounds are identical to the compounds of formula (I) / formula (II) except that one or more atoms have each been replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Isotopically labelled, especially ^{2}H (deuterium) labelled compounds of formula (I) / formula (II) and salts thereof are within the scope of the present invention. Substitution of hydrogen with the heavier isotope ^{2}H (deuterium) may lead to greater metabolic stability, resulting e.g. in increased *in-vivo* half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of formula (I) / formula (II) are not isotopically labelled, or they are labelled only with one or more deuterium atoms. In a sub-embodiment, the compounds of formula (I) / formula (II) are not isotopically labelled at

all. Isotopically labelled compounds of formula (I) / formula (II) 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-1*H*-indol-1-yl group.

In some instances, the compounds of formula (I) / formula (II) 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 formula (I) / formula (II) according to embodiments 1) to 34) is to be understood as referring also to the salts (and especially the pharmaceutically acceptable salts) of such compounds, as appropriate and expedient.

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

Definitions provided herein are intended to apply uniformly to the compounds of formula (I) / formula (II), as defined in any one of embodiments 1) to 25), 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^1 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_{x-y})alkyl" (x and y each being an integer), refers to an alkyl group as defined before, containing x to y carbon atoms. For example a (C_{1-6})alkyl group contains from one to six carbon atoms. Examples of alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, 3-methyl-butyl, 2,2-dimethyl-propyl and 3,3-dimethyl-butyl. For avoidance of any doubt, in case a group is referred to as e.g. propyl or butyl, it is meant to be n-propyl, respectively n-butyl. Preferred are methyl and ethyl. Most preferred is methyl. Preferred for substituents of **Ar^1** 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_{x-y})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_{1-y})alkylene group are in 1,1-diyl, in 1,2-diyl, or in 1,3-diyl arrangement. In case a (C_{0-y})alkylene group is used in combination with another substituent, the term means that either said substituent is linked through a (C_{1-y})alkylene group to the rest of the molecule, or it is directly attached to the rest of the molecule (i.e. a (C_0)alkylene group represents a direct bond linking said substituent to the rest of the molecule). The alkylene group -C_2H_4- refers to -CH_2-CH_2- if not explicitly indicated otherwise. For the linker **X^1**, examples of (C_{1-3})alkylene groups are -CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, and -CH_2-CH_2-, especially -CH_2- and -CH_2-CH_2-. Examples of (C_{0-3})alkylene groups as used in the substituents -(C_{0-3})alkylene-COO**R^{O2}** and (C_{0-3})alkylene-COO**R^{O3}**, respectively, are (C_0)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_{x-y})alkoxy" (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms. For example a (C_{1-4})alkoxy group means a group of the formula (C_{1-4})alkyl-O- in which the term "(C_{1-4})alkyl" has the previously given significance. Examples of alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.-butoxy and tert.-butoxy. Preferred are ethoxy and especially methoxy.

Preferred for substituents of **Ar**^{1} 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_{x-y})fluoroalkyl" (x and y each being an integer) refers to a fluoroalkyl group as defined before containing x to y carbon atoms. For example a (C_{1-3})fluoroalkyl group contains from one to three carbon atoms in which one to seven hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkyl groups include trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl and 2,2,2-trifluoroethyl. Preferred are (C_1)fluoroalkyl groups such as trifluoromethyl. An example of "(C_{1-3})fluoroalkyl, wherein said (C_{1-3})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_{x-y})fluoroalkoxy" (x and y each being an integer) refers to a fluoroalkoxy group as defined before containing x to y carbon atoms. For example a (C_{1-3})fluoroalkoxy group contains from one to three carbon atoms in which one to seven hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkoxy groups include trifluoromethoxy, difluoromethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy and 2,2,2-trifluoroethoxy. Preferred are (C_1)fluoroalkoxy groups such as trifluoromethoxy and difluoromethoxy, as well as 2,2,2-trifluoroethoxy.

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

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

Examples of (C_{3-6})cycloalkyl-oxy are cyclobutyl-oxy, and cyclopentyl-oxy.

Alkylated amino groups -N[(C_{1-4})alkyl]$_2$ as used in groups -**X**^{1}-CO-**R**^{01}, wherein **R**^{01} represents -O-CH_2-CO-**R**^{04}, wherein **R**^{04} repesents -N[(C_{1-4})alkyl]$_2$; or wherein **R**^{01} represents -O-CH_2-CH_2-N[(C_{1-4})alkyl]$_2$ are such that the two

repective (C_{1-4})alkyl groups are independently selected. A preferred example of such amino group -N[(C_{1-4})alkyl]$_2$ is -N(CH_3)$_2$.

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_{x-y})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_{5-6})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_{1-6})alkyl, and -(C_{0-3})alkylene-COO**R^{03}** wherein **R^{03}** repesents hydrogen or (C_{1-3})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_{1-6})alkyl, and -(C_{0-3})alkylene-COO**R^{03}** wherein **R^{03}** repesents hydrogen or (C_{1-3})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, or 1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl.

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.

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**[1] 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**[1] 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.

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-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**[1] 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-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**[1] representing a "8- to 10-membered bicyclic heteroaryl" the term means the above-mentioned 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, quinoxalinyl, isoquinolinyl, quinolinyl, pyrrolopyridinyl, and imidazopyridinyl, 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, as well as 8- to 10-membered bicyclic heteroaryl which are mono-substituted with -(C_{0-3})alkylene-COOR^{O2} 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. In addition, a further example is 7-carboxy-benzothiophen-2-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**^{1}. 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. 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 **HET1**, 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_2)-.

Examples of "**-X2-NRN1RN2**" groups as used for substituents of **Ar1** 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_2H_5)-CO-H, –NH-CO-C_2H_5, -NH-CO-CH_2-CH_2-OH, –NH-CO-O-CH_3, –N(CH_3)-CO-O-CH_3; 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-N**RN5RN6**" as used for substituents of the group **Ar1** are ureido (–NH-CO-NH_2) and 3-ethylureido (–NH-CO-NH-C_2H_5).

Examples of a group "-(CH_2)r-CO-N**RN3RN4** wherein **r** represents the integer 0 or 1" as used for substituents of the group **Ar1** are preferably groups wherein **r** represents the integer 0 and at least one of **RN3** and **RN4** represents hydrogen (or less preferred, methyl). Particular examples of such group -CO-N**RN3RN4** are –CO-NH_2, –CO-NH(CH_3), –CO-N(CH_3)$_2$, –CO-NH(C_2H_5), –CO-NH-O-methyl, –CO-NH-O-ethyl, –CO-NH-O-isopropyl, –CO-NH-C_2H_4-OH, –CO-NH-O-C_2H_4-OH, –CO-NH-C_2H_4-OCH_3, –CO-NH-C_2H_4-N(CH_3)$_2$, and –CO-NH-O-benzyl. Further examples are–CO-NH-isopropyl and –CO-NH-OH, as well as –CO-N(CH_3)$_2$.

Examples of a group "**-X1-CO-RO1**" as used for substituents of the group **Ar1** are especially the following groups:

a) **X1** represents a direct bond; and **RO1** represents -OH; (i.e. -**X1**-CO-**RO1** represents -COOH); or

b) **X1** represents a direct bond; and **RO1** represents -O-(C_{1-4})alkyl (especially ethoxy, or methoxy); (i.e. -**X1**-CO-**RO1** represents -CO-(C_{1-4})alkoxy (especially ethoxycarbonyl, methoxycarbonyl)); or

c) **X1** represents a direct bond; and **RO1** represents -NH-SO_2-**RS3**; wherein **RS3** 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})alkylene wherein the (C_{3-6})cycloalkyl optionally contains a ring oxygen atom; (C_{1-3})fluoroalkyl; phenyl; or -NH_2; (i.e. -**X1**-CO-**RO1** represents -CO-NH-SO_2-**RS3** wherein **RS3** represents the above mentioned groups; notably methyl, ethyl, isopropyl, cyclopropyl, trifluoromethyl, amino; especially -**X1**-CO-**RO1** represents -CO-NH-SO_2-CH_3, -CO-NH-SO_2-C(CH_3)$_2$, -CO-NH-SO_2-cyclopropyl, -CO-NH-SO_2-ethyl, or -CO-NH-SO_2-NH_2); or

d) **X1** represents (C_{1-3})alkylene (especially -CH_2-, -CH_2-CH_2-), -O-(C_{1-3})alkylene-* (especially -O-CH_2-*, -O-CH(CH_3)-*, -O-C(CH_3)$_2$-*, O-CH_2-CH_2-*), -NH-(C_{1-3})alkylene-* (especially -NH-CH_2-*, -NH-CH(CH_3)-*), -S-

CH_2-*, -CF_2-, –CH=CH-, or –CH≡CH- [in a sub-embodiment **X^1** represents especially -O-CH_2-*, -NH-CH_2-*, -S-CH_2-*, or (C_{1-3})alkylene]; wherein the asterisks indicate the bond that is linked to the -CO-**R^{O1}** group; and **R^{O1}** represents -OH (i.e. -**X^1**-CO-**R^{O1}** represents -**X^1**-COOH wherein **X^1** represents the above mentioned groups; especially -**X^1**-CO-**R^{O1}** represents -O-CH_2-COOH or -NH-CH_2-COOH; as well as -CH_2-COOH, -CH_2-CH_2-COOH, -CH=CH-COOH, –CH≡CH-COOH, -O-CH_2-CH_2-COOH, -O-CH(CH_3)-COOH, or -NH-CH(CH_3)-COOH); or

e) -**X^1** represents -NH-CO-* or -CO-; wherein the asterisk indicates the bond that is linked to the -CO-**R^{O1}** group; and **R^{O1}** represents -OH (i.e. -**X^1**-CO-**R^{O1}** represents -**X^1**-COOH wherein **X^1** represents the above mentioned groups; especially -**X^1**-CO-**R^{O1}** represents -NH-CO-COOH, -CO-COOH); or

f) **X^1** represents (C_{3-5})cycloalkylene; and **R^{O1}** represents -OH; (i.e. -**X^1**-CO-**R^{O1}** represents (C_{3-6})cycloalkyl which is mono-substituted with COOH; especially -**X^1**-CO-**R^{O1}** represents 1-carboxy-cyclopropan-1-yl or 1-carboxy-cyclopentan-1-yl); or

g) **X^1** represents a direct bond; and **R^{O1}** represents -O-CH_2-CO-**R^{O4}**, wherein **R^{O4}** repesents hydroxy, or (C_{1-4})alkoxy, or -N[(C_{1-4})alkyl]$_2$; especially -**X^1**-CO-**R^{O1}** represents -CO-O-CH_2-COOH; or

wherein each of the groups a), b), c), d), e), f), and g) forms a particular sub-embodiment.

Compounds of Formula (I) / formula (II) containing a group "-**X^1**-CO-**R^{O1}**" 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_{0-3})alkylene-COO**R^{O2}** wherein **R^{O2}** repesents hydrogen; -(C_{0-3})alkylene-COO**R^{O3}** wherein **R^{O3}** repesents hydrogen; or in the substituents -**X^1**-CO-**R^{O1}** wherein **R^{O1}** represents –OH, especially in the -**X^1**-CO-**R^{O1}** 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**-COOH groups are:

- ester groups -**X^1**-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}-CO-NH-SO_2-**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, -NH_2; (especially **R**^{S3} is (C_{1-4})alkyl, (C_{3-6})cycloalkyl; in particular methyl);
- groups -**X**^{1}-CO-**R**^{O1} wherein **R**^{O1} represents -O-CH_2-CO-**R**^{O4}, wherein **R**^{O4} repesents hydroxy, or (C_{1-4})alkoxy, or -N[(C_{1-4})alkyl]$_2$ (especially -CO-O-CH_2-COOH, -CO-O-CH_2-CO-N(CH_3)$_2$);
- groups -**X**^{1}-CO-**R**^{O1} wherein **R**^{O1} represents -O-CH_2-O-CO-**R**^{O5}, wherein **R**^{O5} repesents (C_{1-4})alkyl or (C_{1-4})alkoxy (especially -CO-O-CH_2-O-CO-O-ethyl, -CO-O-CH_2-O-CO-propyl);
- groups -**X**^{1}-CO-**R**^{O1} wherein **R**^{O1} represents -O-CH_2-CH_2-N[(C_{1-4})alkyl]$_2$ (especially -CO-O-CH_2-CH_2-N(CH_3)$_2$); and
- groups -**X**^{1}-CO-**R**^{O1} wherein **R**^{O1} represents 5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyloxy-.

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

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

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

Examples of a group "-SO_2-**R**^{S1}" as used for substituents of the group **Ar**^{1} are -SO_2-CH_3, -SO_2-NH_2, -SO_2-NH-CH_3.

Examples of a group " S-**R**^{S2} " as used for substituents of the group **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_{1-4})alkoxy" group as used for substituents of the group **Ar**^{1} 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 between 40 ºC and 80 ºC, this means that the end points 40 ºC and 80 ºC are included in the range; or if a variable is defined as being an integer between 1 and 4, this means that the variable is the integer 1, 2, 3, or 4.

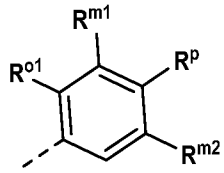
Unless used regarding temperatures, the term “about” placed before a numerical value “X” refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures,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

10ºC to Y plus 10ºC, and preferably to an interval extending from Y minus 5ºC to Y plus 5ºC. Besides, the term "room temperature" as used herein refers to a temperature of about 25°C.

Further embodiments of the invention are presented hereinafter:

9) Another embodiment relates to compounds according to embodiment 8), wherein **Ar^1** represents

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



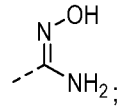
(Ar-I)

wherein

- **R^p** represents
  - **-X^1-CO-R^{O1}**, wherein
    - **X^1** represents a direct bond, (C_{1-3})alkylene (especially -CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -CH_2-CH_2-), -O-(C_{1-3})alkylene-* (especially -O-CH_2-*, -O-$CH(CH_3)$-*, -O-$C(CH_3)_2$-*, -O-CH_2-CH_2-*), -NH-(C_{1-3})alkylene-* (especially -NH-CH_2-*, -NH-$CH(CH_3)$-*), –CH=CH-, –CH≡CH-, -NH-CO-*, or (C_{3-5})cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-**R^{O1}** group; and
    - **R^{O1}** represents
      - -OH;
      - -O-(C_{1-4})alkyl (especially ethoxy, methoxy);
      - -NH-SO_2-**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})alkylene wherein the (C_{3-6})cycloalkyl optionally contains a ring oxygen atom, (C_{1-3})fluoroalkyl, or -NH_2;
      - -O-CH_2-CO-**R^{O4}**, wherein **R^{O4}** repesents hydroxy, or (C_{1-4})alkoxy, or -N[(C_{1-4})alkyl]$_2$;
      - -O-CH_2-O-CO-**R^{O5}**, wherein **R^{O5}** repesents (C_{1-4})alkyl or (C_{1-4})alkoxy;
      - -O-CH_2-CH_2-N[(C_{1-4})alkyl]$_2$ (especially -O-CH_2-CH_2-N(CH_3)$_2$); or
      - (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyloxy-;

    [wherein in particular such group **-X^1-CO-R^{O1}** represents -COOH, -CO-O-CH_3, -CO-O-C_2H_5, -O-CH_2-COOH, -O-$CH(CH_3)$-COOH, -O-$C(CH_3)_2$-COOH, -O-CH_2-CH_2-COOH, -NH-CH_2-COOH, -NH-CH_2-CO-O-CH_3, -NH-$CH(CH_3)$-COOH, -CO-NH-SO_2-CH_3, -CO-NH-SO_2-$C(CH_3)_2$, -CO-NH-SO_2-cyclopropyl, -CO-NH-SO_2-C_2H_5, -CO-NH-SO_2-NH_2, -CO-O-CH_2-COOH, -CO-O-CH_2-CH_2-N(CH_3)$_2$, -CO-O-CH_2-CO-N(CH_3)$_2$, -CO-O-CH_2-O-CO-O-C_2H_5, -CO-O-CH_2-O-CO-propyl, (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyl-O-CO-, -CH_2-COOH, -CH_2-CO-O-CH_3, -CH_2-CO-O-C_2H_5, -

CH_2-CH_2-COOH, -CH=CH-COOH, –CH≡CH-CO-O-C_2H_5, -NH-CO-COOH, 1-carboxy-cyclopropan-1-yl];

-  ;
- -NH-CO-N$R^{N5}R^{N6}$ 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-N$R^{N5}R^{N6}$ are –NH-CO-NH_2, –NH-CO-NH-C_2H_5);
- -(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), 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**^{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 -N$R^{N9}R^{N10}$ 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);

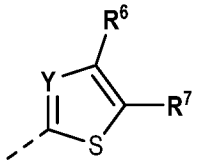
- R^{m1} represents
  - hydrogen;
  - (C_{1-6})alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl);
  - (C_{1-4})alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy);
  - (C_{1-3})fluoroalkyl (especially trifluoromethyl);
  - (C_{1-3})fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
  - halogen (especially fluoro or chloro);
  - (C_{3-6})cycloalkyl (especially cyclopropyl);
  - (C_{3-6})cycloalkyl-oxy (especially cyclopropyl-oxy, cyclobutyl-oxy, cyclopentyl-oxy);
  - hydroxy;
  - hydroxy-(C_{2-4})alkoxy (especially 2-hydroxy-ethoxy);

- -S-R^{S2} wherein R^{S2} represents (C_{1-4})alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C_{3-6})cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);

wherein in a sub-embodiment, R^{m1} especially is different from hydrogen;

- R^{m2} represents hydrogen, methyl, fluoro, or chloro; and
- R^{o1} represents hydrogen; or, in case R^{m2} represents hydrogen, R^{o1} represents hydrogen or fluoro;

- or Ar^1 represents a 5-membered heteroaryl group of the structure (Ar-II):



(Ar-II)

wherein

- **Y** represents CR^8 wherein R^8 represents especially hydrogen, or halogen (notably fluoro, chloro); or **Y** represents N;

- R^7 represents
  - -X^1-CO-R^{O1}, wherein
    - X^1 represents a direct bond, (C_{1-3})alkylene (especially -CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -CH_2-CH_2-), -O-(C_{1-3})alkylene-* (especially -O-CH_2-*, -O-$CH(CH_3)$-*, -O-$C(CH_3)_2$-*, -O-CH_2-CH_2-*), -NH-(C_{1-3})alkylene-* (especially -NH-CH_2-*, -NH-$CH(CH_3)$-*), –CH=CH-, –CH≡CH-, -NH-CO-*, or (C_{3-5})cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-R^{O1} group; and
    - R^{O1} represents
      - -OH;
      - -O-(C_{1-4})alkyl (especially ethoxy, methoxy);
      - -NH-SO_2-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})alkylene wherein the (C_{3-6})cycloalkyl optionally contains a ring oxygen atom, (C_{1-3})fluoroalkyl, or -NH_2;
      - -O-CH_2-CO-R^{O4}, wherein R^{O4} repesents hydroxy, or (C_{1-4})alkoxy, or -N[(C_{1-4})alkyl]$_2$;
      - -O-CH_2-O-CO-R^{O5}, wherein R^{O5} repesents (C_{1-4})alkyl or (C_{1-4})alkoxy; or
      - -O-CH_2-CH_2-N[(C_{1-4})alkyl]$_2$ (especially -O-CH_2-CH_2-N(CH_3)$_2$);
      - (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyloxy-;

    [wherein in particular such group -X^1-CO-R^{O1} represents -COOH, -CO-O-CH_3, -CO-O-C_2H_5, -O-CH_2-COOH, -O-$CH(CH_3)$-COOH, -O-$C(CH_3)_2$-COOH, -O-CH_2-CH_2-COOH, -NH-CH_2-COOH, -NH-CH_2-CO-O-CH_3, -NH-$CH(CH_3)$-COOH, -CO-NH-SO_2-CH_3, -CO-NH-SO_2-$C(CH_3)_2$, -CO-NH-SO_2-

cyclopropyl, -CO-NH-SO_2-C_2H_5, -CO-NH-SO_2-NH_2, -CO-O-CH_2-COOH, -CO-O-CH_2-CH_2-N(CH_3)$_2$, -CO-O-CH_2-CO-N(CH_3)$_2$, -CO-O-CH_2-O-CO-O-C_2H_5, -CO-O-CH_2-O-CO-propyl, (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyl-O-CO-, -CH_2-COOH, -CH_2-CO-O-CH_3, -CH_2-CO-O-C_2H_5, -CH_2-CH_2-COOH, -CH=CH-COOH, –CH≡CH-CO-O-C_2H_5, -NH-CO-COOH, 1-carboxy-cyclopropan-1-yl];

- -NH-CO-N**R^{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-N**R^{N5}R^{N6}** are –NH-CO-NH_2, –NH-CO-NH-C_2H_5);
- -(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), 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^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 -N**R^{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);

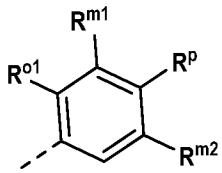
- **R^6** represents
  - (C_{1-6})alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl);
  - (C_{1-4})alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy);
  - (C_{1-3})fluoroalkyl (especially trifluoromethyl);
  - (C_{1-3})fluoroalkoxy (especially difluoromethoxy,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

- or **Ar¹** represents 8- to 10-membered bicyclic heteroaryl (notably 9- or 10-membered bicyclic heteroaryl; especially indazolyl, benzoimidazolyl, indolyl, benzofuranyl, benzooxazolyl, quinoxalinyl, isoquinolinyl, or quinolinyl); wherein said 8- to 10-membered bicyclic heteroaryl independently is mono-substituted with -(C_{0-3})alkylene-COO**R^o2** wherein **R^o2** repesents hydrogen or (C_{1-4})alkyl (especially methyl) (wherein especially such group -(C_{0-3})alkylene-COO**R^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);

wherein in a sub-embodiment, **Ar¹** especially is a phenyl group of the structure (Ar-I) (wherein in particular **R^m1** especially is different from hydrogen), or a 5-membered heteroaryl group of the structure (Ar-II), as defined herein above.

10) Another embodiment relates to compounds according to any one of embodiment 8) to 15), wherein **Ar¹** represents

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



(Ar-I)

wherein

- **R^p** represents
  - **-X¹-CO-R^o1**, wherein
    - **X¹** represents a direct bond, (C_{1-3})alkylene (especially -CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -CH_2-CH_2-), -O-(C_{1-3})alkylene-* (especially -O-CH_2-*, -O-$CH(CH_3)$-*, -O-$C(CH_3)_2$-*, -O-CH_2-CH_2-*), -NH-(C_{1-3})alkylene-* (especially -NH-CH_2-*, -NH-$CH(CH_3)$-*), —CH=CH-, -NH-CO-*, or (C_{3-5})cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-**R^o1** group; and
    - **R^o1** represents
      - -OH;
      - -O-(C_{1-4})alkyl (especially ethoxy, methoxy);
      - -NH-SO_2-**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})alkylene wherein the (C_{3-6})cycloalkyl optionally contains a ring oxygen atom, (C_{1-3})fluoroalkyl, or -NH_2;

[wherein in particular such group -**X**^{1}-CO-**R**^{O1} represents -COOH, -CO-O-CH_3, -CO-O-C_2H_5, -O-CH_2-COOH, -O-CH(CH_3)-COOH, -O-C(CH_3)$_2$-COOH, -O-CH_2-CH_2-COOH, -NH-CH_2-COOH, -NH-CH_2-CO-O-CH_3, -NH-CH(CH_3)-COOH, -CO-NH-SO_2-CH_3, -CO-NH-SO_2-C(CH_3)$_2$, -CO-NH-SO_2-cyclopropyl, -CO-NH-SO_2-C_2H_5, -CO-NH-SO_2-NH_2, -CH_2-COOH, -CH_2-CO-O-CH_3, -CH_2-CO-O-C_2H_5, -CH_2-CH_2-COOH, -CH=CH-COOH, -NH-CO-COOH, 1-carboxy-cyclopropan-1-yl];

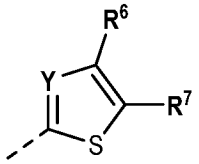
- **HET**^{1}, wherein **HET**^{1} represents 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl (encompassing its tautomeric form 5-hydroxy-[1,2,4]oxadiazol-3-yl), or 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl (encompassing its tautomeric form 3-hydroxy-[1,2,4]oxadiazol-5-yl);
- **HET**, wherein **HET** represents a 5-membered heteroaryl selected from oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl, or tetrazolyl; in particular isoxazolyl and tetrazolyl, wherein said 5-membered heteroaryl is unsubstituted, or mono-substituted, wherein the substituent is 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 -N**R**^{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); [in particular **HET** is unsubstituted or mono-substituted with hydroxy; especially **HET** is 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, or 2-hydroxy-[1,3,4]oxadiazol-4-yl];

- **R**^{m1} represents
  - hydrogen;
  - (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, isobutoxy);
  - (C_{1-3})fluoroalkyl (especially trifluoromethyl);
  - (C_{1-3})fluoroalkoxy (especially difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy);
  - halogen (especially fluoro or chloro);
  - (C_{3-6})cycloalkyl (especially cyclopropyl);
  - (C_{3-6})cycloalkyl-oxy (especially cyclopropyl-oxy, cyclobutyl-oxy, cyclopentyl-oxy);
  - hydroxy;
  - hydroxy-(C_{2-4})alkoxy (especially 2-hydroxy-ethoxy);
  - -S-**R**^{S2} wherein **R**^{S2} represents (C_{1-4})alkyl (especially methyl, ethyl, n-propyl, isopropyl, isobutyl), or (C_{3-6})cycloalkyl optionally containing one ring oxygen atom (especially cyclobutyl, oxetan-3-yl);

  wherein in a sub-embodiment, **R**^{m1} especially is different from hydrogen;

- **R**^{m2} represents hydrogen, methyl, fluoro, or chloro; and
- **R**^{o1} represents hydrogen;

- or **Ar**[1] represents a 5-membered heteroaryl group of the structure (Ar-II):



(Ar-II)

wherein

- **Y** represents CH or N;
- **R**[7] represents
  - -**X**[1]-CO-**R**[O1], wherein
    - **X**[1] represents a direct bond, (C_{1-3})alkylene (especially -CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -CH_2-CH_2-), -O-(C_{1-3})alkylene-* (especially -O-CH_2-*, -O-$CH(CH_3)$-*, -O-$C(CH_3)_2$-*, -O-CH_2-CH_2-*), -NH-(C_{1-3})alkylene-* (especially -NH-CH_2-*, -NH-$CH(CH_3)$-*), -S-CH_2-*, -CF_2-, –CH=CH-, –CH≡CH-, -NH-CO-*, -CO-, or (C_{3-5})cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-**R**[O1] group; and
    - **R**[O1] represents
      - -OH;
      - -O-(C_{1-4})alkyl (especially ethoxy, methoxy);
      - -NH-SO_2-**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})alkylene wherein the (C_{3-6})cycloalkyl optionally contains a ring oxygen atom, (C_{1-3})fluoroalkyl, or -NH_2;

    [wherein in particular such group -**X**[1]-CO-**R**[O1] represents -COOH, -CO-O-CH_3, -CO-O-C_2H_5, -O-CH_2-COOH, -O-$CH(CH_3)$-COOH, -O-$C(CH_3)_2$-COOH, -O-CH_2-CH_2-COOH, -NH-CH_2-COOH, -NH-CH_2-CO-O-CH_3, -NH-$CH(CH_3)$-COOH, -CO-NH-SO_2-CH_3, -CO-NH-SO_2-$C(CH_3)_2$, -CO-NH-SO_2-cyclopropyl, -CO-NH-SO_2-C_2H_5, -CO-NH-SO_2-NH_2, -CH_2-COOH, -CH_2-CO-O-CH_3, -CH_2-CO-O-C_2H_5, -CH_2-CH_2-COOH, -CH=CH-COOH, -NH-CO-COOH, 1-carboxy-cyclopropan-1-yl];

    - **HET**[1], 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), or 3-oxo-2,3-dihydro-[1,2,4]oxadiazol-5-yl (encompassing its tautomeric form 3-hydroxy-[1,2,4]oxadiazol-5-yl);
    - **HET**, wherein **HET** represents a 5-membered heteroaryl selected from oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl, or tetrazolyl; in particular isoxazolyl and tetrazolyl, wherein said 5-membered heteroaryl is unsubstituted, or mono-substituted, wherein the substituent is 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 -N**R**^{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) [in particular **HET** is unsubstituted or mono-substituted with hydroxy; especially **HET** is 1H-tetrazol-5-yl, 3-hydroxy-isoxazol-5-yl, or 2-hydroxy-[1,3,4]oxadiazol-4-yl];

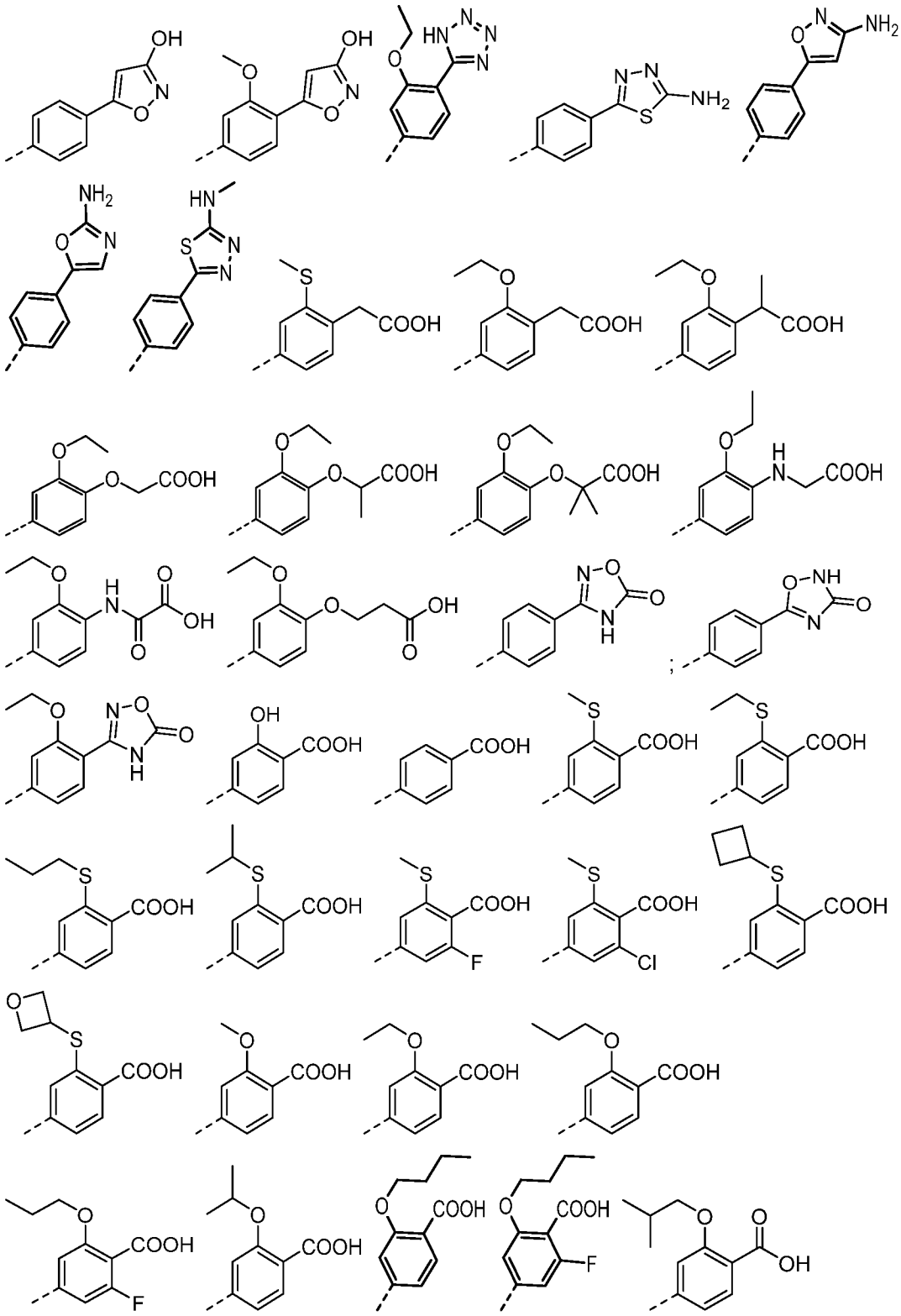
- **R**^{6} represents
  - (C_{1-6})alkyl (especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl);
  - (C_{1-4})alkoxy (especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy);
  - (C_{1-3})fluoroalkyl (especially trifluoromethyl);
  - (C_{1-3})fluoroalkoxy (especially difluoromethoxy,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

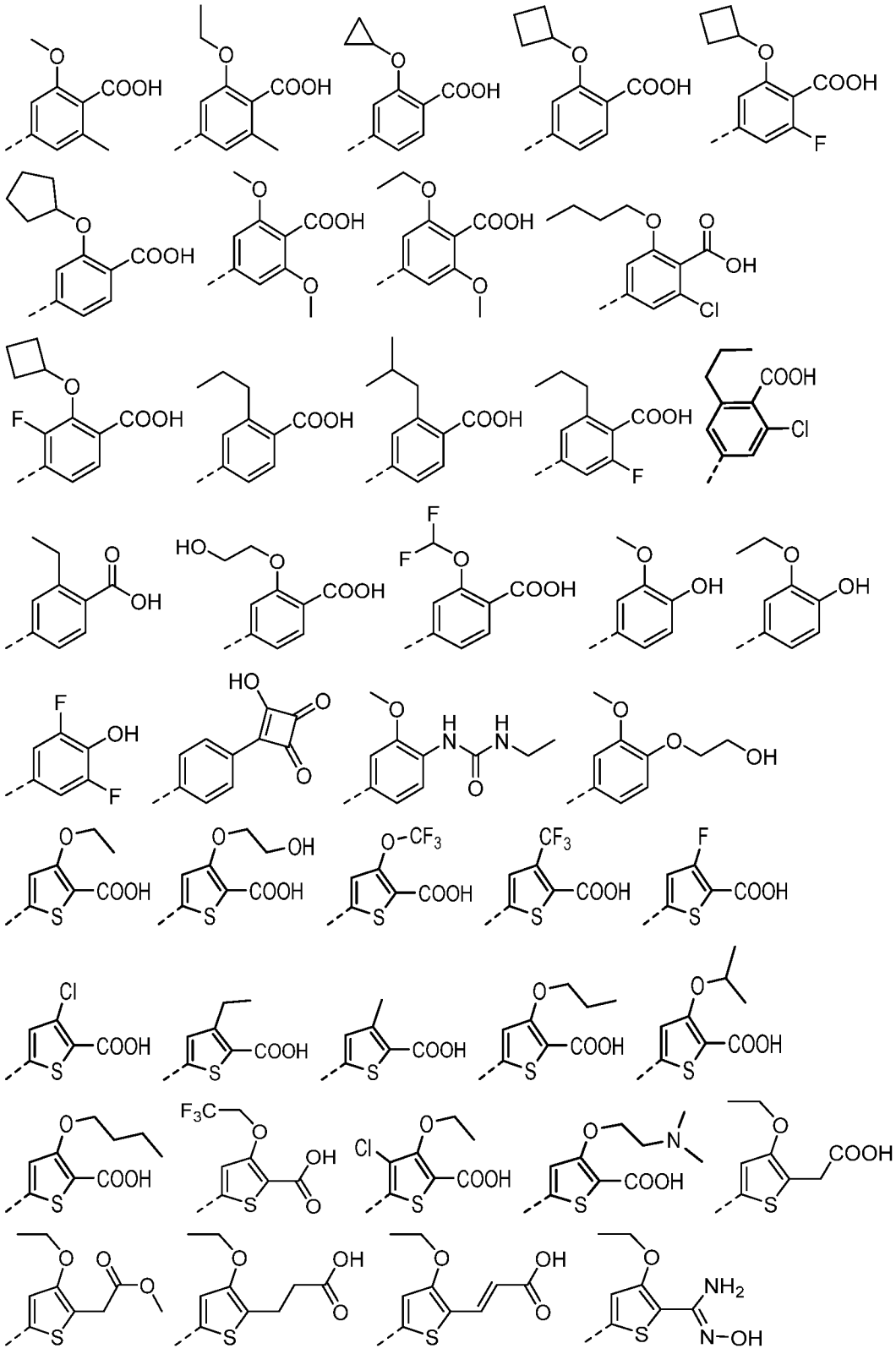
- or **Ar**^{1} represents 8- to 10-membered bicyclic heteroaryl selected from indazolyl, benzoimidazolyl, indolyl, benzofuranyl, benzooxazolyl, quinoxalinyl, isoquinolinyl, and quinolinyl; wherein said 8- to 10-membered bicyclic heteroaryl independently is mono-substituted with -(C_{0-3})alkylene-COO**R**^{O2} wherein **R**^{O2} repesents hydrogen or (C_{1-4})alkyl (especially methyl) (wherein especially such group -(C_{0-3})alkylene-COO**R**^{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);

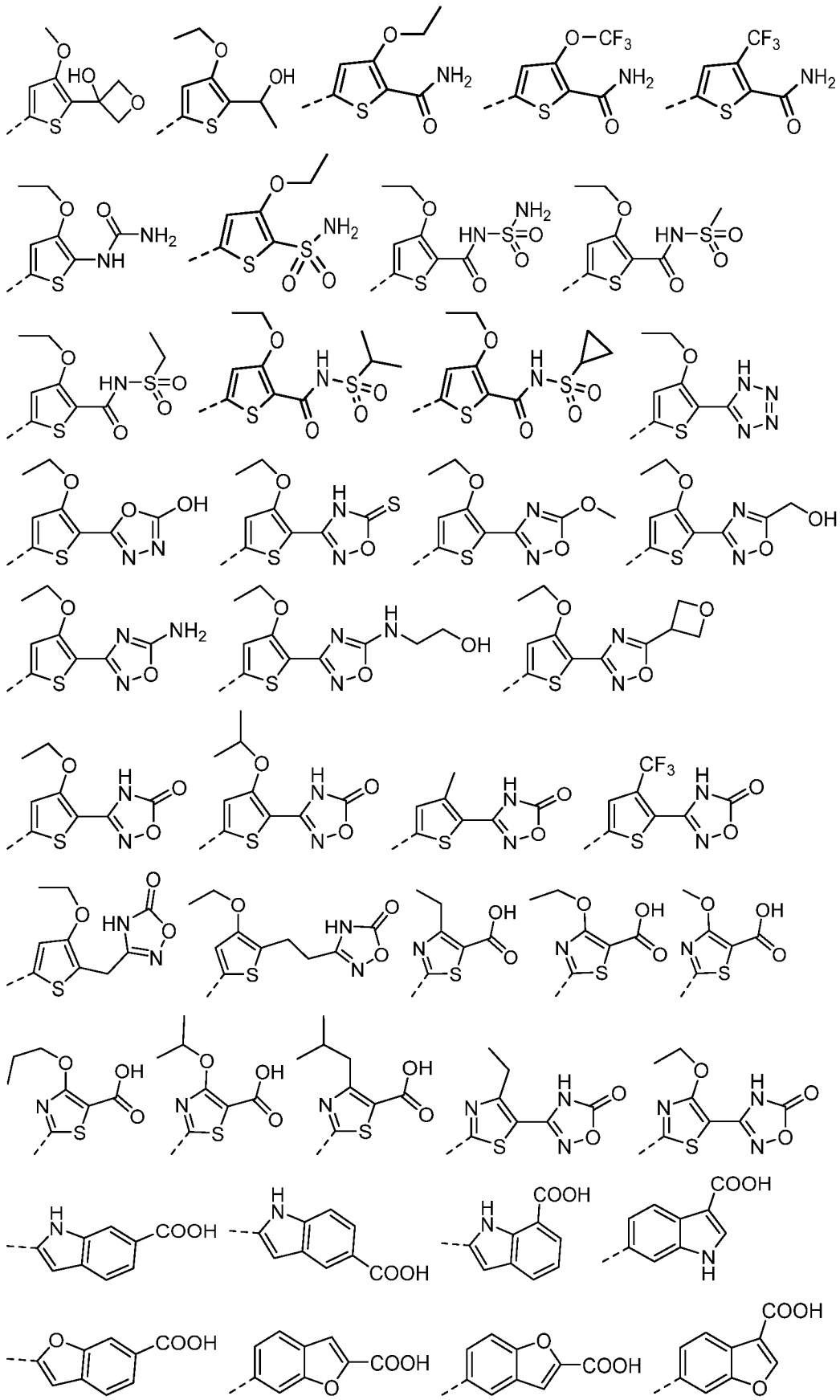
wherein in a sub-embodiment, **Ar**^{1} especially is a phenyl group of the structure (Ar-I) (wherein in particular **R**^{m1} especially is different from hydrogen), or a 5-membered heteroaryl group of the structure (Ar-II), as defined herein above.

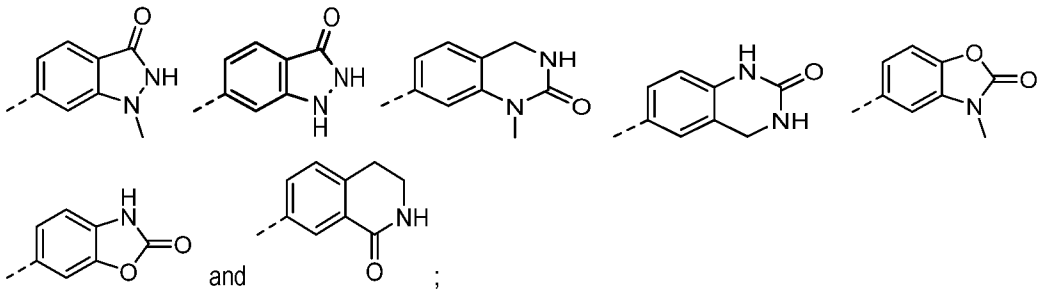
11) Another embodiment relates to compounds according to embodiment 8), wherein **Ar**[1] represents a group selected from:

A)



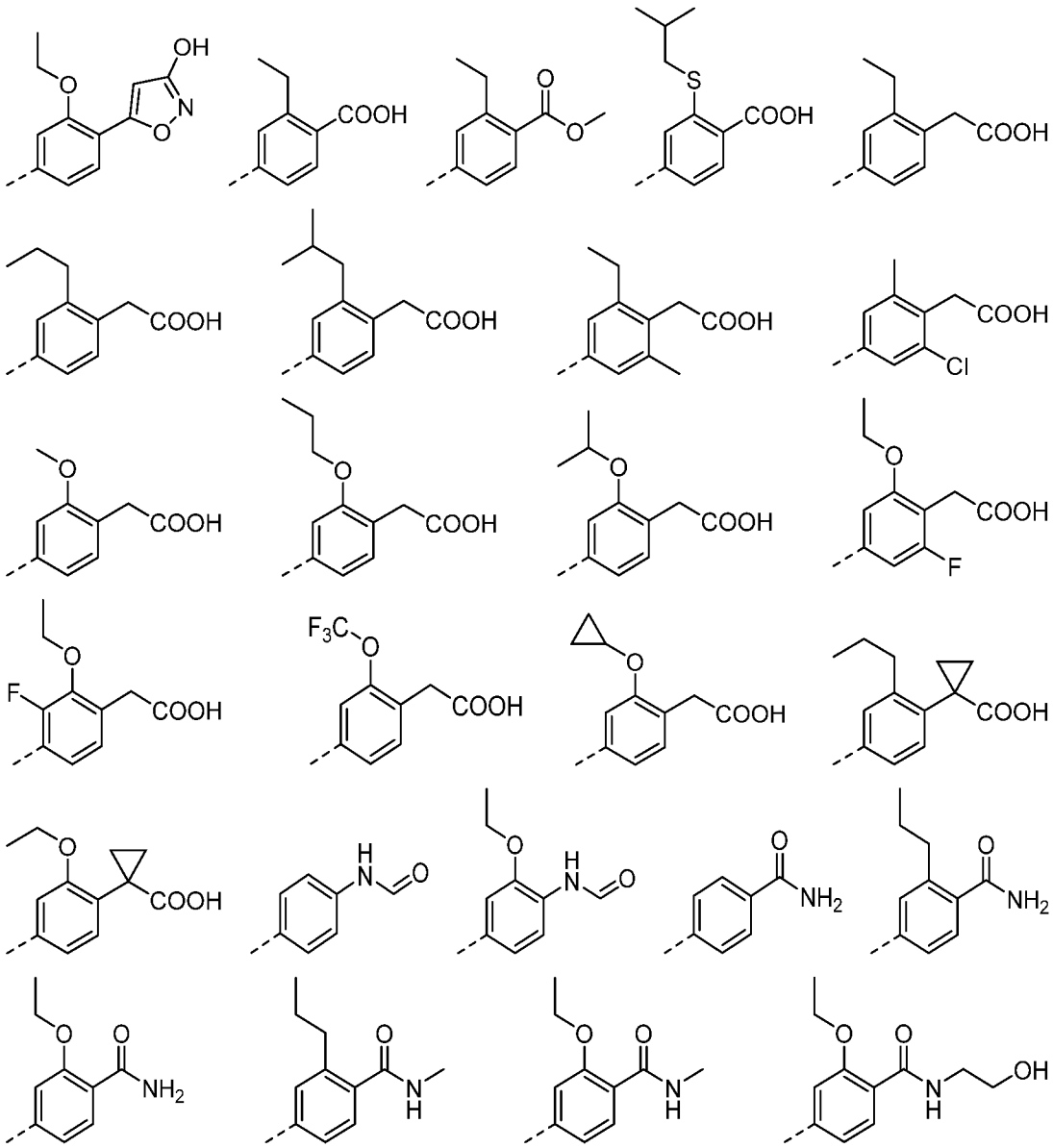


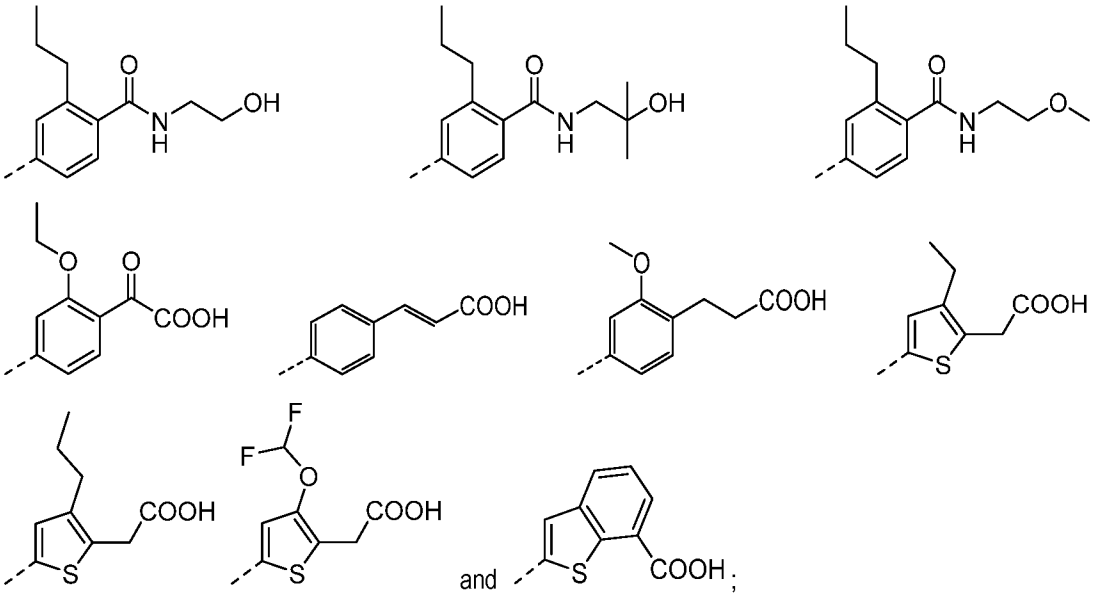



and ;

or, in addition, **Ar**[1] represents a group selected from:

B)





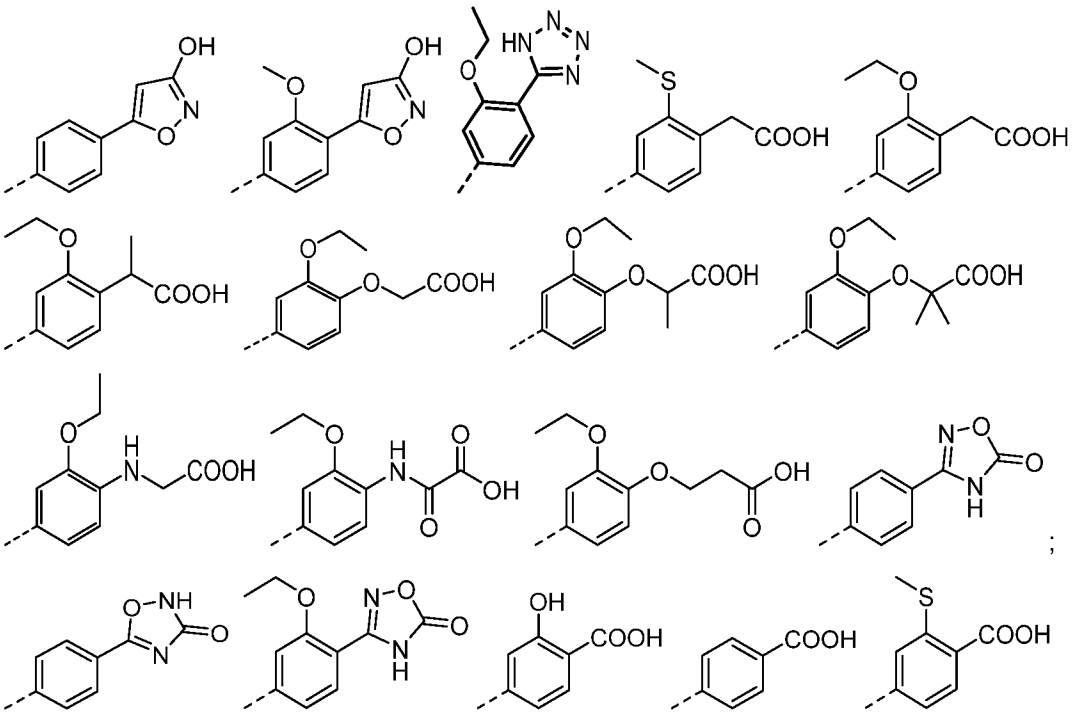
and ;

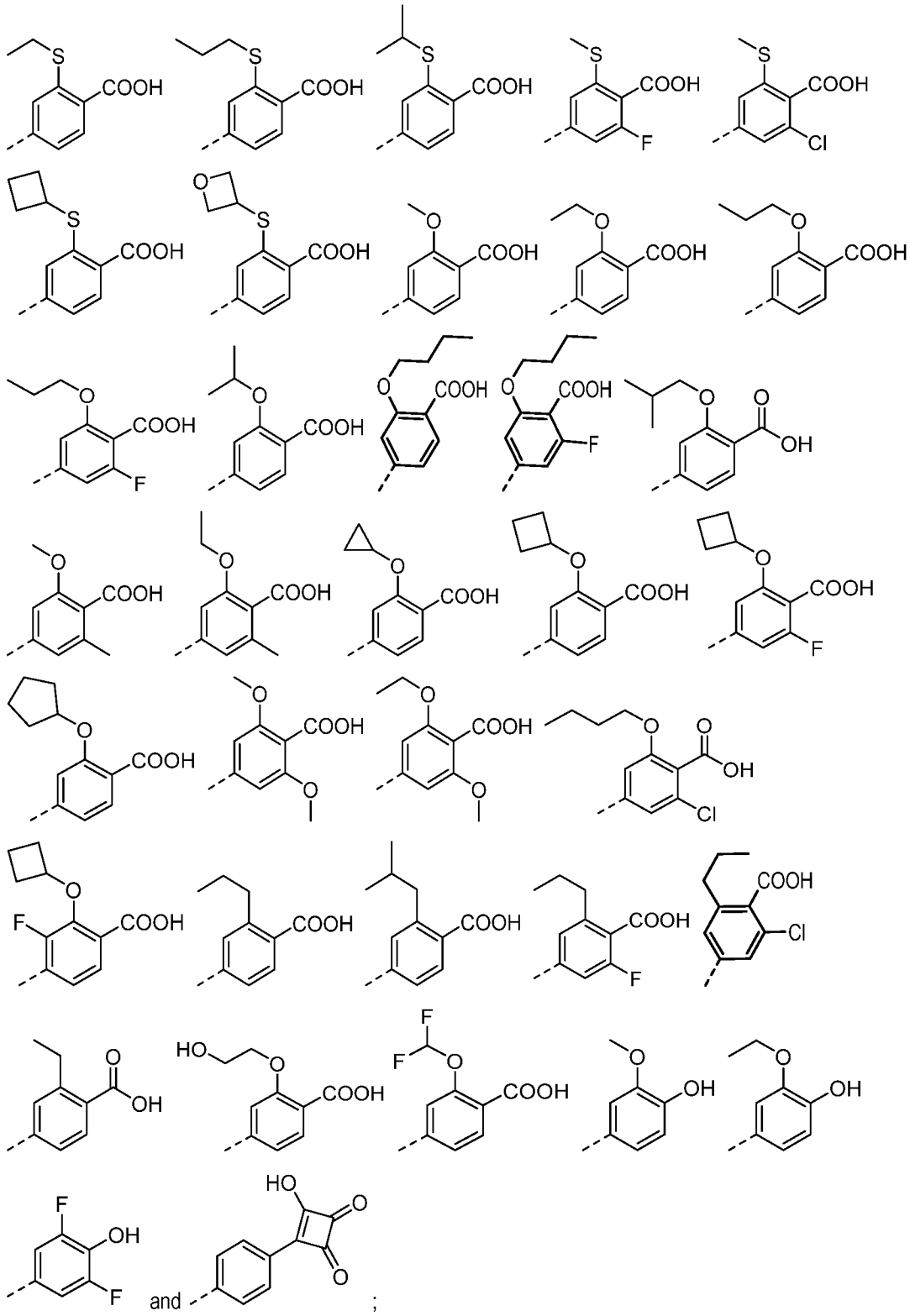
wherein each of the groups A) and B) forms a particular sub-embodiment;

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

12) Another embodiment relates to compounds according to embodiment 8), wherein

a) **Ar**[1] represents a phenyl group selected from:

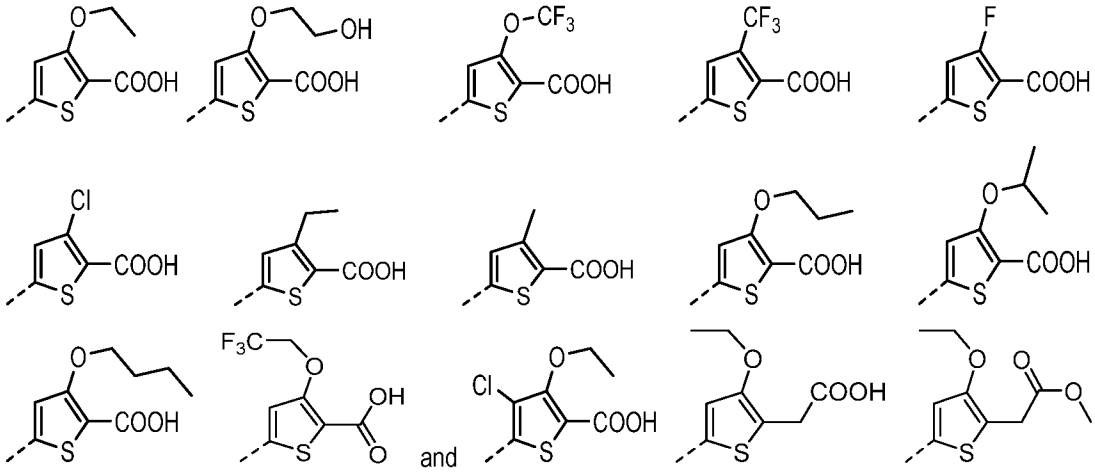


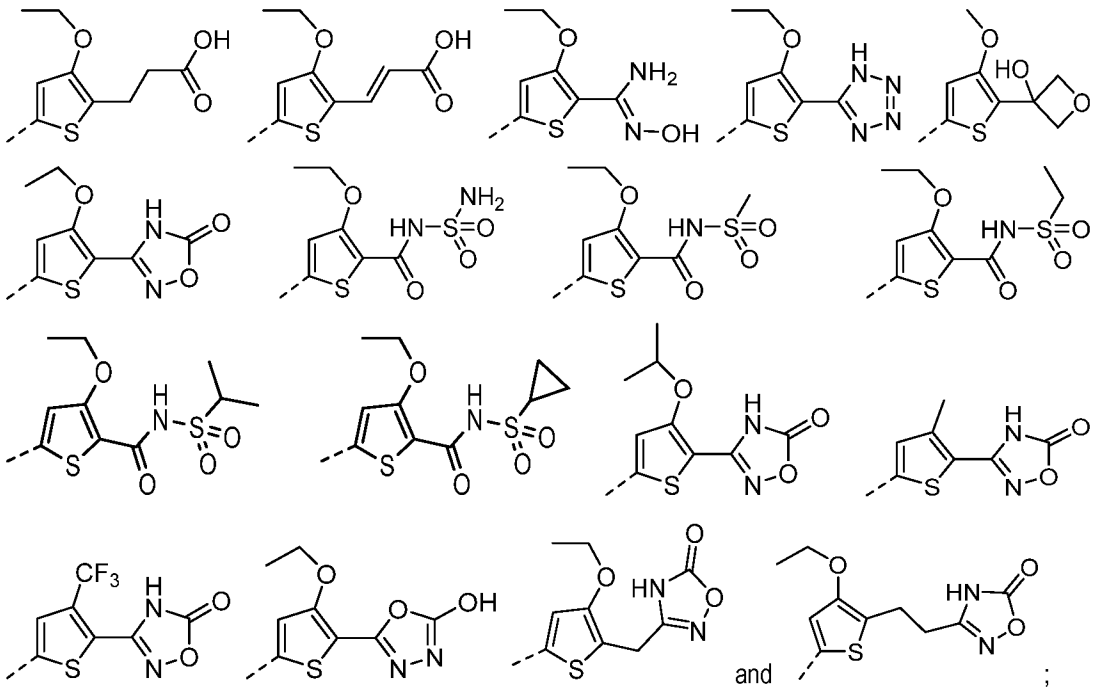


and

;

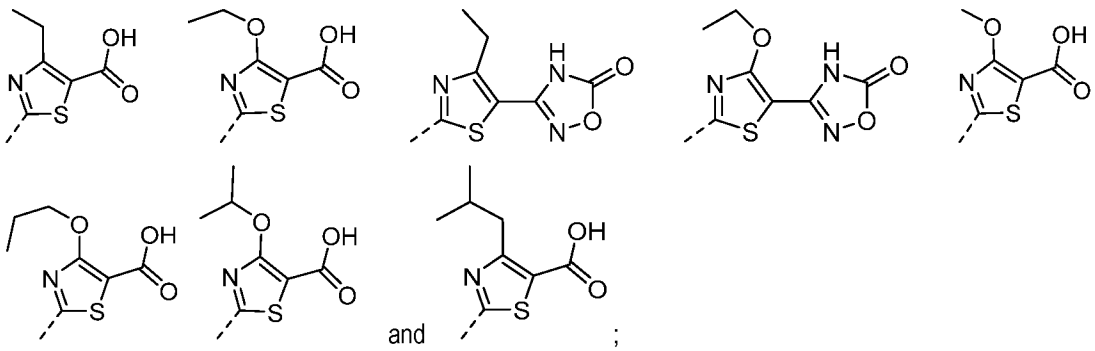
b) or **Ar**[1] represents a thiophenyl group selected from:





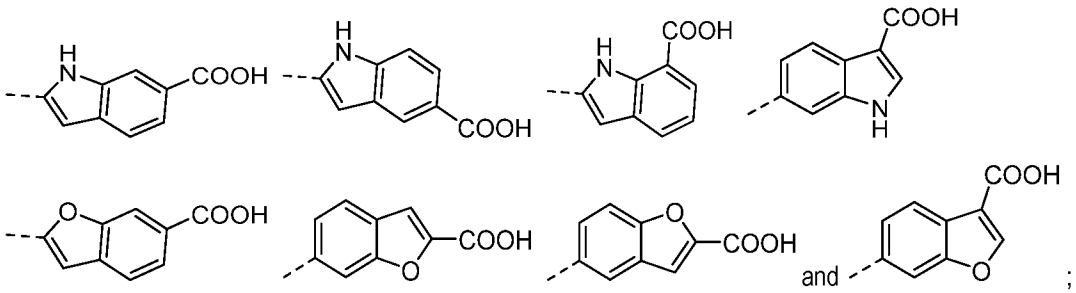
;

c) or **Ar**[1] represents a thiazolyl group selected from:

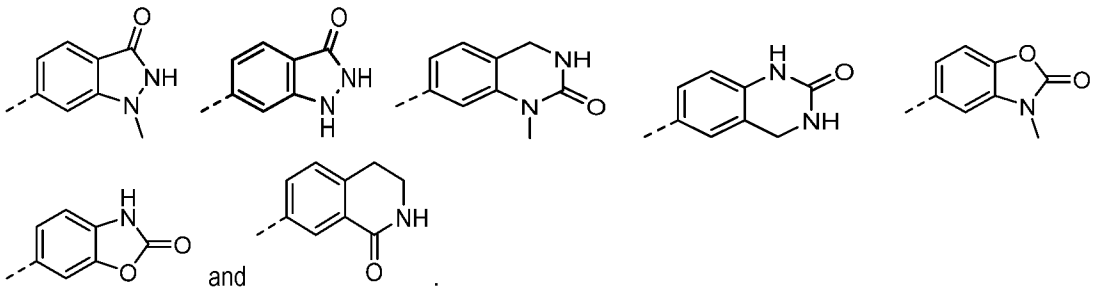


;

- or **Ar**[1] represents 9- or 10-membered bicyclic heteroaryl selected from



- or **Ar**[1] represents a group selected from:

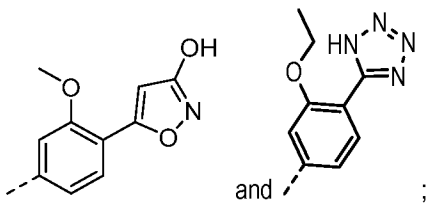


wherein in a sub-embodiment, **Ar**[1] especially is a phenyl group (in particular a di-substituted phenyl group), or a thiophenyl group, or a thiazolyl group, as defined herein above.

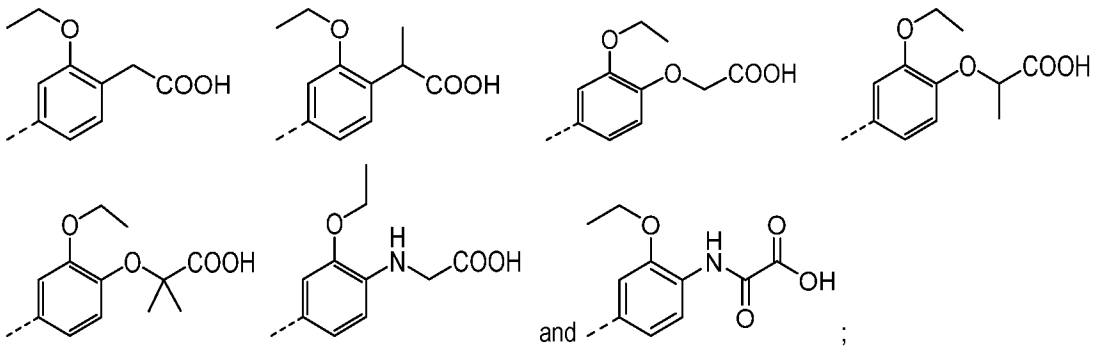
13) Another embodiment relates to compounds according to embodiment 8), wherein

(i) **Ar**[1] represents a phenyl group selected from:

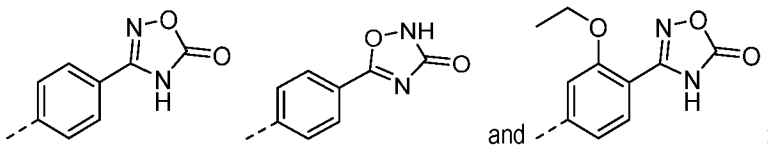
a)



b)

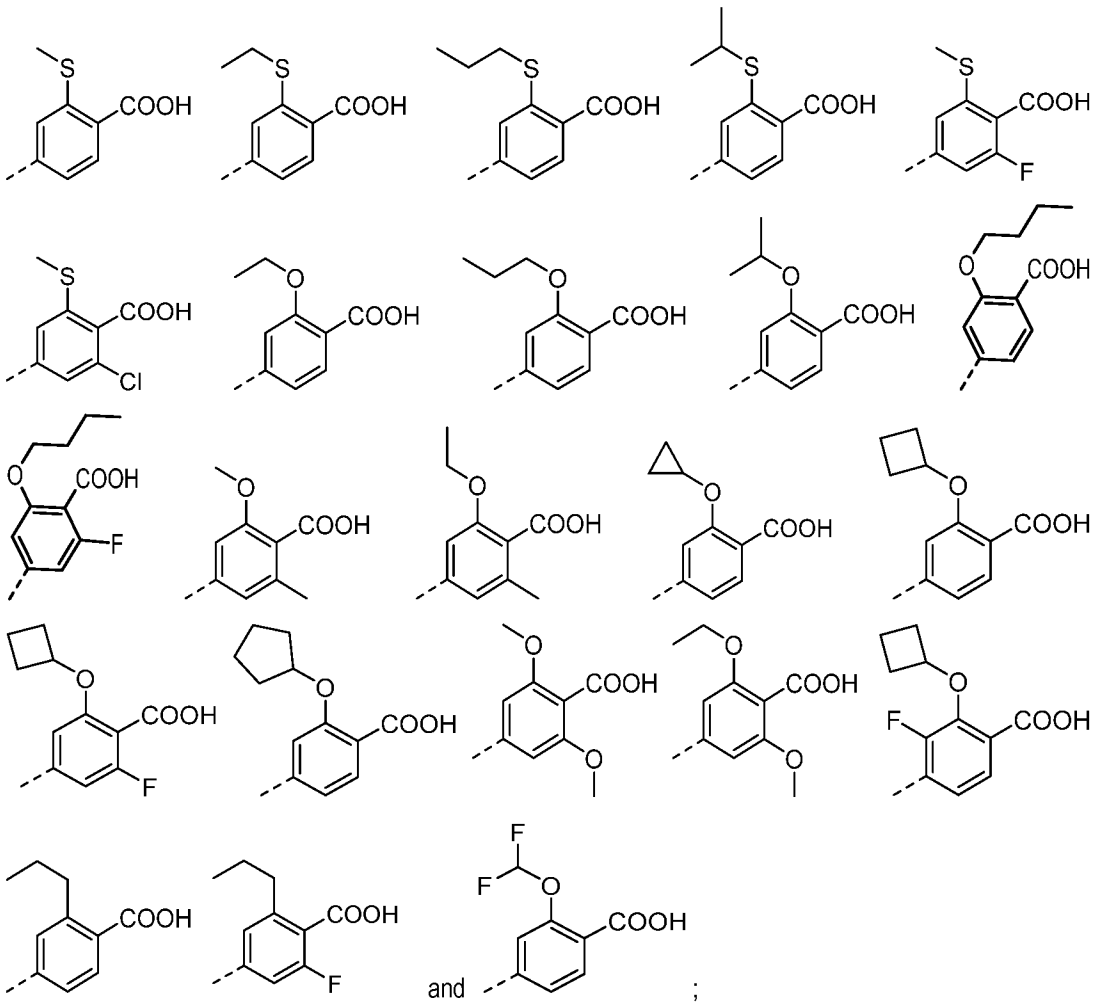


c)



and ;

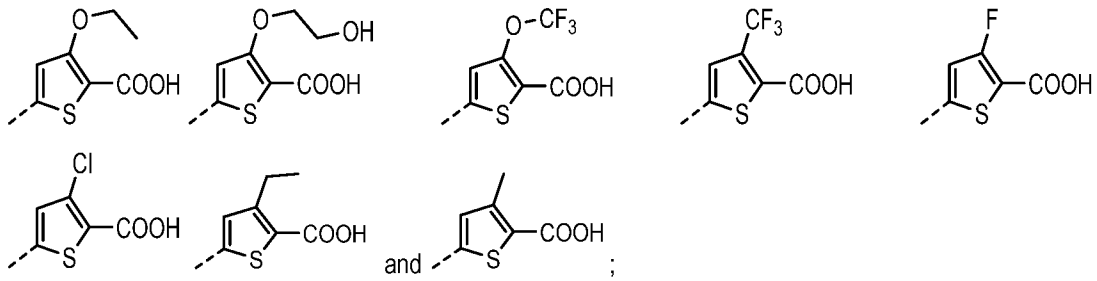
d)



and ;

(ii) or **Ar**[1] represents a thiophenyl group selected from:

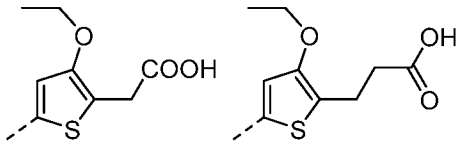
a)



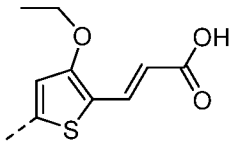
and

;

b)

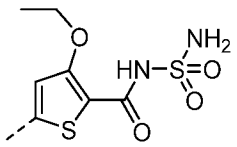


and

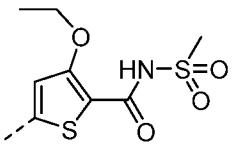


;

c)

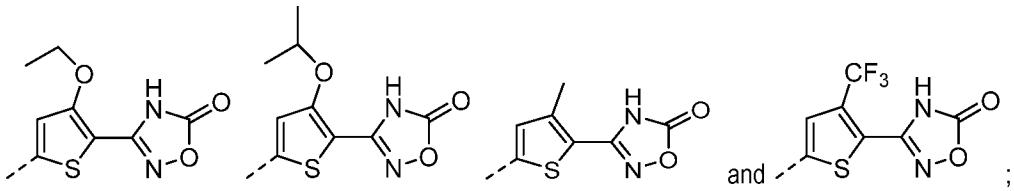


and



;

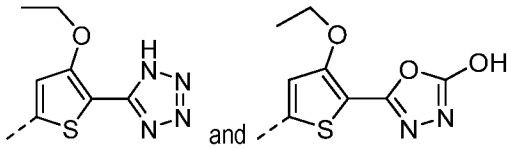
d)



and

;

e)

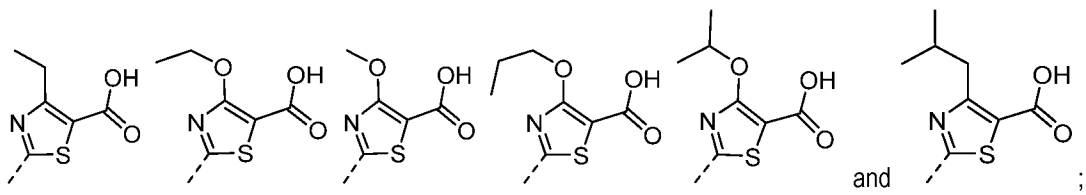


and

;

(iii) or **Ar**[1] represents a thiazolyl group selected from:

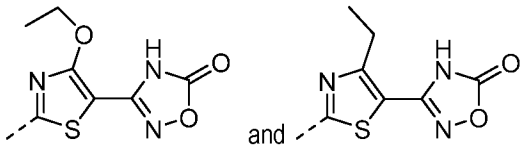
a)



and

;

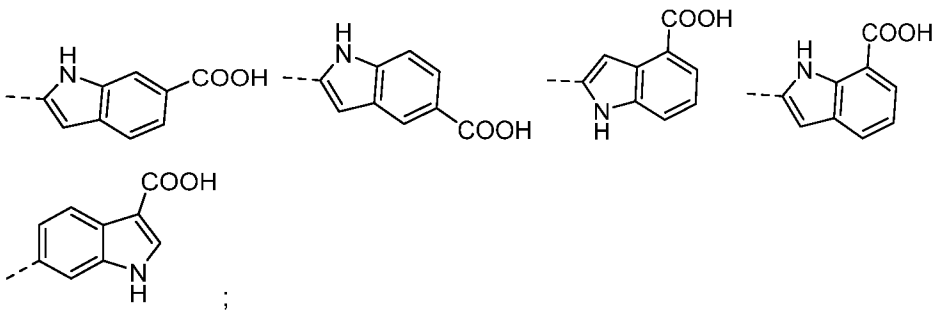
b)



;

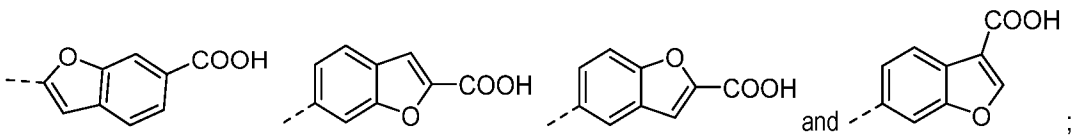
(iv) or **Ar**[1] represents 9- or 10-membered bicyclic heteroaryl selected from

a)



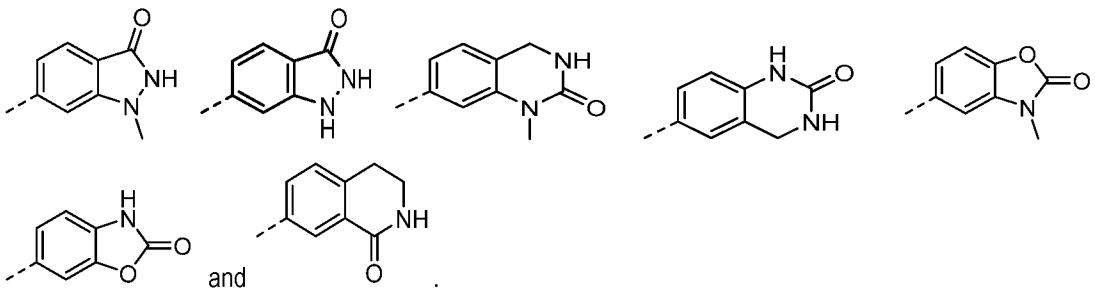
;

b)



;

(v) or **Ar**[1] represents a group selected from:

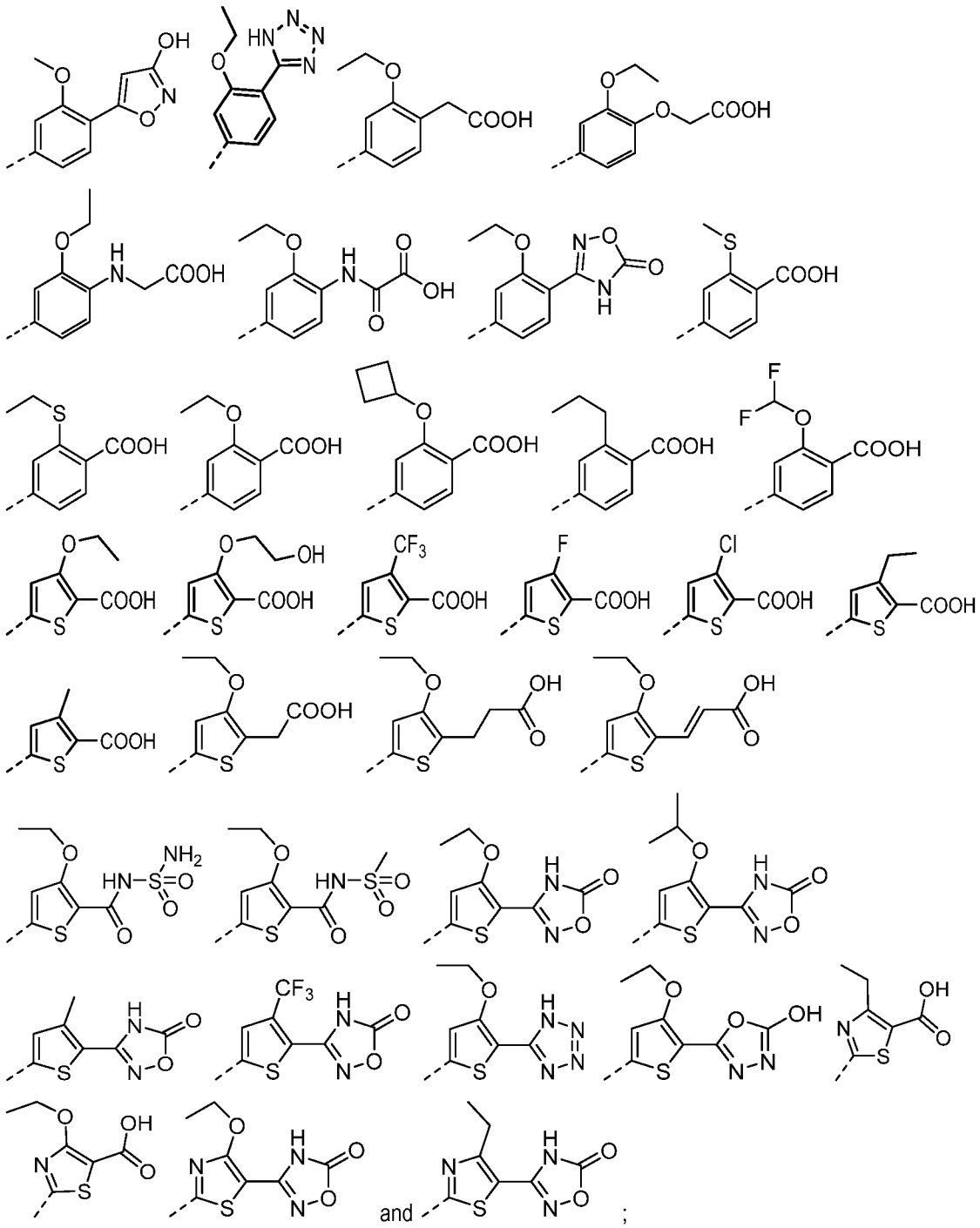


.

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

14) Another embodiment relates to compounds according to embodiment 8), wherein **Ar**[1] represents a group selected from

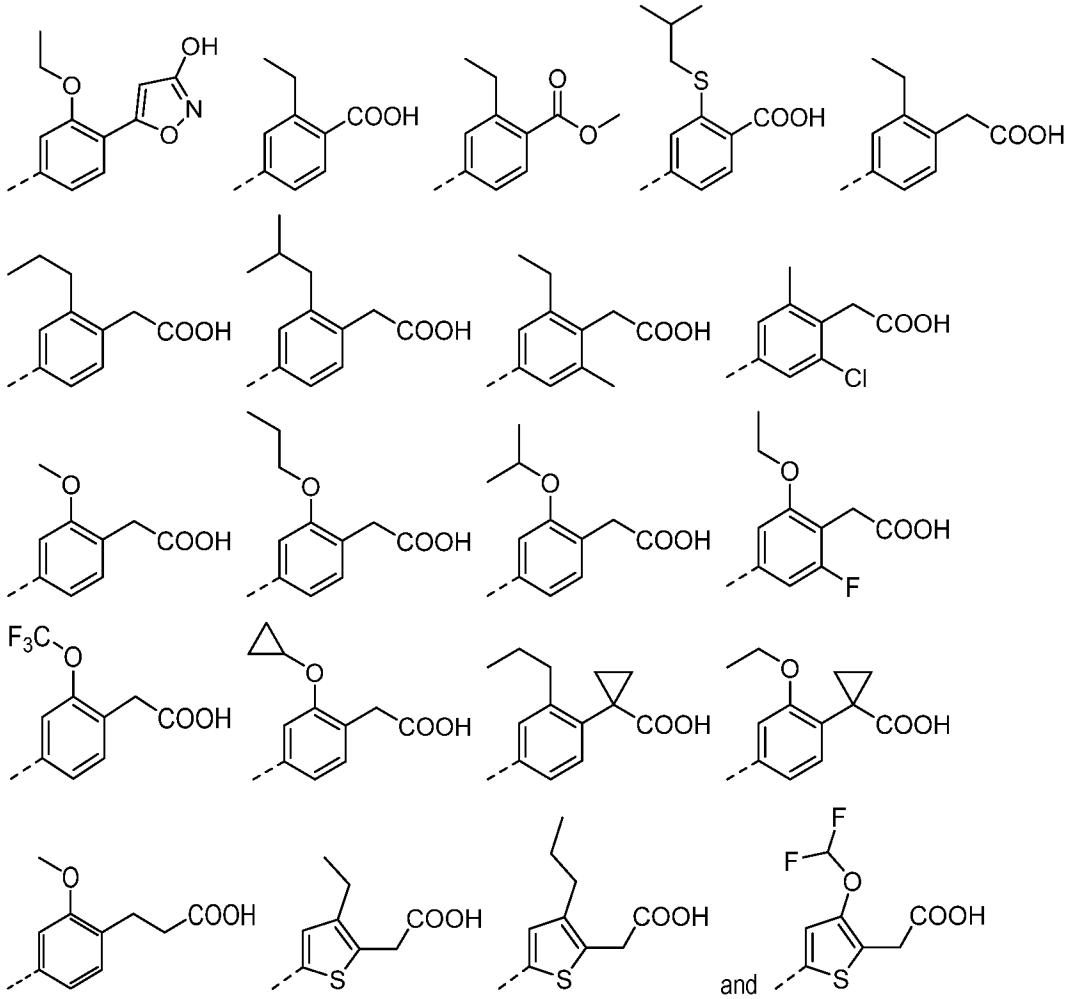
A)



and ;

or, in addition, **Ar**[1] represents a group selected from

B)



and

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

15) Another embodiment relates to compounds of formual (II) according to any one of embodiments 8) to 13), wherein **X** represents S.

16) Another embodiment relates to compounds of formual (II) according to any one of embodiments 8) to 13), wherein **X** represents O.

17) A second embodiment relates to compounds of formual (II) according to any one of embodiments 8) to 15), wherein $\mathbf{R^2}$ represents hydrogen.

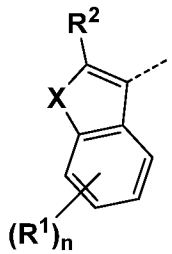
18) Another embodiment relates to compounds of formual (II) according to any one of embodiments 8) to 16), wherein $\mathbf{R^2}$ represents $(C_{1\text{-}4})$alkyl (especially methyl, ethyl), halogen (especially chloro, bromo), or cyano.

19) Another embodiment relates to compounds of formual (II) according to any one of embodiments 8) to 16), wherein $\mathbf{R^2}$ represents $(C_{1\text{-}4})$alkyl (especially methyl, ethyl).

20) Another embodiment relates to compounds of formual (II) according to any one of embodiments 8) to 15), wherein **R²** represents (C_{1-4})alkyl (especially methyl, ethyl), or cyano.

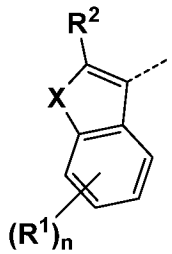
21) Another embodiment relates to compounds of formual (II) according to any one of embodiments 8) to 15), wherein **R²** represents cyano.

22) Another embodiment relates to compounds according to any one of embodiments 8) to 21), wherein in the fragment



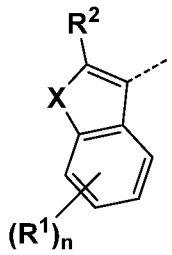
$(R^1)_n$ represents one, two or three substituents (i.e. said fragment is, in addtition to **R²**, substituted with one, two or three **R¹**), wherein said substituents **R¹** are independently selected from (C_{1-3})alkyl (especially methyl), (C_{1-3})alkoxy (especially methoxy), halogen (especially fluoro, or chloro), (C_{1-3})fluoroalkyl (especially trifluoromethyl), (C_{1-3})fluoroalkoxy (especially trifluoromethoxy), or cyano.

23) Another embodiment relates to compounds according to any one of embodiments 8) to 21), wherein in the fragment



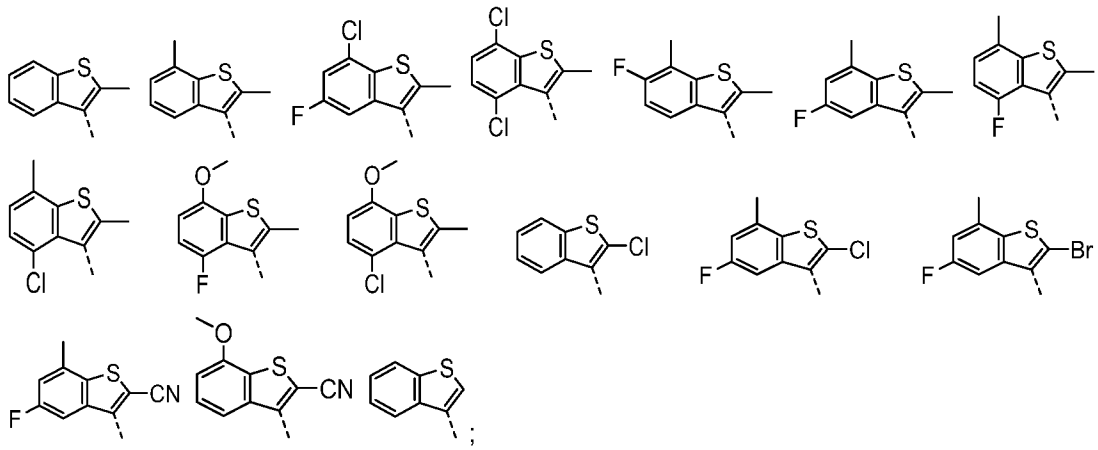
$(R^1)_n$ represents one, two or three substituents (i.e. said fragment is, in addtition to **R²**, substituted with one, two or three **R¹**), wherein said substituents **R¹** are independently selected from (C_{1-3})alkyl (especially methyl), (C_{1-3})alkoxy (especially methoxy), or halogen (especially fluoro, or chloro).

24) Another embodiment relates to compounds according to any one of embodiments 8) to 16), wherein the fragment

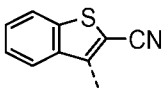


represents

- a benzothiophene selected from:

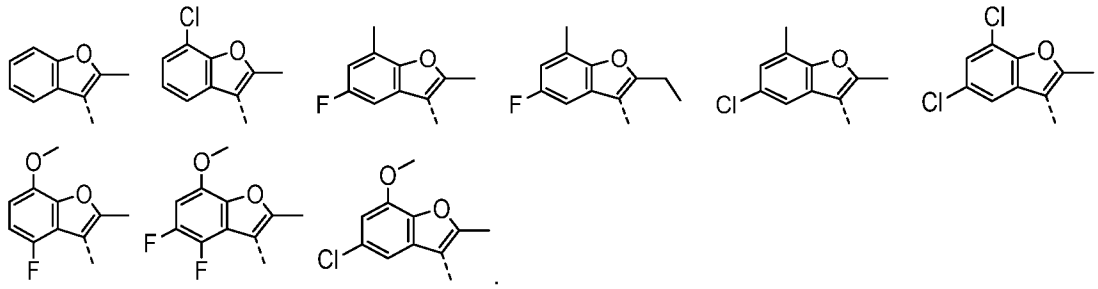


- or, in addition, said fragment may represent the benzothiophene:



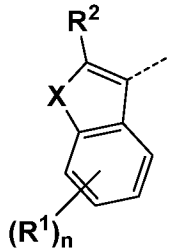
;

- or a benzofurane selected from:

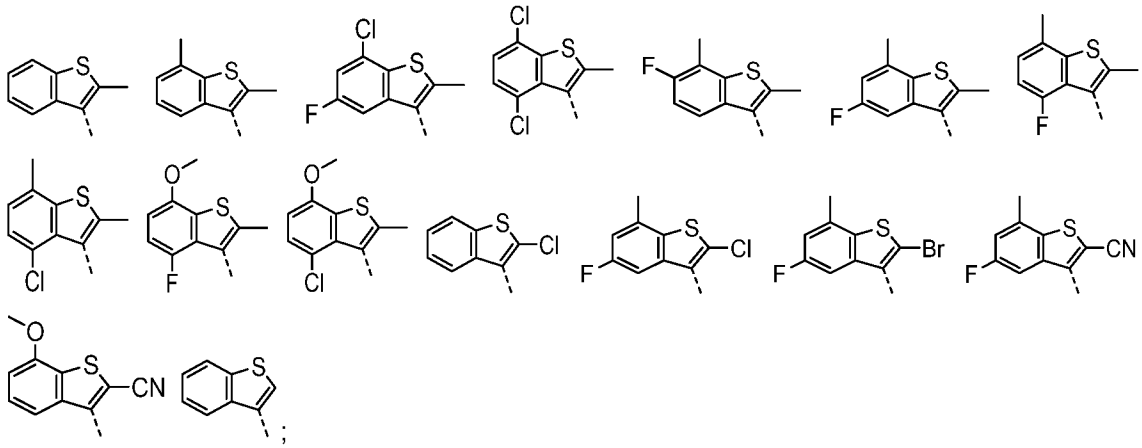


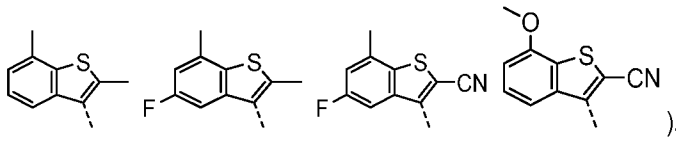
.

25) Another embodiment relates to compounds according to any one of embodiments 8) to 16), wherein the fragment



represents a benzothiophene selected from :



(especially ).

26) 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 25), 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, 9+1, 13+1, 14+1, 15+1, 15+9+1, 15+13+1, 15+14+1, 20+15+1, 20+15+9+1, 20+15+13+1, 20+15+14+1, 24+1, 24+9+1, 24+13+1, 24+15+1, 24+15+9+1, 24+15+13+1, 24+15+14+1, 24+20+15+1, 24+20+15+9+1, 24+20+15+13+1, 24+20+15+14+1, 25+1, 25+9+1, 25+14+1, 25+15+1, 25+15+9+1, 25+15+13+1, 25+15+14+1, 25+20+15+1, 25+20+15+9+1, 25+20+15+13+1, 25+20+15+14+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, "25+15+14+1" for example refers to embodiment 25) depending on embodiment 15), depending on embodiment 14), depending on embodiment 1), i.e. embodiment "25+15+14+8" 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 14), 15), and 25).

27) The invention, thus, further relates to compounds of the formula (II) as defined in embodiment 8), or to such compounds further limited by the characteristics of any one of embodiments 9) to 25), 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 (II) are thus possible and intended and herewith specifically disclosed in individualized form:

8, 9+8, 10+8, 12+8, 13+8, 14+8, 15+8, 15+9+8, 15+10+8, 15+12+8, 15+13+8, 15+14+8, 18+15+8, 18+15+9+8, 18+15+10+8, 18+15+12+8, 18+15+13+8, 18+15+14+8, 20+15+8, 20+15+9+8, 20+15+10+8, 20+15+12+8, 20+15+13+8, 20+15+14+8, 22+8, 22+10+8, 22+15+8, 22+15+9+8, 22+15+10+8, 22+15+12+8, 22+15+13+8, 22+15+14+8, 22+18+15+8, 22+18+15+9+8, 22+18+15+10+8, 22+18+15+12+8, 22+18+15+13+8, 22+18+15+14+8, 24+8, 24+13+8, 24+15+8, 24+15+9+8, 24+15+10+8, 24+15+12+8, 24+15+13+8, 24+15+14+8, 24+20+15+8, 24+20+15+9+8, 24+20+15+10+8, 24+20+15+12+8, 24+20+15+13+8, 24+20+15+14+8, 25+8, 25+14+8, 25+15+8, 25+15+9+8, 25+15+10+8, 25+15+12+8, 25+15+13+8, 25+15+14+8, 25+20+15+8, 25+20+15+9+8, 25+20+15+10+8, 25+20+15+12+8, 25+20+15+13+8, 25+20+15+14+8.

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, "25+15+14+8" for example refers to embodiment 25) depending on embodiment 15), depending on embodiment 14), depending on embodiment 8), i.e. embodiment "25+15+14+8" corresponds to the compounds of formula (II) according to embodiment 8) further limited by all the features of the embodiments 14), 15), and 25).

28) Another embodiment relates to compounds of formula (II) according to embodiment 8), which are selected from the following compounds:

5-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid;

4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

4-{6-[2-(2-Cyano-7-methoxy-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

3-Ethoxy-5-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

5-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

5-{6-[2-(2-Cyano-7-methoxy-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

3-Ethoxy-5-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

5-{6-[2-(4-Chloro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

5-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

5-{6-[2-(4,5-Difluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

5-[6-(2-Benzo[b]thiophen-3-yl-ethylamino)-pyrimidin-4-yl]-3-ethoxy-thiophene-2-carboxylic acid;

3-Ethoxy-5-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

5-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

5-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

5-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

5-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-(2-hydroxy-ethoxy)-thiophene-2-carboxylic acid;

5-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophene-2-carboxylic acid;

4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

4-{6-[2-(2-Cyano-7-methoxy-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

6-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzofuran-2-carboxylic acid;

5-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzofuran-2-carboxylic acid;

5-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-3(2H)-one [tautomeric form: 5-(4-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)phenyl)-[1,2,4]oxadiazol-3-ol];

2-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-indole-4-carboxylic acid;

(E)-3-(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acrylic acid;

(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid;

2-Difluoromethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
(2-Ethoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-acetic acid;
(2-Ethoxy-4-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-acetic acid;
(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenylamino)-acetic acid;
N-(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carbonyl)-methanesulfonamide;
{6-[4-Ethoxy-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-pyrimidin-4-yl}-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethyl]-amine;
3-(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol];
4-Ethoxy-2-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiazole-5-carboxylic acid; and
3-(4-Ethoxy-2-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiazol-5-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-ethoxy-2-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol].

29) In addition to the compounds listed in embodiment 28), further compounds of formula (II) according to embodiment 8), are selected from the following compounds:
5-{6-[2-(5-Fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid;
5-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid;
5-{6-[2-(5-Chloro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid;
3-Methyl-5-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;
4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-hydroxy-benzoic acid;
4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-hydroxy-benzoic acid;
4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
4-{6-[2-(5-Fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
4-{6-[2-(2-Methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
4-{6-[2-(4-Chloro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
4-{6-[2-(4,7-Dichloro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
4-{6-[2-(6-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

4-{6-[2-(7-Chloro-5-fluoro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
4-{6-[2-(2-Methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;
3-Ethoxy-5-{6-[2-(2-ethyl-5-fluoro-7-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;
4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-benzoic acid;
4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethylsulfanyl-benzoic acid;
2-Ethylsulfanyl-4-{6-[2-(2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
2-Ethylsulfanyl-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid;
4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-fluoro-6-methylsulfanyl-benzoic acid;
2-Chloro-4-{6-[2-(2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methylsulfanyl-benzoic acid;
(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acetic acid;
2-Ethoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
4-{6-[2-(2-Bromo-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
4-{6-[2-(2-Chloro-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
2-Ethoxy-4-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
2-Ethoxy-4-{6-[2-(6-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
4-{6-[2-(4,7-Dichloro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
4-{6-[2-(5-Chloro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
4-{6-[2-(7-Chloro-5-fluoro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
4-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
4-{6-[2-(5,7-Dichloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
2-Ethoxy-4-{6-[2-(2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
2-Ethoxy-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;
4-{6-[2-(2-chloro-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;
2-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-indole-6-carboxylic acid;
4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclopropoxy-benzoic acid;
2-Cyclopropoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Cyclopropoxy-4-{6-[2-(4,5-difluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-(2-hydroxy-ethoxy)-benzoic acid;

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propylsulfanyl-benzoic acid;

4-{6-[2-(2-Methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propylsulfanyl-benzoic acid;

4-{6-[2-(2-Methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propylsulfanyl-benzoic acid;

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropylsulfanyl-benzoic acid;

2-Isopropylsulfanyl-4-{6-[2-(2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Isopropylsulfanyl-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Fluoro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-propyl-benzoic acid;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isobutyl-benzoic acid;

4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-benzoic acid;

4-{6-[2-(6-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid;

4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid;

4-{6-[2-(4,7-Dichloro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid;

(4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid;

4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-difluoromethoxy-benzoic acid;

(4-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-acetic acid;

(4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-acetic acid;

2-Cyclobutylsulfanyl-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Cyclobutylsulfanyl-4-{6-[2-(2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-(oxetan-3-ylsulfanyl)-benzoic acid;

4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-benzoic acid;

2-Cyclobutoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-benzoic acid;

2-Cyclobutoxy-4-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-benzoic acid;

2-Cyclobutoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Cyclobutoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

{6-[3-Ethoxy-4-(1H-tetrazol-5-yl)-phenyl]-pyrimidin-4-yl}-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethyl]-amine;

3-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-propionic acid;

2-Butoxy-6-fluoro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

N-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-oxalamic acid;

2-Cyclobutoxy-3-fluoro-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Cyclobutoxy-4-{6-[2-(4,5-difluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-6-fluoro-benzoic acid;

4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-6-fluoro-benzoic acid;

2-Cyclopentyloxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Cyclopentyloxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

3-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(2-ethoxy-4-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)phenyl)-[1,2,4]oxadiazol-5-ol];

3-Ethoxy-5-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)-N-sulfamoylthiophene-2-carboxamide;

4-Ethyl-2-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiazole-5-carboxylic acid; and

3-(4-Ethyl-2-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiazol-5-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-ethyl-2-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol].

30) Another embodiment relates to compounds of formula (I) as defined in embodiment 1) for use according to embodiment 1) which are selected from the compounds according to embodiments 28) and/or 29).

31) In addition to the compounds listed in embodiments 28) and 29), further compounds of formula (II) according to embodiment 8), are selected from the following compounds:

(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-6-fluoro-phenyl)-acetic acid;

4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid;

(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-acetic acid;

(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-phenyl)-acetic acid;

(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-phenyl)-acetic acid;

(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-phenyl)-acetic acid;

4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-benzoic acid;

3-(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-propionic acid;

2-Ethylsulfanyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-4-hydroxy-cyclobut-3-ene-1,2-dione;

(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isobutyl-phenyl)-acetic acid;

(2-Ethyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid;

(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-oxo-acetic acid;

(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-phenyl)-acetic acid;

N-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-formamide;

(2-Ethyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methyl-phenyl)-acetic acid;

2-Cyclopropoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

(2-Cyclopropoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid;

(3-Ethyl-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acetic acid;

(2-Chloro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methyl-phenyl)-acetic acid;

5-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-isoxazol-3-ol [tautomeric form: 5-(2-ethoxy-4-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)phenyl)isoxazol-3(2H)-one];

1-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-cyclopropanecarboxylic acid; and

1-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-phenyl)-cyclopropanecarboxylic acid.

32) In addition to the compounds listed in embodiments 28), 29), and 31), further compounds of formula (II) according to embodiment 8), are selected from the following compounds:

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isobutylsulfanyl-benzoic acid;

4-{6-[2-(2-Cyano-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

(4-{6-[2-(2-Cyano-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid;

3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5-ol];

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzamide;

[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethyl]-[6-(1H-indol-5-yl)-pyrimidin-4-yl]-amine;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isobutoxy-benzoic acid;

(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-phenyl)-acetic acid;

(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-trifluoromethoxy-phenyl)-acetic acid;

N-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-formamide;

(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-phenyl)-acetic acid;

2-Ethyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

5-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-isoxazol-3-ol [tautomeric form: 5-(4-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)-2-methoxyphenyl)isoxazol-3(2H)-one];

5-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methyl-1H-pyrrole-3-carboxylic acid;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzamide;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-2-methyl-propyl)-2-propyl-benzamide;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-(2-methoxy-ethyl)-2-propyl-benzamide;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-ethyl)-2-propyl-benzamide;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-methyl-2-propyl-benzamide;

2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-ethyl)-benzamide;

2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-methyl-benzamide;

2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzamide;

(2-Ethoxy-3-fluoro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid;

(5-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-propyl-thiophen-2-yl)-acetic acid;

(3-Difluoromethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acetic acid;

2-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-indole-7-carboxylic acid;

2-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzo[b]thiophene-7-carboxylic acid; and

3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-propionic acid.

33) In addition to the compounds listed in embodiments 28), 29), 31) and 32), a further compound of formula (II) according to embodiment 8) is:

(4-{6-[2-(2-Cyano-7-methoxy-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid.

34) Another embodiment relates to compounds of formula (I) as defined in embodiment 1) for use according to embodiment 1) which are selected from the compounds according to embodiments 31 to 33); as well as the following compounds:

3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid;

1-Ethyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid; and

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1-propyl-1H-pyrrole-2-carboxylic acid.

The compounds of formula (I) / formula (II) according to embodiments 1) to 34) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral (such especially oral e.g. in form of a tablet or a capsule) or parenteral administration (including topical application or inhalation).

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

The present invention also relates to a method for the prevention / prophylaxis or treatment of a disease or disorder mentioned herein comprising administering to a subject a pharmaceutically active amount of a compound of formula (I) / formula (II) according to embodiments 1) to 34).

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.

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

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

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

The compounds of formula (I) / formula (II) according to embodiments 1) to 34) are useful for the prevention / prophylaxis or treatment of disorders relating to the EP2 and/or EP4 receptors.

Certain compounds of formula (I) / formula (II) according to embodiments 1) to 34) 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.

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.

Further diseases or disorders relating to the EP2 and/or EP4 receptors are autoimmune disorders such as especially multiple sclerosis, rheumatoid arthritis and osteoarthritis; and osteoporosis.

The compounds of formula (I) / formula (II) according to any one of embodiments 1) to 34) 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 formula (I) / formula (II) according to any one of embodiments 1) to 34);
- 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 formula (I) / formula (II) according to any one of embodiments 1) to 34);
- 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 progammed 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 formula (I) / formula (II), 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, tremilmumab; 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 (GMCSF) 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) Indoleamin-2,3-Dioxgenase (IDO) and/or Tryptophane-2,3-Dioxygenase (TDO) inhibitors (for example RG6078 / NLG919 / GDC-0919; Indoximod / 1MT (1-methyltryptophan), INCB024360 / Epacadostat, 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 formula (I) / formula (II), immune checkpoint inhibitors such as those listed under d), and especially those targeting the progammed 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 drug at a time (single-agent chemotherapy) or several drugs at once (combination chemotherapy or polychemotherapy). Chemotherapy using drugs that convert to cytotoxic activity only upon light exposure is called photochemotherapy or photodynamic therapy.

The term “cytotoxic chemotherapy agent” or “chemotherapy agent” as used herein refers to an active anti-neoplastic agent inducing apoptosis or necrotic cell death. When used in combination with the compounds of formula (I) / formula (II), 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);
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);
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 formula (I) / formula (II), preferred cytotoxic chemotherapy agents 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.

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 formula (I) / formula (II) 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 formula (I) / formula (II) as defined in embodiments 1) to 34) 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 formula (I) / formula (II) [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-γ and/or TNF-α 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 immunsuppression).

The compounds of formula (I) / formula (II) as defined in embodiments 1) to 34) 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 formula (I) / formula (II) [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 formula (I) / formula (II) as defined in embodiments 1) to 34) are also useful in a method of modulating an immmune response in a subject having a tumor, comprising the administration of an effective amount of the compound of formula (I) / formula (II) [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 formula (II) (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).

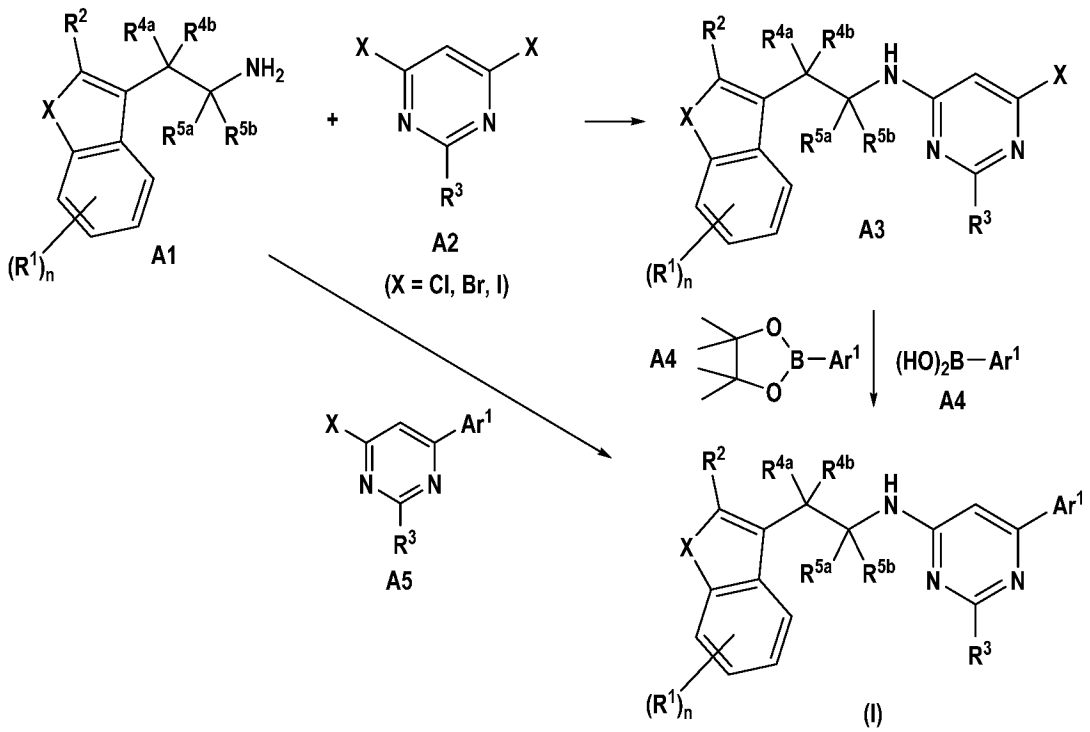
Preparation of compounds of formula (I):

The compounds of formula (I) / formula (II) 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 $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^{4a}}$, $\mathbf{R^{4b}}$, $\mathbf{R^{5a}}$, $\mathbf{R^{5b}}$ and $\mathbf{Ar^1}$ are as defined for formula (I). Other abbreviations used herein are explicitly defined, or are as defined in the experimental section. In some instances the generic groups $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^{4a}}$, $\mathbf{R^{4b}}$, $\mathbf{R^{5a}}$, $\mathbf{R^{5b}}$ and $\mathbf{Ar^1}$ 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 formula (I) / formula (II) of the present invention can be prepared according to the general sequence of reactions outlined below.

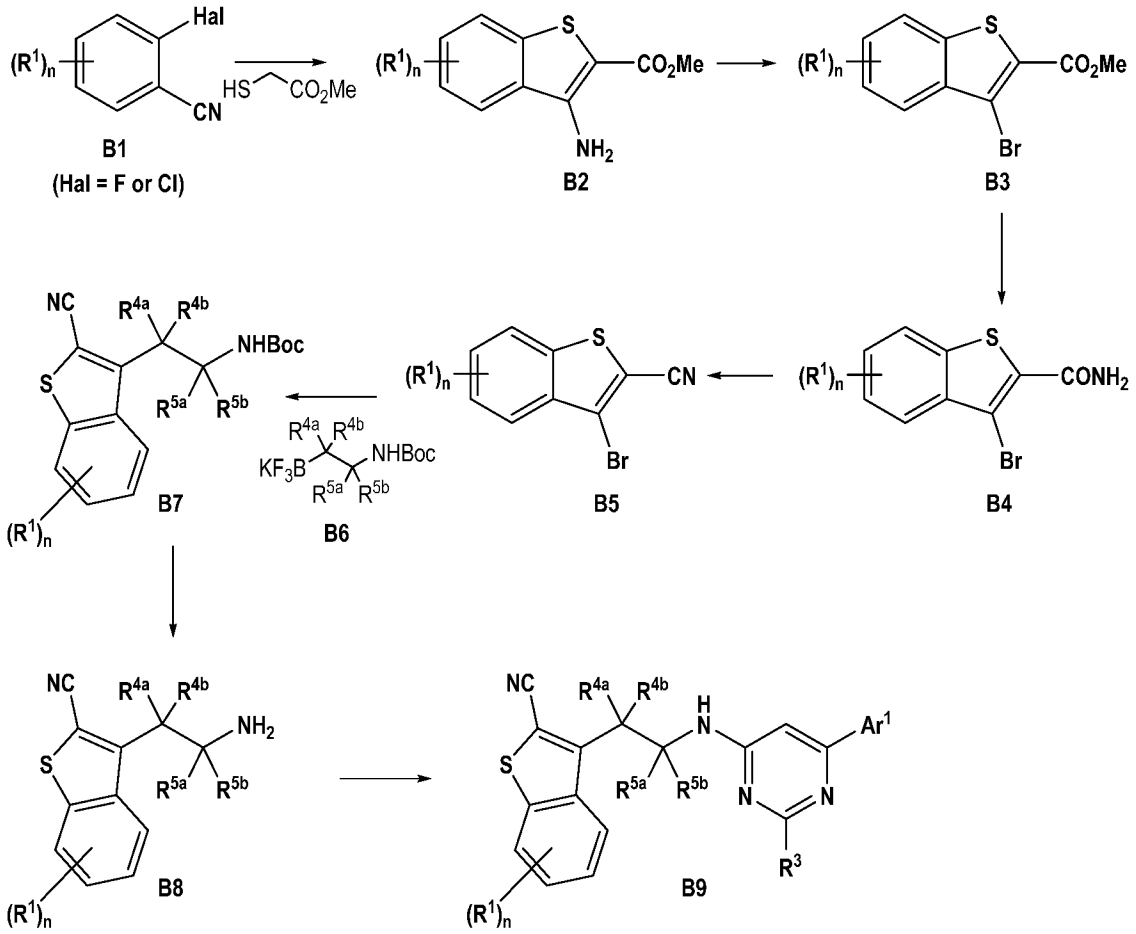
A general synthetic route allowing the preparation of compounds of formula (I) is presented in *scheme 1*. Thus, precursors **A3** can be obtained by nucleophilic aromatic substitutions between primary amines **A1** and pyrimidine halides **A2** (wherein X is a chlorine, a bromine or an iodine), in the presence of a base such as TEA, DIPEA or K_2CO_3, in a solvent such as isopropanol, butanol, DMF or THF, at RT or at elevated temperatures. Compounds of formula (I) can be produced via Suzuki cross-coupling reactions of the pyrimidine halides **A3** with boronic acids or boronate esters **A4**. Typical Suzuki cross-coupling reactions may be carried out in the presence of a base such as K_2CO_3, Cs_2CO_3, Na_2CO_3, K_3PO_4, or CsF and a catalyst such as $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$ or $Pd(OAc)_2$, in a solvent like ethanol, THF, water, or mixtures thereof, typically at elevated temperatures. Boronic acids or boronate esters **A4** 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 $Pd(dppf)Cl_2$. 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 tri-isopropylborate or isopropoxyboronic acid pinacol ester, in a solvent such as diethyl ether or THF. In a variant, compounds of formula (I) can be prepared via nucleophilic aromatic substitutions between primary amines **A1** and substituted pyrimidine halides **A5**, wherein X is a chlorine, a bromine or an iodine (*scheme 1*).



Scheme 1. General preparations of compounds of formula (I); in *scheme 1*, X represents Cl, Br or I.

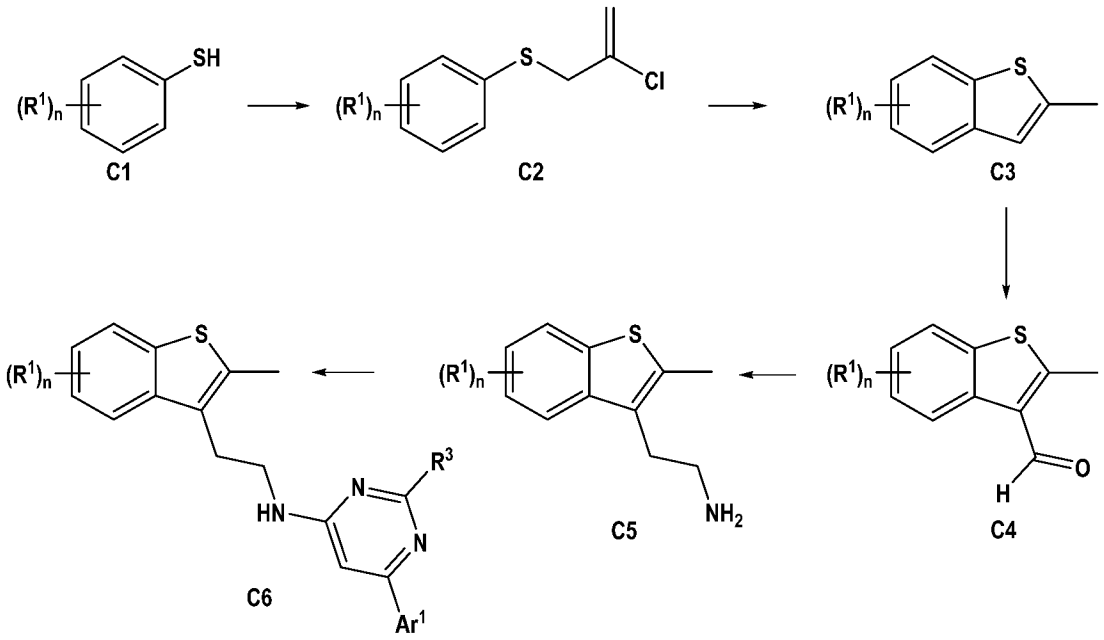
Alternatively, compounds of formula (I) can be synthesized by reacting a compound of formula **A1** with a compound of formula **A5** wherein X represents OH, in presence of a coupling agent such as (benzotriazol-1-yloxy)-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), (benzotriazol-1-yl-oxy)-tripyrrolidino-phosphonium 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.

Substituted benzothiophenes corresponding to compounds of formula (I) (with R^2 representing CN) can be prepared according to the synthetic route described in *scheme 2*. Ortho-fluorobenzonitriles or ortho-chlorobenzonitriles **B1** can undergo aromatic nucleophilic substitutions by treatment with methyl 2-mercaptoacetate in the presence of a base (K_2CO_3/DMF), and benzothiophenes **B2** can be obtained after a subsequent ring closure. The related 3-bromobenzothiophenes **B3** can be obtained via deaminative bromination (tert-butyl nitrite/copper(II) bromide/MeCN), and alkaline hydrolysis of the ester functionality in **B3** followed by coupling of the corresponding acid chlorides with ammonium hydroxide can provide primary amides **B4**. A dehydration of the primary amide moiety in **B4** (cyanuric chloride//DMF) can furnish the benzo[b]thiophene-2-carbonitrile derivatives **B5**. A subsequent Suzuki-Miyaura aminoethylation [$Pd(OAc)_2$/RuPhos/Cs_2CO_3/toluene/H_2O] of bromobenzothiophenes **B5** using Boc-protected potassium β-aminoethyltrifluoroborates **B6** can furnish derivatives **B7** that can be converted to primary amines **B8** after Boc-deprotection under acidic conditions. Finally, target products **B9** corresponding to compounds of formula (I) can be obtained from **B8** with the preparations described in *scheme 1*.



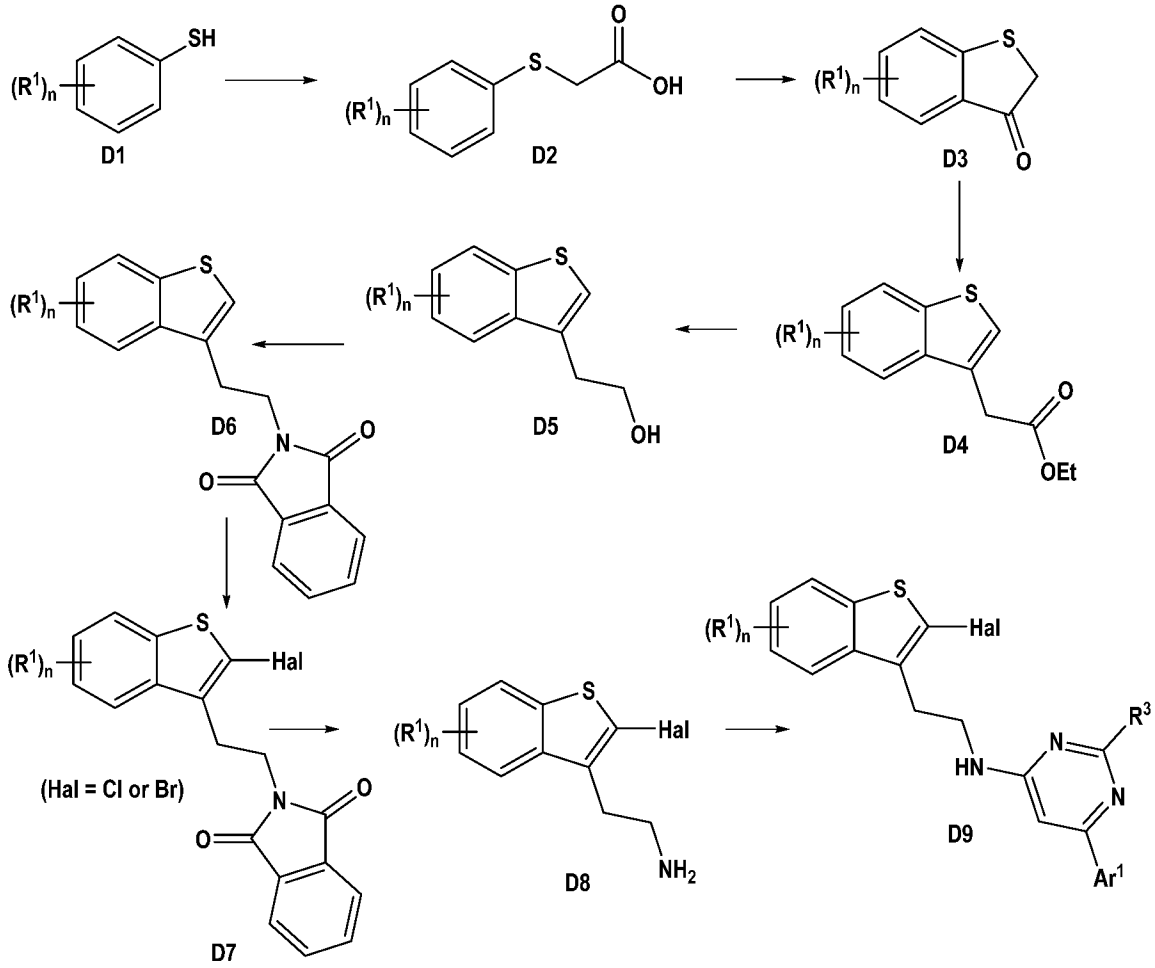
Scheme 2. Preparation of substituted benzothiophenes **B9** corresponding to compounds of formula (I) with X representing S and R^2 representing CN; in *scheme 2*, Hal represents F or Cl.

Substituted benzothiophenes corresponding to compounds of formula (I) (with R^2 representing Me) can be prepared according to the synthetic route described in *scheme 3*. This multi-step synthesis started with the preparation of 2-methylbenzothiophenes **C3** via a thio-Claisen rearrangement. Thus, S-alkylation of thiophenols **C1** by treatment with 2,3-dichloropropene in the presence of potassium carbonate can introduce the required 2-chloropropene moiety in derivatives **C2**. A subsequent thio-Claisen rearrangement in refluxing N,N-diethylaniline can convert the S-alkylated derivatives **C2** into the target 2-methylbenzothiophenes **C3**. The aldehyde functionality can be introduced at the unsubstituted 3-position via selective formylation of the thiophene ring under mild conditions (dichloromethyl methyl ether/tin(IV) chloride) affording compounds **C4**. The β-aminoethyl side-chain in **C5** can result from the reduction (lithium aluminum hydride/THF/heating) of the corresponding nitroalkenes that can be prepared from aldehydes **C4** via Henry reaction (nitromethane/butylamine/acetic acid/heating). Finally, target products **C6** corresponding to compounds of formula (I) can be obtained according to the sequences described in *scheme 1*.



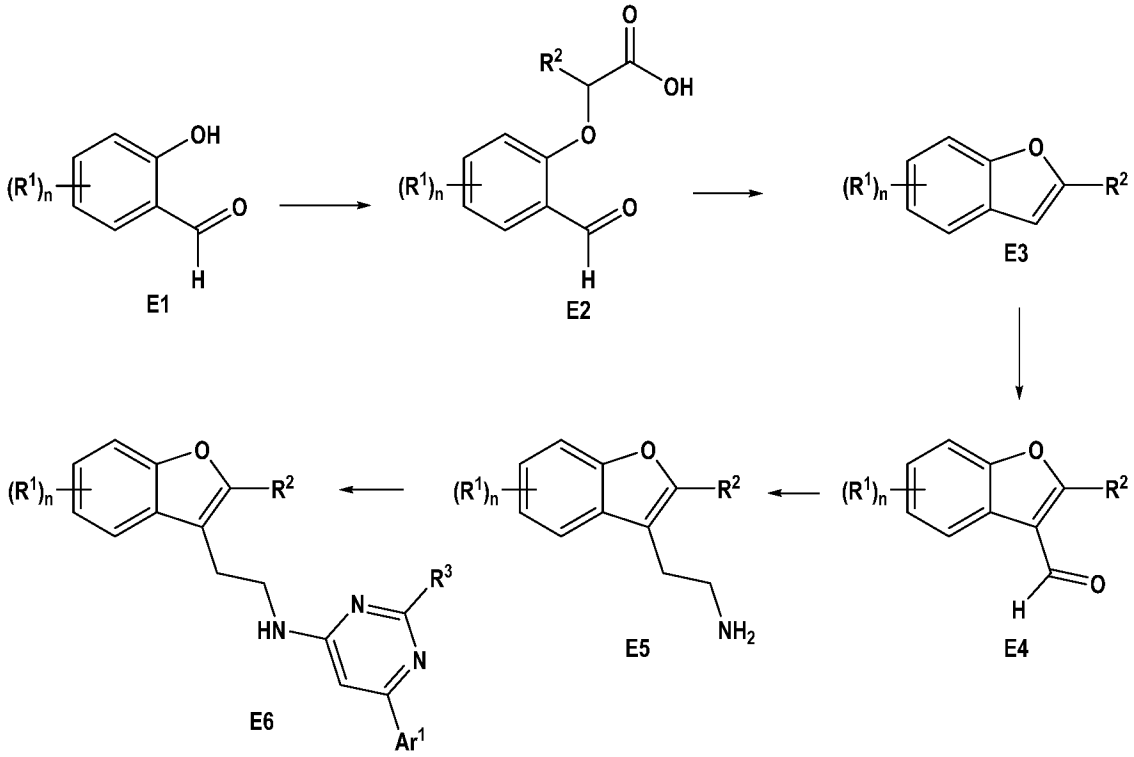
Scheme 3. Preparation of substituted benzothiophenes **C6** corresponding to compounds of formula (I) with X representing S and R^2 representing Me.

Substituted benzothiophenes corresponding to compounds of formula (I) (with R^2 representing Cl or Br) can be prepared according to the sequence of reactions described in *scheme 2*. This multi-step synthesis started with the preparation of 2-unsubstituted benzothiophenes **D6** as precursors for the planned halogenation at position-2. Thus, S-alkylation of thiophenols **D1** (methyl bromoacetate/potassium carbonate) followed by alkaline hydrolysis of the ester functionality can provide the 2-(phenylthio)acetic acid derivatives **D2**. Conversion of the carboxylic acids **D2** into the corresponding acid chlorides, and subsequent Friedel-Crafts acylation (aluminum chloride/DCM) can deliver benzo[b]thiophen-3(2H)-ones **D3**. The substituted benzothiophenes **D4** can be obtained via Wittig olefination of **D3** [(carbethoxymethylene)triphenylphosphorane/toluene/reflux], and the protected β-aminoethyl side-chain in **D6** can result from the reduction of the ester functionality in **D4** followed by reaction of the resulting primary alcohols **D5** with phthalimide under Mitsunobu conditions (diethyl azodicarboxylate/triphenylphosphine/THF). A subsequent regioselective chlorination (N-chlorosuccinimide/DMF/heating) or bromination (N-bromosuccinimide/DMF/heating) of the unsubstituted 2-position of the thiophene ring in **D6** can deliver the corresponding derivatives **D7**, and primary amines **D8** can be obtained after cleavage of the phthalimide moiety (hydrazine hydrate/MeOH/heating). Finally, target products **D9** corresponding to compounds of formula (I) can be obtained from **D8** with the sequence of reactions described in *scheme 1*.



Scheme 4. Preparation of substituted benzothiophenes **D9** corresponding to compounds of formula (I) with X representing S and R^2 representing Cl or Br.

Substituted benzofurans corresponding to compounds of formula (I) [with R^2 representing (C_{1-4})alkyl] can be prepared according to the synthetic route shown in *scheme 5*. Ortho-hydroxybenzaldehydes **E1** can be converted to the corresponding carboxylic acids **E2** via *O*-alkylation with the appropriate electrophile followed by saponification of the ester functionality. Subsequent heating of the produced carboxylic acids **E2** with sodium acetate in acetic anhydride can deliver the substituted benzofurans **E3**. The aldehyde functionality in **E4** can be introduced at the unsubstituted 3-position of benzofurans **E3** via regioselective formylation of the furan ring under mild conditions (dichloromethyl methyl ether/tin(IV) chloride). The β-aminoethyl side-chain in **E5** can result from the reduction of the corresponding nitroalkenes that can be prepared from aldehydes **E4** via Henry reaction (nitromethane/butylamine/acetic acid). Finally, target products **E6** corresponding to compounds of formula (I) can be obtained with the sequence of reactions described in *scheme 1*.



Scheme 5. Preparation of substituted benzofurans **E6** corresponding to compounds of formula (I) with X representing O and R^2 representing (C_{1-4})alkyl.

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

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 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), such compounds are marked accordingly.

Analytical LC-MS equipment:

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

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 μm, 4.6 x 50 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B → 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

Method B: Column: Zorbax RRHD SB-aq (1.8 μm, 2.1 x 50 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B → 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 1.7um 2.1x50 mm from Waters, thermostated in the Acquity UPLC Column Manager at 60°C. Eluents: A: H2O + 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, tR is given in min.

LC-MS with basic conditions

Method D: Column: Waters BEH C_{18} (3.0 x 50mm, 2.5μm). Eluents: A: Water/NH3 [c(NH_3) = 13 mmol/l], B: MeCN, Method: 5%B to 95%B in 2min, Flow 1.6ml/min, Detection UV: 214nm.

Preparative HPLC equipment:

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_4OH (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

Column: Waters Atlantis T3 (10 µm, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% HCO_2H [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

Abbreviations (as used hereinbefore or hereinafter):

AcOH	acetic acid
anh.	anhydrous
aq.	aqueous
atm	atmosphere
Boc	tert-butyloxycarbonyl
BOP	(benzotriazol-1-yloxy)-tris(dimethylamino)-phosphonium hexafluorophosphate
d	days
DCM	dichloromethane
DIPEA	diisopropyl-ethylamine, Hünig's base
DMAP	4-Dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
Et	ethyl
Et_2O	diethylether
EtOAc	ethyl acetate
EtOH	ethanol
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
hept	heptane(s)
HCl	hydrochloric acid or hydrogen chloride
HPLC	high performance liquid chromatography

HV	high vacuum conditions
^{i}Bu	isobutyl
^{i}Pr	isopropyl
LC-MS	liquid chromatography – mass spectrometry
Lit.	Literature
M	mol/l
Me	methyl
MeCN	acetonitrile
MeOH	methanol
$MgSO_4$	magnesium sulfate
mL	milliliter
min	minute(s)
MW	microwave
$NaHCO_3$	sodium hydrogencarbonate
NaOH	sodium hydroxide
NMP	N-methyl-2-pyrrolidone
^{n}Pr	n-propyl
OAc	acetate
Pd_2dba_3	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	[1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (II)
$Pd(dppf)Cl_2$·DCM	[1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (II) complex with dichloromethane
$Pd(OAc)_2$	palladium(II) acetate
Ph	phenyl
PPh_3	triphenyl phosphine
prep.	Preparative
PyBOP	(benzotriazol-1-yl-oxy)-tripyrrolidino-phosphonium hexafluorophosphate
rac	racemic
RM	reaction mixture
RT	room temperature
RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
s	second(s)
sat.	saturated (if not indicated otherwise: sat. aq.)
tBu	tert-butyl = tertiary butyl
TEA	triethylamine
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin layer chromatography
tosyl	p-toluene-sulfonyl
t_R	retention time
triflate	trifluoromethanesulfonate

A- Preparation of precursors and intermediates for benzothiophene derivatives

A.1. Synthesis of pyrimidine halide derivatives of formula (A3) [X = S]

A.1.1. 6-Chloro-N-(2-(2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)pyrimidin-4-amine

To a solution of 2-(2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine (4.32 g, 21.03 mmol) in 2-propanol (100 mL) at RT are added TEA (10.3 mL, 73.89 mmol) and 4,6-dichloropyrimidine (3.84 g, 25.26 mmol). The RM is refluxed (90°C), under nitrogen, for 1.5h and is then allowed to cool to RT. DCM (150 mL) and water (75 mL) are added and the layers are separated. The aq. layer is extracted twice with DCM and the combined organic layers are then washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (DCM) affords 6-chloro-N-(2-(2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)pyrimidin-4-amine as a beige solid (4.30 g, 64%). LC-MS A: t_R = 0.96 min; $[M+H]^+$ = 318.03 .

A.1.1.1. 2-(2,7-Ddimethylbenzo[b]thiophen-3-yl)ethan-1-amine

To a solution of 2,7-dimethylbenzo[b]thiophene-3-carbaldehyde (5.84 g, 30.69 mmol) in nitromethane (85 mL) are added successively molecular sieves (4 angstrom, 0.90 g), butylamine (0.362 mL, 3.62 mmol) and acetic acid (0.359 mL, 6.26 mmol). The RM is heated to 95°C, under nitrogen, for 2h. The RM is then filtered and the filtrate is concentrated to dryness under reduced pressure. Purification by FC (heptane/DCM = 4/1) affords 2,7-dimethyl-3-(2-nitrovinyl)benzo[b]thiophene as a yellow solid (5.09 g, 71%). LC-MS A: t_R = 0.97 min; no ionisation.

To a cooled (0°C) solution of lithium aluminum hydride (2 M in THF, 37 mL, 74 mmol) in anh. THF (80 mL) is added dropwise a solution of 2,7-dimethyl-3-(2-nitro-vinyl)benzo[b]thiophene (4.94 g, 21.17 mmol) in anh. THF (60 mL). The mixture is then heated at reflux (80°C), under nitrogen, for 2.5h. The cooled (0°C) RM is treated successively with water (2.8 mL), 15% aq. NaOH (2.8 mL), and water (8.5 mL). The resulting heterogeneous mixture is then filtered and the separated solid is washed with Et_2O. The layers of the filtrate are separated and the aqueous layer is extracted with Et_2O. The combined organic layers are then dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure affording 2-(2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine as an orange oil (4.32 g, 99%). LC-MS A: t_R = 0.62 min; $[M+H]^+$ = 206.11 .

A.1.1.2. 2,7-Dimethylbenzo[b]thiophene-3-carbaldehyde

To a cooled (0°C) solution of 2,7-dimethylbenzo[b]thiophene (2.65 g, 16.33 mmol) in anh. DCM (40 mL) is added dropwise tin(IV) chloride (3.83 mL, 32.72 mmol) and the mixture is further stirred at 0°C, under

nitrogen, for 15 min. Dichloromethyl methyl ether (1.81 mL, 19.61 mmol) is then added and the mixture is allowed to stir at RT, under nitrogen, for 1h. The resulting RM is then poured onto ice-water (100 mL) and 1 M aq. HCl (75 mL) is added. The layers are separated and the aq. layer is extracted twice with DCM. The combined organic layers are dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (heptane/DCM = 7/3) affords 2,7-dimethylbenzo[b]thiophene-3-carbaldehyde as a yellow solid (2.96 g, 95%). LC-MS A: t_R = 0.89 min; no ionization.

A.1.1.3. 2,7-Dimethylbenzo[b]thiophene

To a solution of 2-methylbenzenethiol (8.00 mL, 66.52 mmol) in anh. acetone (70 mL) are added successively potassium carbonate (11.95 g, 86.46 mmol) and 2,3-dichloroprop-1-ene (6.13 mL, 66.50 mmol). The RM is heated at reflux (60°C), under nitrogen, for 1h. The RM is then allowed to cool to RT and is concentrated to dryness under reduced pressure. EtOAc (100 mL) and water (100 mL) are added and the layers are separated. The aq. layer is extracted twice with EtOAc and the combined organic layers are dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure giving (2-chloroallyl)(o-tolyl)sulfane as a dark yellow oil (13.22 g, 100%). LC-MS A: t_R = 0.95 min; no ionization.

A solution of (2-chloroallyl)(o-tolyl)sulfane (13.22 g, 66.52 mmol) in N,N-diethylaniline (150 mL) is heated to 185°C, under nitrogen, for 45h. The resulting RM is then allowed to cool to RT, diluted with EtOAc (300 mL) and washed with 1 M aq. HCl (4 x 200 mL). The organic layer is then dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (heptane/DCM = 19/1) affords 2,7-dimethylbenzo[b]thiophene as a yellow oil (7.97 g, 74%). LC-MS A: t_R = 0.93 min; no ionization.

A.1.2. N-(2-(Benzo[b]thiophen-3-yl)ethyl)-6-chloropyrimidin-4-amine

The title compound is prepared according to the procedure described above in A.1.1. using 2-(benzo[b]thiophen-3-yl)ethan-1-amine. LC-MS A: t_R = 0.90 min; $[M+H]^+$ = 289.94 .

A.1.2.1. 2-(Benzo[b]thiophen-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in A.1.1.1. using benzo[b]thiophene-3-carbaldehyde. LC-MS A: t_R = 0.54 min; $[M+H]^+$ = 178.30 .

A.1.3. 6-Chloro-N-(2-(2-methylbenzo[b]thiophen-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in A.1.1. using 2-(2-methylbenzo[b]thiophen-3-yl)ethan-1-amine. LC-MS A: t_R = 0.93 min; $[M+H]^+$ = 304.03 .

A.1.3.1. 2-(2-Methylbenzo[b]thiophen-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in A.1.1.1. using 2-methylbenzo[b]thiophene-3-carbaldehyde. LC-MS A: t_R = 0.57 min; $[M+H]^+$ = 192.29 .

A.1.4. 6-Chloro-N-(2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in A.1.1. using 2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine. LC-MS A: t_R = 0.98 min; $[M+H]^+$ = 336.23 .

A.1.4.1. 2-(5-Fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in A.1.1.1. using 5-fluoro-2,7-dimethylbenzo[b]thiophene-3-carbaldehyde. LC-MS A: t_R = 0.65 min; $[M+H]^+$ = 224.26 .

A.1.4.2. 5-Fluoro-2,7-dimethylbenzo[b]thiophene-3-carbaldehyde

The title compound is prepared according to the procedure described above in A.1.1.2. using 5-fluoro-2,7-dimethylbenzo[b]thiophene. LC-MS A: t_R = 0.92 min; $[M+H]^+$ = 209.24 .

A.1.4.3. 5-Fluoro-2,7-dimethylbenzo[b]thiophene

The title compound is prepared according to the procedure described above in A.1.1.3. using 4-fluoro-2-methylbenzenethiol. LC-MS A: t_R = 0.96 min; no ionization.

A.1.5. 6-Chloro-N-(2-(4-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in A.1.1. using 2-(4-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine. LC-MS A: t_R = 0.99 min; $[M+H]^+$ = 336.11 .

A.1.5.1. 2-(4-Fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in A.1.1.1. using 4-fluoro-2,7-dimethylbenzo[b]thiophene-3-carbaldehyde. LC-MS A: t_R = 0.64 min; $[M+H]^+$ = 224.09 .

A.1.5.2. 4-Fluoro-2,7-dimethylbenzo[b]thiophene-3-carbaldehyde

The title compound is prepared according to the procedure described above in A.1.1.2. using 4-fluoro-2,7-dimethylbenzo[b]thiophene. LC-MS A: t_R = 0.92 min; $[M+H]^+$ = 209.05 .

A.1.5.3. 4-Fluoro-2,7-dimethylbenzo[b]thiophene

The title compound is prepared according to the procedure described above in A.1.1.3. using 5-fluoro-2-methylbenzenethiol. LC-MS D: t_R = 1.28 min; no ionization.

A.1.6. 6-Chloro-N-(2-(4-chloro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in A.1.1. using 2-(4-chloro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine. LC-MS A: t_R = 1.02 min; $[M+H]^+$ = 352.04 .

A.1.6.1. 2-(4-Chloro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in A.1.1.1. using 4-chloro-2,7-dimethylbenzo[b]thiophene-3-carbaldehyde. LC-MS A: t_R = 0.65 min; $[M+H]^+$ = 240.16 .

A.1.6.2. 4-Chloro-2,7-dimethylbenzo[b]thiophene-3-carbaldehyde

The title compound is prepared according to the procedure described above in A.1.1.2. using 4-chloro-2,7-dimethylbenzo[b]thiophene. LC-MS A: t_R = 0.97 min; $[M+H]^+$ = 224.48 .

A.1.6.3. 4-Chloro-2,7-dimethylbenzo[b]thiophene

The title compound is prepared according to the procedure described above in A.1.1.3. using 5-chloro-2-methylbenzenethiol. LC-MS D: t_R = 1.36 min; no ionization.

A.1.7. 6-Chloro-N-(2-(6-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in A.1.1. using 2-(6-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine. LC-MS A: t_R = 0.98 min; $[M+H]^+$ = 336.55 .

A.1.7.1. 2-(6-Fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in A.1.1.1. using 6-fluoro-2,7-dimethylbenzo[b]thiophene-3-carbaldehyde. LC-MS A: t_R = 0.64 min; $[M+H]^+$ = 224.48 .

A.1.7.2. 6-Fluoro-2,7-dimethylbenzo[b]thiophene-3-carbaldehyde

The title compound is prepared according to the procedure described above in A.1.1.2. using 6-fluoro-2,7-dimethylbenzo[b]thiophene. LC-MS A: t_R = 0.92 min; no ionization.

A.1.7.3. 6-Fluoro-2,7-dimethylbenzo[b]thiophene

The title compound is prepared according to the procedure described above in A.1.1.3. using 3-fluoro-2-methylbenzenethiol. LC-MS A: t_R = 0.96 min; $[M+H]^+$ = 181.27 .

A.1.8. 6-Chloro-N-(2-(4-fluoro-7-methoxy-2-methylbenzo[b]thiophen-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in A.1.1. using 2-(4-fluoro-7-methoxy-2-methylbenzo[b]thiophen-3-yl)ethan-1-amine. LC-MS A: t_R = 0.96 min; $[M+H]^+$ = 352.06 .

A.1.8.1. 2-(4-Fluoro-7-methoxy-2-methylbenzo[b]thiophen-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in A.1.1.1. using 4-fluoro-7-methoxy-2-methylbenzo[b]thiophene-3-carbaldehyde. LC-MS A: t_R = 0.61 min; $[M+H]^+$ = 240.11 .

A.1.8.2. 4-Fluoro-7-methoxy-2-methylbenzo[b]thiophene-3-carbaldehyde

The title compound is prepared according to the procedure described above in A.1.1.2. using 4-fluoro-7-methoxy-2-methylbenzo[b]thiophene. LC-MS A: t_R = 0.91 min; $[M+H]^+$ = 225.11 .

A.1.8.3. 4-Fluoro-7-methoxy-2-methylbenzo[b]thiophene

The title compound is prepared according to the procedure described above in A.1.1.3. using 5-fluoro-2-methoxybenzenethiol. LC-MS A: t_R = 0.94 min; no ionization.

A.1.9. 6-Chloro-N-(2-(4-chloro-7-methoxy-2-methylbenzo[b]thiophen-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in A.1.1. using 2-(4-chloro-7-methoxy-2-methylbenzo[b]thiophen-3-yl)ethan-1-amine. LC-MS A: t_R = 0.99 min; $[M+H]^+$ = 368.07 .

A.1.9.1. 2-(4-Chloro-7-methoxy-2-methylbenzo[b]thiophen-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in A.1.1.1. using 4-chloro-7-methoxy-2-methylbenzo[b]thiophene-3-carbaldehyde. LC-MS A: t_R = 0.63 min; $[M+H]^+$ = 256.11 .

A.1.9.2. 4-Chloro-7-methoxy-2-methylbenzo[b]thiophene-3-carbaldehyde

The title compound is prepared according to the procedure described above in A.1.1.2. using 4-chloro-7-methoxy-2-methylbenzo[b]thiophene. LC-MS A: t_R = 0.94 min; $[M+H]^+$ = 241.09 .

A.1.9.3. 4-Chloro-7-methoxy-2-methylbenzo[b]thiophene

The title compound is prepared according to the procedure described above in A.1.1.3. using 5-chloro-2-methoxybenzenethiol. LC-MS A: t_R = 0.97 min; no ionization.

A.1.10. 6-Chloro-N-(2-(7-chloro-5-fluoro-2-methylbenzo[b]thiophen-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in A.1.1. using 2-(7-chloro-5-fluoro-2-methylbenzo[b]thiophen-3-yl)ethan-1-amine. LC-MS A: t_R = 1.00 min; $[M+H]^+$ = 356.05 .

A.1.10.1. 2-(7-Chloro-5-fluoro-2-methylbenzo[b]thiophen-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in A.1.1.1. using 7-chloro-5-fluoro-2-methylbenzo[b]thiophene-3-carbaldehyde. LC-MS A: t_R = 0.67 min; no ionization.

A.1.10.2. 7-Chloro-5-fluoro-2-methylbenzo[b]thiophene-3-carbaldehyde

The title compound is prepared according to the procedure described above in A.1.1.2. using 7-chloro-5-fluoro-2-methylbenzo[b]thiophene. LC-MS A: t_R = 0.94 min; no ionization.

A.1.10.3. 7-Chloro-5-fluoro-2-methylbenzo[b]thiophene

The title compound is prepared according to the procedure described above in A.1.1.3. using 2-chloro-4-fluorobenzenethiol. LC-MS A: t_R = 0.97 min; no ionization.

A.1.11. 6-Chloro-N-(2-(4,7-dichloro-2-methylbenzo[b]thiophen-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in A.1.1. using 2-(4,7-dichloro-2-methylbenzo[b]thiophen-3-yl)ethan-1-amine. LC-MS A: t_R = 1.03 min; $[M+H]^+$ = 372.00 .

A.1.11.1. 2-(4,7-Dichloro-2-methylbenzo[b]thiophen-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in A.1.1.1. using 4,7-dichloro-2-methylbenzo[b]thiophene-3-carbaldehyde. LC-MS A: t_R = 0.68 min; $[M+H]^+$ = 260.07 .

A.1.11.2. 4,7-Dichloro-2-methylbenzo[b]thiophene-3-carbaldehyde

The title compound is prepared according to the procedure described above in A.1.1.2. using 4,7-dichloro-2-methylbenzo[b]thiophene. LC-MS A: t_R = 0.98 min; no ionization.

A.1.11.3. 4,7-Dichloro-2-methylbenzo[b]thiophene

The title compound is prepared according to the procedure described above in A.1.1.3. using 2,5-dichlorobenzenethiol. LC-MS A: t_R = 1.01 min; no ionization.

A.1.12. 3-(2-((6-Chloropyrimidin-4-yl)amino)ethyl)-7-methoxybenzo[b]thiophene-2-carbonitrile

To a solution of 3-(2-aminoethyl)-7-methoxybenzo[b]thiophene-2-carbonitrile hydrochloride (485 mg, 1.79 mmol) in 2-propanol (20 mL) at RT are added TEA (0.87 mL, 6.25 mmol) and 4,6-dichloropyrimidine (319 mg, 2.14 mmol). The RM is refluxed (90°C), under nitrogen, for 15h and is then allowed to cool to RT. DCM and water are added and the layers are separated. The aq. layer is extracted twice with DCM and the combined organic layers are then washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords 3-(2-((6-chloropyrimidin-4-yl)amino)ethyl)-7-

methoxybenzo[b]thiophene-2-carbonitrile as a colorless solid (254 mg, 41%). LC-MS B: t_R = 1.00 min; $[M+H]^+$ = 345.05 .

A.1.12.1. 3-(2-Aminoethyl)-7-methoxybenzo[b]thiophene-2-carbonitrile hydrochloride

To a solution of tert-butyl (2-(2-cyano-7-methoxybenzo[b]thiophen-3-yl)ethyl)carbamate (672 mg, 1.88 mmol) in DCM (20 mL) is added 4 M HCl in dioxane (4.65 mL, 18.60 mmol) and the RM is stirred at RT for 4h. The RM is then concentrated to dryness under reduced pressure affording 3-(2-aminoethyl)-7-methoxybenzo[b]thiophene-2-carbonitrile hydrochloride as a pale green solid (485 mg, 96%). LC-MS B: t_R = 0.61 min; $[M+H]^+$ = 233.11 .

A.1.12.2. Tert-butyl (2-(2-cyano-7-methoxybenzo[b]thiophen-3-yl)ethyl)carbamate

A mixture of 3-bromo-7-methoxybenzo[b]thiophene-2-carbonitrile (1.500 g, 5.15 mmol), potassium (2-((tert-butoxycarbonyl)amino)ethyl)trifluoroborate (1.496 g, 5.66 mmol) and cesium carbonate (5.031 g, 15.40 mmol) in toluene (40 mL) and water (13 mL) is degassed three times. Palladium(II) acetate (57.8 mg, 0.25 mmol) and RuPhos (253 mg, 0.51 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 RM is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 4/1) affords tert-butyl (2-(2-cyano-7-methoxybenzo[b]thiophen-3-yl)ethyl)carbamate as an orange solid (672 mg, 39%). LC-MS B: t_R = 1.04 min; $[M+H]^+$ = 333.11 .

A.1.12.3. 3-Bromo-7-methoxybenzo[b]thiophene-2-carbonitrile

To a cooled (0°C) solution of 3-bromo-7-methoxybenzo[b]thiophene-2-carboxamide (5.28 g, 14.20 mmol) in anh. DMF (70 mL) is added portionwise cyanuric chloride (3.97 g, 21.30 mmol) and the RM is stirred at 0°C, under nitrogen, for 1.5h. Water is added and the RM is extracted three times with Et_2O. The combined organic layers are washed successively with water and brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 4/1) affords 3-bromo-7-methoxybenzo[b]thiophene-2-carbonitrile as a beige solid (3.412 g, 90%). LC-MS B: t_R = 1.05 min; no ionization.

A.1.12.4. 3-Bromo-7-methoxybenzo[b]thiophene-2-carboxamide

To a cooled (0°C) solution of 3-bromo-7-methoxybenzo[b]thiophene-2-carboxylic acid (5.873 g, 15.90 mmol) and anh. DMF (a few drops) in anh. DCM (80 mL) is added dropwise oxalyl chloride (1.88 mL, 21.80 mmol). The mixture is stirred at 0°C, under nitrogen, for 10 min and then at RT for 2h. The RM is then cooled to 0°C, treated dropwise with a solution of ammonium hydroxide (25% NH_3 in H_2O, 18.8 mL, 252 mmol), and stirred at RT for 2h. DCM is then removed under reduced pressure, 10% aq. NaOH is added to the aqueous residue, and the RM is extracted three times with EtOAc. The combined organic layers are washed successively with water and brine, dried over anh. $MgSO_4$, filtered and concentrated to

dryness under reduced pressure affording 3-bromo-7-methoxybenzo[b]thiophene-2-carboxamide as a brown solid (5.28 g, quantitative). LC-MS B: t_R = 0.83 min; $[M+H]^+$ = 285.99 .

A.1.12.5. 3-Bromo-7-methoxybenzo[b]thiophene-2-carboxylic acid

To a solution of methyl 3-bromo-7-methoxybenzo[b]thiophene-2-carboxylate (6.151 g, 15.90 mmol) in MeOH (40 mL) and THF (40 mL) is added 1 M aq. NaOH (40.0 mL, 40.0 mmol) and the RM is stirred at RT for 2.5h. The organic solvents are then removed under reduced pressure. Water (50 mL) is added and the mixture is extracted three times with EtOAc. The aqueous layer is then acidified with 1 M aq. HCl and extracted three times with EtOAc. The combined organic extracts are washed successively with water and brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure affording 3-bromo-7-methoxybenzo[b]thiophene-2-carboxylic acid as a brown solid (5.873 g, quantitative). LC-MS B: t_R = 0.88 min; $[M+H]^+$ = 286.91 .

A.1.12.6. Methyl 3-bromo-7-methoxybenzo[b]thiophene-2-carboxylate

To a cooled (0°C) mixture of tert-butyl nitrite (3.90 mL, 29.50 mmol) and copper(II) bromide (7.295 g, 32.30 mmol) in anh. MeCN (80 mL) is added portionwise methyl 3-amino-7-methoxybenzo[b]thiophene-2-carboxylate (5.000 g, 20.90 mmol). The RM is stirred at 0°C for 30 min, and then at RT for 30 min. 1 M aq. HCl (50 mL) is then added and the mixture is extracted three times with EtOAc. The combined organic layers are dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure affording methyl 3-bromo-7-methoxybenzo[b]thiophene-2-carboxylate as an orange solid (6.150 g, 98%). LC-MS B: t_R = 1.05 min; $[M+H]^+$ = 300.97 .

A.1.12.7. Methyl 3-amino-7-methoxybenzo[b]thiophene-2-carboxylate

To a mixture of 2-fluoro-3-methoxybenzonitrile (7.000 g, 45.90 mmol) and potassium carbonate (12.802 g, 91.70 mmol) in DMF (50 mL) is added dropwise methyl 2-mercaptoacetate (4.53 mL, 48.10 mmol). The RM is stirred at RT, under nitrogen, for 1.5h. Water is then added, and the resulting suspension is filtered. The separated solid is then washed with water and dried under high vacuum to give methyl 3-amino-7-methoxybenzo[b]thiophene-2-carboxylate as a beige solid (10.200 g, 94%). LC-MS B: t_R = 0.90 min; $[M+H]^+$ = 238.07 .

A.1.13. 3-(2-((6-Chloropyrimidin-4-yl)amino)ethyl)-5-fluoro-7-methylbenzo[b]thiophene-2-carbonitrile

To a solution of 3-(2-aminoethyl)-5-fluoro-7-methylbenzo[b]thiophene-2-carbonitrile hydrochloride (688 mg, 1.96 mmol) in 2-propanol (25 mL) at RT are added TEA (1.16 mL, 8.36 mmol) and 4,6-dichloropyrimidine (427 mg, 2.87 mmol). The RM is refluxed (90°C), under nitrogen, for 16h and is then allowed to cool to RT. DCM and water are added and the layers are separated. The aq. layer is extracted twice with DCM and the combined organic layers are then washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords 3-(2-((6-chloropyrimidin-4-yl)amino)ethyl)-5-fluoro-7-methylbenzo[b]thiophene-2-carbonitrile as an orange solid (380 mg, 46%). LC-MS B: t_R = 1.05 min; $[M+H]^+$ = 347.11 .

A.1.13.1. 3-(2-Aminoethyl)-5-fluoro-7-methylbenzo[b]thiophene-2-carbonitrile hydrochloride

To a solution of tert-butyl (2-(2-cyano-5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)carbamate (819 mg, 1.96 mmol) in DCM (20 mL) is added 4 M HCl in dioxane (4.90 mL, 19.60 mmol) and the RM is stirred at RT for 15h. The RM is then concentrated to dryness under reduced pressure affording 3-(2-aminoethyl)-5-fluoro-7-methylbenzo[b]thiophene-2-carbonitrile hydrochloride as a pale green solid (688 mg, quantitative). LC-MS B: t_R = 0.63 min; $[M+H]^+$ = 234.96 .

A.1.13.2. Tert-butyl (2-(2-cyano-5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)carbamate

A mixture of 3-bromo-5-fluoro-7-methylbenzo[b]thiophene-2-carbonitrile (1.622 g, 5.58 mmol), potassium (2-((tert-butoxycarbonyl)amino)ethyl)trifluoroborate (1.624 g, 6.14 mmol) and cesium carbonate (5.458 g, 16.80 mmol) in toluene (40 mL) and water (13 mL) is degassed three times. Palladium(II) acetate (62.7 mg, 0.27 mmol) and RuPhos (274 mg, 0.55 mmol) are then added and the mixture is heated to 95°C, under nitrogen, for 15h. The RM is allowed to cool to RT. Water is added and the RM is extracted twice with EtOAc. The combined organic layers are then washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 4/1) affords tert-butyl (2-(2-cyano-5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)carbamate as a yellow solid (818 mg, 44%). LC-MS B: t_R = 1.08 min; $[M+H]^+$ = 335.12 .

A.1.13.3. 3-Bromo-5-fluoro-7-methylbenzo[b]thiophene-2-carbonitrile

To a cooled (0°C) solution of 3-bromo-5-fluoro-7-methylbenzo[b]thiophene-2-carboxamide (4.508 g, 12.50 mmol) in anh. DMF (60 mL) is added portionwise cyanuric chloride (3.759 g, 20.20 mmol) and the RM is stirred at 0°C, under nitrogen, for 2h. Water is added and the RM is extracted three times with Et_2O. The combined organic layers are washed successively with water and brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 4/1) affords 3-bromo-5-fluoro-7-methylbenzo[b]thiophene-2-carbonitrile as a colorless solid (3.244 g, 89%). LC-MS B: t_R = 1.07 min; no ionization.

A.1.13.4. 3-Bromo-5-fluoro-7-methylbenzo[b]thiophene-2-carboxamide

To a cooled (0°C) solution of 3-bromo-5-fluoro-7-methylbenzo[b]thiophene-2-carboxylic acid (4.240 g, 12.50 mmol) and anh. DMF (a few drops) in anh. DCM (60 mL) is added dropwise oxalyl chloride (1.40 mL, 16.20 mmol). The mixture is stirred at 0°C, under nitrogen, for 10 min and then at RT for 1.5h. The RM is then cooled to 0°C, treated dropwise with a solution of ammonium hydroxide (25% NH_3 in H_2O, 14 mL, 187 mmol), and stirred at RT for 2h. DCM is then removed under reduced pressure, water is added, and the resulting suspension is filtered. The isolated solid is further dried under high vacuum affording 3-bromo-5-fluoro-7-methylbenzo[b]thiophene-2-carboxamide as a colorless solid (4.508 g, quantitative). LC-MS B: t_R = 0.88 min; $[M+H]^+$ = 287.98 .

A.1.13.5. 3-Bromo-5-fluoro-7-methylbenzo[b]thiophene-2-carboxylic acid

To a solution of methyl 3-bromo-5-fluoro-7-methylbenzo[b]thiophene-2-carboxylate (5.093 g, 15.10 mmol) in MeOH (40 mL) and THF (40 mL) is added 1 M aq. NaOH (38.0 mL, 38.0 mmol) and the RM is stirred at RT for 1h. The organic solvents are then removed under reduced pressure, water is added to the residue, and the mixture is acidified with 2 M aq. HCl. EtOAc is then added and the resulting suspension is filtered. The isolated solid is further dried under high vacuum affording 3-bromo-5-fluoro-7-methylbenzo[b]thiophene-2-carboxylic acid as a colorless solid (4.240 g, 97%). LC-MS B: t_R = 0.94 min; no ionization.

A.1.13.6. Methyl 3-bromo-5-fluoro-7-methylbenzo[b]thiophene-2-carboxylate

To a cooled (0°C) mixture of tert-butyl nitrite (4.35 mL, 32.90 mmol) and copper(II) bromide (8.145 g, 36.10 mmol) in anh. MeCN (120 mL) is added portionwise methyl 3-amino-5-fluoro-7-methylbenzo[b]thiophene-2-carboxylate (5.629 g, 23.30 mmol). The RM is stirred at 0°C for 15 min, and then at RT for 30 min. 1 M aq. HCl (50 mL) is then added and the mixture is extracted three times with EtOAc. The combined organic layers are dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 4/1) affords methyl 3-bromo-5-fluoro-7-methylbenzo[b]thiophene-2-carboxylate as a light yellow solid (5.093 g, 72%). LC-MS B: t_R = 1.10 min; no ionization.

A.1.13.7. Methyl 3-amino-5-fluoro-7-methylbenzo[b]thiophene-2-carboxylate

To a cooled (0°C) mixture of 2,5-difluoro-3-methylbenzonitrile (5.000 g, 32.00 mmol) and potassium carbonate (8.934 g, 64.00 mmol) in DMF (30 mL) is added dropwise a solution of methyl 2-mercaptoacetate (3.01 mL, 32.00 mmol) in DMF (5 mL). The RM is stirred at 0°C, under nitrogen, for 3.5h and then at RT for 1.5h. Water is added and the resulting suspension is filtered. The separated solid is then washed with water, dissolved in EtOAc and the resulting solution is dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 4/1) affords methyl 3-amino-5-fluoro-7-methylbenzo[b]thiophene-2-carboxylate as a pale yellow solid (4.914 g, 64%). LC-MS B: t_R = 0.97 min; $[M+H]^+$ = 240.06 .

A.1.14. Ethyl 4-(6-chloropyrimidin-4-yl)-2-ethoxybenzoate

To a solution of 4,6-dichloropyrimidine (1.00 g, 6.71 mmol) in EtOH (100 mL) is added ethyl 2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2.149 g, 6.71 mmol) and 2 M aq. Na_2CO_3 (10.1 mL, 20.2 mmol). The mixture is then degassed with nitrogen and $Pd(PPh_3)_4$ (388 mg, 0.33 mmol) is added. The RM is then heated to 90°C, under nitrogen, for 1.5h. The RM is allowed to cool to RT, diluted with DCM and water is added. The layers are separated and the aqueous layer is extracted twice with DCM. The combined organic layers are then washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (DCM/MeOH = 50/1) affords ethyl 4-(6-chloropyrimidin-4-yl)-2-ethoxybenzoate as a colorless solid (720 mg, 35%). LC-MS A: t_R = 0.93 min; $[M+H]^+$ = 307.01 .

A.1.14.1. Ethyl 2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

To a solution of ethyl 4-bromo-2-ethoxybenzoate (1.79 g, 6.55 mmol) in anh. DMF (35 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.496 g, 9.83 mmol), potassium acetate (1.930 g, 19.70 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (384 mg, 0.52 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 Et_2O. The filtrate is washed with water and the aqueous layer is extracted twice with Et_2O. The combined organic layers are then washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to dryness under reduced pressure. Purification by FC (from DCM to DCM/MeOH = 50/1) affords ethyl 2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate as a yellow oil (1.85 g, 88%). LC-MS A: t_R = 0.98 min; $[M+H]^+$ = 321.13 .

A.1.14.2. Ethyl 4-bromo-2-ethoxybenzoate

To a solution of 4-bromo-2-hydroxybenzoic acid (2.00 g, 9.22 mmol) in anh. DMF (15 mL) at RT are added potassium carbonate (2.547 g, 18.40 mmol) and iodoethane (1.48 mL, 18.40 mmol) and the RM is heated to 80°C for 16h. 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 to dryness under reduced pressure. Purification by FC (from heptane/DCM = 3/7 to DCM) affords ethyl 4-bromo-2-ethoxybenzoate as a yellow solid (1.79 g, 71%). LC-MS A: t_R = 0.92 min; $[M+H]^+$ = 273.07 .

A.1.15. 3-(2-((6-chloropyrimidin-4-yl)amino)ethyl)benzo[b]thiophene-2-carbonitrile

To a solution of 3-(2-aminoethyl)benzo[b]thiophene-2-carbonitrile hydrochloride (1480 mg, 6.12 mmol) in 2-propanol (30 mL) at RT under N_2 is added 4,6-dichloropyrimidine (1094 mg, 7.34 mmol) and TEA (2.98 mL, 21.4 mmol). The RM is heated at 90°C overnight, then cooled to RT, DCM and water are added, the phases are separated and the aqueous layer is extracted twice with DCM. Organic layers are combined and washed with brine, dried over a phase separator and concentrated under reduced pressure. The residue is purified by FC (Hept:EtOAc, 100:0 to 20:80), yielding the title compound as a light orange powder (828 mg, 43%). LC-MS A: t_R = 0.96 min; $[M+H]^+$ = 315.09.

A.1.15.1. 3-(2-Aminoethyl)benzo[b]thiophene-2-carbonitrile hydrochloride

Following the procedure described in A.1.12.1., using tert-butyl (2-(2-cyanobenzo[b]thiophen-3-yl)ethyl)carbamate, the title compound is obtained as a yellow powder. LC-MS A: t_R = 0.582 min; $[M+H]^+$ = 203.21.

A.1.15.2. 3-(2-Aminoethyl)benzo[b]thiophene-2-carbonitrile hydrochloride

Following the procedure described in A.1.12.2., using 3-bromobenzo[b]thiophene-2-carbonitrile and potassium tert-butyl N-[2-(trifluoroboranuidyl)ethyl]carbamate, the title compound is obtained as a yellow powder. LC-MS A: t_R = 1.01 min; no ionization. ^1H NMR (400 MHz, d6-DMSO) δ: 8.09 (dd, J1 = 8.0 Hz, J2 = 33.7 Hz, 2 H), 7.58-7.65 (m, 2 H), 7.02 (t, J = 5.7 Hz, 1 H), 3.15-3.27 (m, 4 H), 1.32 (s, 9 H).

A.2. Synthesis of substituted 2-(benzo[b]thiophen-3-yl)ethan-1-amine derivatives of formula (A1) [X = S]

A.2.1. 2-(2-Bromo-5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethan-1-amine

To a suspension of 2-(2-(2-bromo-5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)isoindoline-1,3-dione (335 mg, 0.80 mmol) in MeOH (5 mL) at RT is added hydrazine hydrate (50-60% hydrazine, 0.39 mL) and the mixture is heated to 50°C, under nitrogen, for 2h. The RM is allowed to cool to RT and a precipitate corresponding to 2,3-dihydrophthalazine-1,4-dione is separated by filtration. The filtrate is concentrated to dryness under reduced pressure and the obtained solid is triturated in DCM. The heterogeneous mixture is then filtered and the filtrate is concentrated to dryness under reduced pressure affording 2-(2-bromo-5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethan-1-amine as a yellow solid (200 mg, 87%). LC-MS A: t_R = 0.66 min; $[M+H]^+$ = 288.00 .

A.2.1.1. 2-(2-(2-Bromo-5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)isoindoline-1,3-dione

To a solution of 2-(2-(5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)isoindoline-1,3-dione (500 mg, 1.47 mmol) in DMF (4 mL) is added dropwise a solution of N-bromosuccinimide (344 mg, 1.93 mmol) in DMF (4 mL). The RM is heated to 70°C, under nitrogen, for 1.5h. A second addition of N-bromosuccinimide (131 mg, 0.73 mmol) is then performed and the mixture is further heated to 70°C for 1h. The RM is allowed to cool to RT. Water and Et_2O are then added and the obtained precipitate is filtered affording 2-(2-(2-bromo-5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)isoindoline-1,3-dione as a colorless solid that is further dried under high vacuum (335 mg, 54%). LC-MS A: t_R = 1.05 min; no ionization.

A.2.1.2. 2-(2-(5-Fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)isoindoline-1,3-dione

To a solution of 2-(5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethan-1-ol (5.54 g, 26.34 mmol) in THF (110 mL) at RT are added successively triphenylphosphine (10.36 g, 39.49 mmol) and phthalimide (5.87 g, 39.89). A solution of diethyl azodicarboxylate (4.98 mL, 27.16 mmol) in THF (20 mL) is then added dropwise and the RM is stirred at RT, under nitrogen, for 1.5h. The RM is concentrated to dryness under reduced pressure. The obtained solid is triturated in EtOAc, filtered, and stirred in EtOH for 0.5h. A subsequent filtration affords 2-(2-(5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)isoindoline-1,3-dione as a colorless solid that is further dried under high vacuum (7.43 g, 83%). LC-MS A: t_R = 1.00 min; no ionization.

A.2.1.3. 2-(5-Fluoro-7-methylbenzo[b]thiophen-3-yl)ethan-1-ol

To a cooled (-78°C) solution of ethyl 2-(5-fluoro-7-methylbenzo[b]thiophen-3-yl)acetate (6.88 g, 27.26 mmol) in anh. toluene (80 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in toluene, 81.8 mL, 81.8 mmol). The mixture is further stirred at -78°C, under nitrogen, for 5 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 (75 mL) and with 1 N aq. NaOH (150 mL). The mixture is then allowed to warm-up to RT and the layers are separated. The aqueous layer is extracted twice with EtOAc. The combined organic layers are dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC

(DCM) affords 2-(5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethan-1-ol as a yellow oil (5.54 g, 97%) LC-MS A: t_R = 0.80 min; no ionization.

A.2.1.4. Ethyl 2-(5-fluoro-7-methylbenzo[b]thiophen-3-yl)acetate

To a solution of 5-fluoro-7-methylbenzo[b]thiophen-3(2H)-one (9.21 g, 50.54 mmol) in anh. toluene (250 mL) is added (carbethoxymethylene)triphenylphosphorane (17.61 g, 50.54 mmol) and the RM is heated at reflux, under nitrogen, for 21h. The RM is allowed to cool to RT and is concentrated to dryness under reduced pressure. DCM is added and the obtained precipitate is separated by filtration. The filtrate is then concentrated to dryness under reduced pressure and the residue is purified by FC (from heptane/DCM = 9/1 to DCM) affording ethyl 2-(5-fluoro-7-methylbenzo[b]thiophen-3-yl)acetate as a pale orange solid (6.88 g, 54%). LC-MS A: t_R = 0.94 min; no ionization.

A.2.1.5. 5-Fluoro-7-methylbenzo[b]thiophen-3(2H)-one

To a cooled (0°C) solution of 2-((4-fluoro-2-methylphenyl)thio)acetic acid (13.37 g, 66.77 mmol) in anh. THF (150 mL) are added dropwise oxalyl chloride (11.80 mL, 133.87 mmol) and anh. DMF (5 drops). The mixture is allowed to warm-up to RT and is further stirred at RT, under nitrogen, for 20 min. The RM is then concentrated to dryness under reduced pressure and the residue is dissolved in anh. DCM (50 mL). The obtained solution is added dropwise to a cooled (0°C) suspension of aluminum chloride (13.49 g, 101.16 mmol) in anh. DCM (100 mL) and the RM is stirred overnight at RT. The cooled (0°C) RM is then treated carefully with ice and is allowed to warm-up to RT. The layers are separated and the aqueous layer is extracted twice with DCM. The combined organic layers are then washed with aq. sat. $NaHCO_3$, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (from heptane/DCM = 9/1 to DCM) affords 5-fluoro-7-methylbenzo[b]thiophen-3(2H)-one as an orange-brown solid (9.21 g, 76%). LC-MS A: t_R = 0.81 min; no ionization.

A.2.1.6. 2-((4-Fluoro-2-methylphenyl)thio)acetic acid

To a solution of ethyl 2-((4-fluoro-2-methylphenyl)thio)acetate (15.25 g, 66.80 mmol) in EtOH (90 mL) is added dropwise 1 M aq. NaOH (87.0 mL, 87.0 mmol) and the resulting solution is stirred at RT for 45 min. The cooled (0°C) RM is then acidified by addition of 1 M aq. HCl. EtOH is then removed under reduced pressure, DCM is added and the layers are separated. The aqueous layer is extracted twice with DCM and the combined organic layers are dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure affording 2-((4-fluoro-2-methylphenyl)thio)acetic acid as a pale yellow solid (13.89 g, quantitative). LC-MS A: t_R = 0.74 min; no ionization.

A.2.1.7. Ethyl 2-((4-fluoro-2-methylphenyl)thio)acetate

To a solution of 4-fluoro-2-methylbenzenethiol (10.00 g, 66.80 mmol) in anh. DMF (120 mL) are added successively potassium carbonate (10.15 g, 73.43 mmol), potassium iodide (0.555 g, 3.34 mmol) and ethyl bromoacetate (8.72 mL, 73.50 mmol). The RM is heated to 80°C, under nitrogen, for 1h. The RM is allowed to cool to RT, water is then added and this mixture is extracted three times with Et_2O. The

combined organic layers are washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure affording ethyl 2-((4-fluoro-2-methylphenyl)thio)acetate as a yellow oil (16.59 g, quantitative). LC-MS A: t_R = 0.90 min; no ionization.

A.2.2. 2-(2-Chloro-5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in A.2.1. using 2-(2-(2-chloro-5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)isoindoline-1,3-dione. LC-MS A: t_R = 0.65 min; $[M+H]^+$ = 243.97 .

A.2.2.1. 2-(2-(2-Chloro-5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)isoindoline-1,3-dione

To a solution of 2-(2-(5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)isoindoline-1,3-dione (150 mg, 0.44 mmol; preparation described in A.2.1.2.) in DMF (1.2 mL) is added dropwise a solution of N-chlorosuccinimide (88 mg, 0.66 mmol) in DMF (1.2 mL). The RM is heated to 70°C, under nitrogen, for 1.5h. The RM is allowed to cool to RT. Water and Et_2O are then added and the layers are separated. The aqueous layer is further extracted with Et_2O and the combined organic layers are washed with aq. sat. $NaHCO_3$, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. The obtained solid is triturated in EtOH and filtered affording 2-(2-(2-chloro-5-fluoro-7-methylbenzo[b]thiophen-3-yl)ethyl)isoindoline-1,3-dione as a colorless solid that is further dried under high vacuum (174 mg, quantitative). LC-MS A: t_R = 1.04 min; no ionization.

B- Preparation of precursors and intermediates for benzofuran derivatives

B.1. Synthesis of pyrimidine halide derivatives of formula (A3) [X = O]

B.1.1. 6-Chloro-N-(2-(7-chloro-2-methylbenzofuran-3-yl)ethyl)pyrimidin-4-amine

To a solution of 2-(7-chloro-2-methylbenzofuran-3-yl)ethan-1-amine (4.90 g, 23.36 mmol) in 2-propanol (90 mL) at RT are added TEA (11.5 mL, 82.62 mmol) and 4,6-dichloropyrimidine (4.27 g, 28.66 mmol). The RM is refluxed (90°C), under nitrogen, for 1h and is then allowed to cool to RT. DCM (150 mL) and water (75 mL) are added and the layers are separated. The aq. layer is extracted twice with DCM and the combined organic layers are then washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (DCM/MeOH = 50/1) affords 6-chloro-N-(2-(7-chloro-2-methylbenzofuran-3-yl)ethyl)pyrimidin-4-amine (3.57 g, 47%). LC-MS A: t_R = 0.95 min; $[M+H]^+$ = 321.94 .

B.1.1.1. 2-(7-Chloro-2-methylbenzofuran-3-yl)ethan-1-amine

To a solution of 7-chloro-2-methylbenzofuran-3-carbaldehyde (4.78 g, 24.56 mmol) in nitromethane (115 mL) are added successively molecular sieves (4 angstrom, 0.74 g), butylamine (0.290 mL, 2.92 mmol) and acetic acid (0.287 mL, 5.01 mmol). The RM is heated to 95°C, under nitrogen, for 2h. The RM is then filtered and the filtrate is concentrated to dryness under reduced pressure affording 7-chloro-2-methyl-3-(2-nitrovinyl)benzofuran as a brown solid (5.84 g) that is used in the subsequent reduction without additional purification. LC-MS A: t_R = 0.95 min; no ionization.

To a cooled (0°C) solution of lithium aluminum hydride (2 M in THF, 42.4 mL, 84.8 mmol) in anh. THF (140 mL) is added dropwise a solution of 7-chloro-2-methyl-3-(2-nitrovinyl)benzofuran (5.84 g, 24.56 mmol) in anh. THF (160 mL). The mixture is then heated at reflux (80°C), under nitrogen, for 0.5h. The cooled (0°C) RM is treated successively with water (3.2 mL), 15% aq. NaOH (3.2 mL), and water (9.6 mL). The resulting heterogeneous mixture is then filtered and the separated solid is washed with Et_2O. The layers of the filtrate are separated and the aqueous layer is extracted with Et_2O. The combined organic layers are then washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure affording 2-(7-chloro-2-methylbenzofuran-3-yl)ethan-1-amine as a brown oil (4.90 g, 95%). LC-MS A: t_R = 0.59 min; $[M+H]^+$ = 210.08 .

B.1.1.2. 7-Chloro-2-methylbenzofuran-3-carbaldehyde

To a cooled (0°C) solution of 7-chloro-2-methylbenzofuran (4.42 g, 26.52 mmol) in anh. DCM (55 mL) is added dropwise tin(IV) chloride (6.22 mL, 53.14 mmol) and the mixture is further stirred at 0°C, under nitrogen, for 15 min. Dichloromethyl methyl ether (2.94 mL, 32.50 mmol) is then added and the mixture is allowed to stir at RT, under nitrogen, for 1.5h. The resulting RM is then poured onto ice-water (200 mL) and 1 M aq. HCl (75 mL) is added. The layers are separated and the aq. layer is extracted twice with DCM. The combined organic layers are dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (from heptane/DCM = 9/1 to heptane/DCM = 1/1) affords 7-chloro-2-methylbenzofuran-3-carbaldehyde as a yellow solid (4.78 g, 93%). LC-MS A: t_R = 0.86 min; no ionization.

B.1.1.3. 7-Chloro-2-methylbenzofuran

To a solution of 3-chloro-2-hydroxybenzaldehyde (5.00 g, 31.93 mmol) in anh. DMF (30 mL) at RT are added successively ethyl 2-bromopropanoate (4.52 mL, 34.80 mmol), potassium carbonate (4.58 g, 33.13 mmol) and potassium iodide (262 mg, 1.57 mmol). The RM is heated to 80°C, under nitrogen, for 40 min. The RM is then allowed to cool to RT. Water (100 mL) and Et_2O (150 mL) are added and the layers are separated. The aq. layer is extracted twice with Et_2O and the combined organic layers are washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure giving ethyl 2-(2-chloro-6-formylphenoxy)propanoate as a light brown oil (8.20 g, quantitative). LC-MS A: t_R = 0.88 min; $[M+H]^+$ = 256.99 .

To a solution of ethyl 2-(2-chloro-6-formylphenoxy)propanoate (8.20 g, 31.93 mmol) in MeOH (120 mL) and water (30 mL) at RT is added 1 M aq. NaOH (36 mL, 36 mmol) and the RM is heated to 50°C, under nitrogen, for 1h. The RM is then allowed to cool to RT and is treated with 1 M aq. HCl (36 mL). MeOH is removed under reduced pressure and the residual aqueous mixture is extracted twice with DCM. The combined organic layers are washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure affording 2-(2-chloro-6-formylphenoxy)propanoic acid as a light yellow solid (7.30 g, quantitative). LC-MS A: t_R = 0.72 min; $[M+H]^+$ = 228.93 .

A mixture of 2-(2-chloro-6-formylphenoxy)propanoic acid (7.30 g, 31.93 mmol) in acetic anhydride (39 mL, 412 mmol) at RT is treated with sodium acetate (8.14 g, 99.23 mmol) and is then heated at reflux (150°C), under nitrogen, for 14h. The RM is allowed to cool to RT, diluted with toluene (50 mL) and treated with 1 M aq. NaOH (40 mL). After stirring at RT for 30 min, the RM is diluted with water and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (heptane) affords 7-chloro-2-methylbenzofuran as a yellow oil (4.43 g, 83%). LC-MS A: t_R = 0.90 min; no ionization.

B.1.2. 6-Chloro-N-(2-(2-methylbenzofuran-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in B.1.1. using 2-(2-methylbenzofuran-3-yl)ethan-1-amine. LC-MS A: t_R = 0.90 min; $[M+H]^+$ = 288.06 .

B.1.2.1. 2-(2-Methylbenzofuran-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in B.1.1.1. using 2-methylbenzofuran-3-carbaldehyde. LC-MS A: t_R = 0.54 min; $[M+H]^+$ = 176.27 .

B.1.3. 6-Chloro-N-(2-(5-fluoro-2,7-dimethylbenzofuran-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in B.1.1. using 2-(5-fluoro-2,7-dimethylbenzofuran-3-yl)ethan-1-amine. LC-MS A: t_R = 0.96 min; $[M+H]^+$ = 320.06 .

B.1.3.1. 2-(5-Fluoro-2,7-dimethylbenzofuran-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in B.1.1.1. using 5-fluoro-2,7-dimethylbenzofuran-3-carbaldehyde. LC-MS A: t_R = 0.61 min; $[M+H]^+$ = 208.14 .

B.1.3.2. 5-Fluoro-2,7-dimethylbenzofuran-3-carbaldehyde

The title compound is prepared according to the procedure described above in B.1.1.2. using 5-fluoro-2,7-dimethylbenzofuran. LC-MS A: t_R = 0.87 min; no ionization.

B.1.3.3. 5-Fluoro-2,7-dimethylbenzofuran

The title compound is prepared according to the procedure described above in B.1.1.3. using 5-fluoro-2-hydroxy-3-methylbenzaldehyde. LC-MS A: t_R = 0.92 min; no ionization.

B.1.4. 6-Chloro-N-(2-(2-ethyl-5-fluoro-7-methylbenzofuran-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in B.1.1. using 2-(2-ethyl-5-fluoro-7-methylbenzofuran-3-yl)ethan-1-amine. LC-MS A: t_R = 0.99 min; $[M+H]^+$ = 333.97 .

B.1.4.1. 2-(2-Ethyl-5-fluoro-7-methylbenzofuran-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in B.1.1.1. using 2-ethyl-5-fluoro-7-methylbenzofuran-3-carbaldehyde. LC-MS A: t_R = 0.65 min; $[M+H]^+$ = 222.06 .

B.1.4.2. 2-Ethyl-5-fluoro-7-methylbenzofuran-3-carbaldehyde

The title compound is prepared according to the procedure described above in B.1.1.2. using 2-ethyl-5-fluoro-7-methylbenzofuran. LC-MS A: t_R = 0.91 min; no ionization.

B.1.4.3. 2-Ethyl-5-fluoro-7-methylbenzofuran

The title compound is prepared according to the procedure described above in B.1.1.3. using 5-fluoro-2-hydroxy-3-methylbenzaldehyde and methyl 2-bromobutanoate. LC-MS A: t_R = 0.96 min; no ionization.

B.1.5. 6-Chloro-N-(2-(5-chloro-2,7-dimethylbenzofuran-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in B.1.1. using 2-(5-chloro-2,7-dimethylbenzofuran-3-yl)ethan-1-amine. LC-MS A: t_R = 0.99 min; $[M+H]^+$ = 336.18 .

B.1.5.1. 2-(5-Chloro-2,7-dimethylbenzofuran-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in B.1.1.1. using 5-chloro-2,7-dimethylbenzofuran-3-carbaldehyde. LC-MS A: t_R = 0.66 min; $[M+H]^+$ = 223.69 .

B.1.5.2. 5-Chloro-2,7-dimethylbenzofuran-3-carbaldehyde

The title compound is prepared according to the procedure described above in B.1.1.2. using 5-chloro-2,7-dimethylbenzofuran. LC-MS A: t_R = 0.90 min; no ionization.

B.1.5.3. 5-Chloro-2,7-dimethylbenzofuran

The title compound is prepared according to the procedure described above in B.1.1.3. using 5-chloro-2-hydroxy-3-methylbenzaldehyde. LC-MS A: t_R = 0.95 min; no ionization.

B.1.6. 6-Chloro-N-(2-(5,7-dichloro-2-methylbenzofuran-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in B.1.1. using 2-(5,7-dichloro-2-methylbenzofuran-3-yl)ethan-1-amine. LC-MS A: t_R = 1.00 min; $[M+H]^+$ = 355.99 .

B.1.6.1. 2-(5,7-Dichloro-2-methylbenzofuran-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in B.1.1.1. using 5,7-dichloro-2-methylbenzofuran-3-carbaldehyde. LC-MS A: t_R = 0.66 min; no ionization.

B.1.6.2. 5,7-Dichloro-2-methylbenzofuran-3-carbaldehyde

The title compound is prepared according to the procedure described above in B.1.1.2. using 5,7-dichloro-2-methylbenzofuran. LC-MS A: t_R = 0.92 min; no ionization.

B.1.6.3. 5,7-Dichloro-2-methylbenzofuran

The title compound is prepared according to the procedure described above in B.1.1.3. using 3,5-dichloro-2-hydroxybenzaldehyde. LC-MS A: t_R = 0.96 min; no ionization.

B.1.7. 6-Chloro-N-(2-(5-chloro-7-methoxy-2-methylbenzofuran-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in B.1.1. using 2-(5-chloro-7-methoxy-2-methylbenzofuran-3-yl)ethan-1-amine. LC-MS A: t_R = 0.95 min; $[M+H]^+$ = 352.10 .

B.1.7.1. 2-(5-Chloro-7-methoxy-2-methylbenzofuran-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in B.1.1.1. using 5-chloro-7-methoxy-2-methylbenzofuran-3-carbaldehyde. LC-MS A: t_R = 0.60 min; $[M+H]^+$ = 240.17 .

B.1.7.2. 5-Chloro-7-methoxy-2-methylbenzofuran-3-carbaldehyde

The title compound is prepared according to the procedure described above in B.1.1.2. using 5-chloro-7-methoxy-2-methylbenzofuran. LC-MS A: t_R = 0.90 min; $[M+H]^+$ = 225.01 .

B.1.7.3. 5-Chloro-7-methoxy-2-methylbenzofuran

The title compound is prepared according to the procedure described above in B.1.1.3. using 5-chloro-2-hydroxy-3-methoxybenzaldehyde. LC-MS A: t_R = 0.92 min; no ionization.

B.1.8. 6-Chloro-N-(2-(4,5-difluoro-7-methoxy-2-methylbenzofuran-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in B.1.1. using 2-(4,5-difluoro-7-methoxy-2-methylbenzofuran-3-yl)ethan-1-amine. LC-MS A: t_R = 0.95 min; $[M+H]^+$ = 353.95 .

B.1.8.1. 2-(4,5-Difluoro-7-methoxy-2-methylbenzofuran-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in B.1.1.1. using 4,5-difluoro-7-methoxy-2-methylbenzofuran-3-carbaldehyde. LC-MS A: t_R = 0.61 min; $[M+H]^+$ = 242.02 .

B.1.8.2. 4,5-Difluoro-7-methoxy-2-methylbenzofuran-3-carbaldehyde

The title compound is prepared according to the procedure described above in B.1.1.2. using 4,5-difluoro-7-methoxy-2-methylbenzofuran. LC-MS A: t_R = 0.86 min; $[M+H]^+$ = 227.06 .

B.1.8.3. 4,5-Difluoro-7-methoxy-2-methylbenzofuran

The title compound is prepared according to the procedure described above in B.1.1.3. using 2,3-difluoro-6-hydroxy-5-methoxybenzaldehyde. LC-MS A: t_R = 0.91 min; no ionization.

B.1.8.4. 2,3-Difluoro-6-hydroxy-5-methoxybenzaldehyde

To a cooled (-78°C) solution of 2,3-difluoro-5,6-dimethoxybenzaldehyde (1.14 g, 5.63 mmol) in anh. DCM (10 mL) is added dropwise a solution of boron trichloride (1 M in DCM, 6.2 mL, 6.2 mmol) and the RM is further stirred at -78°C, under nitrogen, for 10 min and then at RT for 16h. The RM is cooled (0°C), treated carefully with water (10 mL) and stirred at RT for 1.5h. Water and DCM are added and the layers are separated. The aq. layer is extracted twice with DCM and the combined organic layers are dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure affording 2,3-difluoro-6-hydroxy-5-methoxybenzaldehyde as a yellow solid (0.97 g, 91%). LC-MS A: t_R = 0.73 min; no ionization.

B.1.8.5. 2,3-Difluoro-5,6-dimethoxybenzaldehyde

To a cooled (-78°C) solution of 1,2-difluoro-4,5-dimethoxybenzene (1.00 g, 5.74 mmol) in anh. THF (20 mL) is added dropwise a solution of n-butyllithium (2.5 M in hexanes, 2.53 mL, 6.32 mmol) and the RM is further stirred at -78°C, under nitrogen, for 1h. Anh. DMF (0.667 mL, 8.61 mmol) is then added dropwise to the previous mixture and stirring at -78°C is continued for 3h. The RM is treated carefully with sat. aq. NH_4Cl (50 mL). Water (50 mL) and EtOAc (100 mL) are then added and the layers are separated. The aq. layer is further extracted with EtOAc and the combined organic layers are dried over anh. $MgSO_4$, filtered

and concentrated to dryness under reduced pressure affording 2,3-difluoro-5,6-dimethoxybenzaldehyde as a yellow solid (1.14 g, 98%). LC-MS A: t_R = 0.77 min; $[M+H]^+$ = 203.10 .

B.1.9. 6-Chloro-N-(2-(4-fluoro-7-methoxy-2-methylbenzofuran-3-yl)ethyl)pyrimidin-4-amine

The title compound is prepared according to the procedure described above in B.1.1. using 2-(4-fluoro-7-methoxy-2-methylbenzofuran-3-yl)ethan-1-amine. LC-MS A: t_R = 0.92 min; $[M+H]^+$ = 335.93 .

B.1.9.1. 2-(4-Fluoro-7-methoxy-2-methylbenzofuran-3-yl)ethan-1-amine

The title compound is prepared according to the procedure described above in B.1.1.1. using 4-fluoro-7-methoxy-2-methylbenzofuran-3-carbaldehyde. LC-MS A: t_R = 0.58 min; $[M+H]^+$ = 223.90 .

B.1.9.2. 4-Fluoro-7-methoxy-2-methylbenzofuran-3-carbaldehyde

The title compound is prepared according to the procedure described above in B.1.1.2. using 4-fluoro-7-methoxy-2-methylbenzofuran. LC-MS A: t_R = 0.82 min; no ionization.

B.1.9.3. 4-Fluoro-7-methoxy-2-methylbenzofuran

The title compound is prepared according to the procedure described above in B.1.1.3. using 6-fluoro-2-hydroxy-3-methoxybenzaldehyde. LC-MS A: t_R = 0.88 min; no ionization.

B.1.9.4. 6-Fluoro-2-hydroxy-3-methoxybenzaldehyde

The title compound is prepared according to the procedure described above in B.1.8.4. using 6-fluoro-2,3-dimethoxybenzaldehyde. LC-MS A: t_R = 0.69 min; no ionization.

B.1.9.5. 6-Fluoro-2,3-dimethoxybenzaldehyde

The title compound is prepared according to the procedure described above in B.1.8.5. using 4-fluoro-1,2-dimethoxybenzene. LC-MS A: t_R = 0.71 min; $[M+H]^+$ = 185.23 .

C- Synthesis of boronic acid derivatives of formula (A4)

C.1.1. 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)thiophene-2-carboxylic acid

Lithium diisopropylamide solution (2.0 M in THF/hexanes, 2.53 mL, 5.05 mmol) is added dropwise to a solution of 3-(trifluoromethyl)thiophene-2-carboxylic acid (330 mg, 1.68 mmol) in THF (7 mL) at -78°C. The RM is stirred for 30 min at -78°C then at 0°C for 10 min. Back at -78°C, a solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.771 mL, 3.7 mmol) in THF (15 mL) is added dropwise and the RM is slowly allowed to warm to RT overnight. HCl 0.5N (20 mL) is added and the mixture is extracted with EtOAc. The combined organic layers are washed with brine, dried over $MgSO_4$ and the solvent is removed. The crude product is purified by FC (DCM/MeOH 1:0 to 19:1) to afford the title compound as a light orange solid (443 mg, 82%). LC-MS A: t_R = 0.59 min; no ionization.

C.1.1.1. 3-(Trifluoromethyl)thiophene-2-carboxylic acid

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 RM 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 $MgSO_4$ and concentrated under vacuum, affording the title compound as a pale yellow solid (0.72 g, quantitative). LC-MS A: t_R = 0.69 min; no ionization.

C.1.2. 3-Ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylic acid

The title compound is prepared according to the synthesis of C.1.1. using 3-ethoxythiophene-2-carboxylic acid. LC-MS A: t_R = 0.48 min; $[M+H]^+$ = 217.07 (boronic acid, from hydrolysis of the pinacol ester on the LC-MS-column).

C.1.3. 5-(2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-tetrazole

A mixture of 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) is 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 $MgSO_4$ and concentrated under vacuum. The residue is purified via FC, eluting with a gradient from Heptane:EtOAc 100:0 to 10:90. This affords the title compound as a white solid (135 mg, 23%). LC-MS B: t_R = 0.87 min; [M+H]+ = 317.14.

C.1.3.1. 2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile

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_2CO_3 (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 RM is cooled down to RT, partitioned between DCM and 1N $NaHCO_3$. The aqueous layer is re-extracted with DCM, the combined organics are dried ($MgSO_4$), and concentrated under reduced pressure. This affords the title compound as a beige solid (1.31 g, 78%). LC-MS B: t_R = 0.96 min; $[M+MeCN+H]^+$ = 315.10.

C.1.4. 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 extrated (x2) with EtOAc. Organic layers are combined, washed with brine, dried over $MgSO_4$, 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_R = 0.37 min; $[M+H]^+$ = 313.11.

Following the procedure described for the synthesis of C.1.4. described above, the following boronic acid derivatives are synthesized, starting from the corresponding halides (see table 3).

Table 3: Boronic acid derivatives C.1.5. – C.1.8.

No.	Compound	t_R [min] (LC-MS)	MS Data m/z $[M+H]^+$
C.1.5.	2-Cyclobutoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid	0.91 (A)	319.11
C.1.6.	5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoxazol-3-ol	0.85 (A)	288.17
C.1.7.	2-Methoxy-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid	0.80 (A)	293.16
C.1.8.	Methyl 2-(methylthio)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate	0.96 (A)	309.18

C.1.9. 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 C.1.4. starting with 4-bromo-2-fluoro-6-propylbenzoic acid. LC-MS E: t_R = 0.48 min; $[M-H]^+$ = 307.11.

C.1.9.1. 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 $MgSO_4$, 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_R = 0.84 min; no ionization.

C.1.10. 2-(2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)acetic acid

A solution of ethyl 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)acetate (1.285 g, 3.82 mmol) in EtOH (15 mL) is treated with NaOH 10% (7.64 mL, 19.1 mmol) and the RM is stirred at 50°C for 30 min. The RM is cooled to RT and diluted with EtOAc. HCl 2N (15 mL) is added to reach acidic pH (<1). The aqueous layer is extracted twice with EtOAc. The resulting organic phase is dried over $MgSO_4$ and concentrated, affording the title compound as an orange paste. LC-MS A: t_R = 0.80 min; $[M+H]^+$ = 323.12.

C.1.10.1. Ethyl 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)acetate

A solution of 2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (3.47 g, 12.5 mmol) in anhydrous DMF (50 mL) is treated successively with cesium carbonate (6.10 g, 18.7 mmol) and ethyl bromoacetate (1.48 mL, 13.1 mmol). The RM is stirred at RT for 1h. Water is added, and the mixture is extracted with Et_2O (x 3). The combined organic layers are then washed successively with water (x 2) and brine, dried over $MgSO_4$,

filtered, and concentrated to dryness under reduced pressure to afford the pure product as a colorless oil (1.46g, 77%). LC-MS A: t_R = 0.94 min; $[M+H]^+$ = 351.18.

C.1.11. (2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)glycine

To a solution of methyl (2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)glycinate (207 mg, 0.61 mmol) in THF/H_2O (4:1) (5 mL) is added LiOH.H_2O (51 mg, 1.21 mmol) and the mixture is stirred at RT for 2h. The mixture is treated with HCl 1N (1 mL) and extracted with EtOAc, dried over $MgSO_4$ and concentrated, affording the title compound as a brown oil (0.151 g, 78%). LC-MS A: t_R = 0.82 min; $[M+H]^+$ = 322.07.

C.1.11.1. 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 C.1.4., starting with methyl (4-bromo-2-ethoxyphenyl)glycinate. LC-MS A: t_R = 0.93 min; $[M+H]^+$ = 336.28.

C.1.11.2. 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 MW 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.

C.1.12. 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 C.1.4., 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.

C.1.12.1. 3-(4-Bromo-2-ethoxyphenyl)-[1,2,4]oxadiazol-5(4H)-one

A solution of 4-bromo-2-ethoxy-N'-hydroxybenzimidamide (1.395 g, 5.38 mmol), 1,1'-carbonyldiimidazole (1.31 g, 8.08 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (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 N2 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.

C.1.12.2. 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 $NaHCO_3$ (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 under high vacuum, washing with water and some Et_2O. A first crop of pure title compound (947mg) is thus obtained as white solid. The filtrate is extracted with EtOAc. The organic layer is then washed twice with brine, dried over $MgSO_4$, filtered and concentrated. The residue is purified by FC (hept/EtOAc 5:5) 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.

C.1.13. 3-(2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)propanoic acid

The title compound is prepared according to the procedure described for C.1.4., starting with 3-(4-bromo-2-ethoxyphenoxy)propanoic acid. LC-MS E: t_R = 0.45 min; $[M-H]^+$ = 335.18.

C.1.13.1. 3-(4-Bromo-2-ethoxyphenoxy)propanoic acid

A MW vial is charged with 4-bromo-2-ethoxyphenol (1300 mg, 5.98 mmol), H_2O (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 at high energy level. The RM is diluted in water and pH is decreased to pH9 with HCl 2N then is extracted twice with EtOAc. The basic aqueous layer is then acidified to pH2 and extracted twice with EtOA, the combined organic extracts are washed with water, brine, dried over $MgSO_4$, filtered and evaporated to dryness, yielding the title compound as a a white powder (0.448 g, 56%). LC-MS B: t_R = 0.89 min; $[M+H]^+$ = 289.10.

C.1.14. Methyl *(E)*-3-(3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)acrylate

The title compound is prepared according to the procedure described for C.1.1 starting with methyl *(E)*-3-(3-ethoxythiophen-2-yl)acrylate. LC-MS A: t_R = 1.02 min; $[M+H]^+$ = 339.14.

C.1.14.1. 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 $NaHCO_3$ (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 (2.9 g, 100%). LC-MS A: t_R = 0.69 min; $[M+MeCN]^+$ = 198.26.

C.1.15. 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 [C.1.14.] (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-MS A: t_R = 0.86 min; $[M+H]^+$ = 327.09.

C.1.16. 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'-dipyridyl (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.

C.1.16.1. 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. NaHCO3 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%). LC-MS B: t_R = 0.86 min, $[M+H]^+$ = 201.14.

C.1.16.2. 2-Diazo-1-(3-ethoxythiophen-2-yl)ethan-1-one

A solution of 3-ethoxythiophene-2-carboxylicacid (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. $NaHCO_3$ and with brine, dried ($MgSO_4$) 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_R = 0.78min, $[M+H]^+$ = 197.15.

C.1.17. 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 C.1.4., starting with ethyl 2-((4-bromo-2-ethoxyphenyl)amino)-2-oxoacetate. LC-MS A: t_R = 0.98 min; $[M+H]^+$ = 364.21.

C.1.17.1. 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 ethyl acetate and saturated aqueous solution of $NaHCO_3$. The two layers are separated and the organic layers washed with water, brine then dried over $MgSO_4$, filtered and solvent removed under vacuo, affording the title compound as a brown solid (1.52 g, 99%). LC-MS A: t_R = 0.92 min; $[M+MeCN]^+$ = 316.04.

C.1.18. 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 C.2.4., starting with 4-bromo-2-butoxy-6-fluorobenzoic acid. LC-MS A: t_R = 0.92 min; $[M+H]^+$ = 339.21.

C.1.18.1. 4-Bromo-2-butoxy-6-fluorobenzoic acid

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 then 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, affording the title compound as a white solid. LC-MS E: t_R = 0.52 min; $[M-H]^+$ = 290.89.

C.1.18.2. Methyl 4-bromo-2-butoxy-6-fluorobenzoate

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 MW. 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.

C.1.19. Propyl 2-(propylthio)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The title compound is prepared according to the procedure described for C.1.4., starting with propyl 4-bromo-2-(propylthio)benzoate. LC-MS A: t_R = 1.06 min; $[M+H]^+$ = 365.04.

C.1.19.1. Propyl 4-bromo-2-(propylthio)benzoate

Propyl iodide (1.51 mL, 15.3 mmol) is added dropwise to a 0°C solution of 4-bromo-2-sulfanylbenzoic acid (1.50 g, 6.11 mmol) and Cs_2CO_3 (4.18 g, 12.8 mmol) in DMF (60 mL). The RM is stirred for 15 min at 0°C and then at RT for 16h. The RM is quenched with water, then EtOAc is added and layers are separated. The aqueous layer is extracted twice with EtOAc. The combined organic layers are washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue is purified by FC, eluting with Heptane to give the title compound as a pale yellow solid (1.66 g, 86%). LC-MS A: t_R = 1.04 min; no ionization.

C.1.20. Isopropyl 2-(isopropylthio)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The title compound is prepared according to the procedure described for C.1.4, starting with isopropyl 4-bromo-2-(isopropylthio)benzoate. LC-MS A: t_R = 1.06 min; $[M+H]^+$ = 365.21.

C.1.20.1. Isopropyl 4-bromo-2-(isopropylthio)benzoate

The title compound is prepared according to the procedure described C.1.19.1., using isopropyl iodide. LC-MS A: t_R = 1.04 min; no ionization.

C.1.21. Cyclobutyl 2-(cyclobutylthio)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The title compound is prepared according to the procedure described for C.1.4., starting with cyclobutyl 4-bromo-2-(cyclobutylthio)benzoate. LC-MS A: t_R = 1.10 min; $[M+H]^+$ = 389.26.

C.1.21.1. Cyclobutyl 4-bromo-2-(cyclobutylthio)benzoate

The title compound is prepared according to the procedure described for C.1.19., using bromocyclobutane. LC-MS A: t_R = 1.07 min; no ionization.

C.1.22. Methyl 2-ethoxy-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The title compound is prepared according to the procedure described for C.1.4., starting with 4-bromo-2-ethoxy-6-methylbenzoic acid. LC-MS A: t_R = 0.97 min; $[M+H]^+$ = 321.16.

C.1.22.1. Methyl 4-bromo-2-ethoxy-6-methylbenzoate

A mixture of methyl 4-bromo-2-hydroxy-6-methylbenzoate (600 mg, 2.45 mmol), Cs_2CO_3 (1994 mg, 6.12 mmol) and iodoethane (0.435 mL, 5.39 mmol) in DMF (4 mL) is stirred at 130°C for 3h. Once cooled down at RT, water is added and the RM is extracted with Et_2O. The organic layer is successively washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue is purified by FC (Heptane/EtOAc 7/3), affording the title compound as a yellow oil (595 mg, 89%). LC-MS A: t_R = 0.91 min; $[M+H]^+$ = 273.05.

C.1.23. Methyl 2-(cyclopentyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The title compound is prepared according to the procedure described for C.1.4., starting with methyl 5-bromo-2-(cyclopentyloxy)benzoate. LC-MS A: t_R = 1.01 min; $[M+H]^+$ = 347.15.

C.1.23.1. Methyl 5-bromo-2-(cyclopentyloxy)benzoate

To a solution of methyl 4-bromo-2-hydroxybenzoate (2.00 g, 8.4 mmol) in DMF (20 mL), bromocyclobutane (1.01 mL, 9.24 mmol) and K_2CO_3 (1.74 g, 12.6 mmol) aere added. The RM is stirred at 80°C for 19h, cooled to RT, and partitioned between water and Et_2O. Organic layers are combined and washed with additional water, dried over $MgSO_4$ and concentrated to dryness. The crude product is purified by FC, eluting with Heptane/DCM (100:0 to 40:60) to the product as a colourless oil (1.88 g, 75%). LC-MS A: t_R = 0.97 min; $[M+H]^+$ = 298.89.

C.1.24. Methyl 2-fluoro-6-(methylthio)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The title compound is prepared according to the procedure described for C.1.4., using methyl 4-bromo-2-fluoro-6-(methylthio)benzoate. LC-MS A: t_R = 0.98 min; $[M+H]^+$ = 327.11.

C.1.24.1. Methyl 4-bromo-2-fluoro-6-(methylthio)benzoate

Iodomethane (0.113 mL, 1.81 mmol) is added dropwise to a solution of 4-bromo-2-fluoro-6-(methylthio)benzoic acid (500 mg,1.51 mmol) and Cs_2CO_3 (492 mg, 1.51 mmol) in anhydrous DMF (20 mL)

at 0°C. The RM is stirred for 15 min at 0°C and then at RT for 1h. It is quenched with water, then EtOAc is added and layers are separated. The aqueous layer is extracted twice with EtOAc. The organic layers are combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced. The crude product is purified by FC, eluting with heptane to give the title compound as a colorless oil (173 mg, 41%). LC-MS A: t_R = 0.90 min; no ionization.

C.1.24.2. 4-Bromo-2-fluoro-6-(methylthio)benzoic acid

To a suspension of freshly powdered sodium hydroxide (397 mg, 9.92 mmol) in DMF (20 mL) at 0° is added 4-bromo-2,6-difluorobenzoic acid (2.00 g, 8.27 mmol, 1 eq) and the RM is stirred at 0°C for 10 min. Sodium thiomethoxide (732 mg, 9.92 mmol) is added and the resulting RM is allowed to warm up to RT and stirred for 2h. It is quenched with 2N HCl, and extracted with EtOAc (3x). The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product quantitatively as a yellow oil. LC-MS A: t_R = 0.76 min; no ionization.

C.1.25. Methyl 2-chloro-6-(methylthio)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The title compound is prepared according to the procedure described for C.1.4., using methyl 4-bromo-2-fluoro-6-(methylthio)benzoate. LC-MS A: t_R = 1.00 min; $[M+H]^+$ = 343.14.

C.1.25.1. Methyl 4-bromo-2-chloro-6-(methylthio)benzoate

The title compound is prepared according to the procedure described for C.1.24.1., using 4-bromo-2-chloro-6-(methylthio)benzoic acid. LC-MS A: t_R = 0.93 min; no ionization.

C.1.25.2. 4-Bromo-2-chloro-6-(methylthio)benzoic acid

The title compound is prepared according to the procedure described for C.1.24.2., using 4-bromo-2-fluoro-6-chlorobenzoic acid. LC-MS A: t_R = 0.77 min; no ionization.

C.1.26. 5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,2,4-]oxadiazol-3-ol

The title compound is prepared according to the procedure described for C.1.4., using 5-(4-bromophenyl)-[1,2,4]oxadiazol-3-ol. LC-MS A: t_R = 0.82 min; $[M+H]^+$ = 290.10.

C.1.27. 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 C.1.4., starting with methyl 4-bromo-2-(2-hydroxyethoxy)benzoate. LC-MS B: t_R = 0.89 min; $[M+H]^+$ = 323.26.

C.1.27.1. 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 $MgSO_4$,

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_R = 0.77 min; $[M+H]^+$ = 275.14.

C.1.28. 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 C.1.16.., starting with 2,3-dihydro-5H-thieno[3,2-e][1,4]dioxepin-5-one. LC-MS B: t_R = 0.51 min; $[M+H]^+$ = 215.41 (mass from boronic acid from pinacol ester cleavage during LC-MS analysis).

C.1.28.1. 2,3-Dihydro-5H-thieno[3,2-e][1,4]dioxepin-5-one

A MW vial is charged with K_2CO_3 (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 fo 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 $MgSO_4$, filtered and concentrated under reduced pressure, affording the crude title compound as a brownish solid (338 mg, quantitative). LC-MS B: t_R = 0.61 min; $[M+H]^+$ = 170.94.

C.1.29. methyl 2-cyclobutoxy-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

To a solution of methyl 4-bromo-2-cyclobutoxy-3-fluorobenzoate (435 mg, 1.44 mmol) in anh. DMF (7 mL) are added at RT 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (547 mg, 2.15 mmol), potassium acetate (423 mg, 4.31 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (84 mg, 0.11 mmol). The RM is heated to 90°C, under nitrogen, for 14h. The RM is then allowed to cool to RT and is filtered through a pad of celite, washing with Et_2O. The filtrate is washed with water and the aqueous layer is extracted twice with Et_2O. The combined organic layers are then washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to dryness under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 7/3) affords methyl 2-cyclobutoxy-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate as a pale yellow solid (235 mg, 47%). LC-MS A: t_R = 1.01 min; $[M+H]^+$ = 351.27 .

C.1.29.1. methyl 4-bromo-2-cyclobutoxy-3-fluorobenzoate

To a solution of methyl 4-bromo-3-fluoro-2-hydroxybenzoate (553 mg, 2.22 mmol) in anh. DMF (30 mL) at RT is added cesium carbonate (1.085 g, 3.33 mmol) and the mixture is stirred at RT for 15 min. The mixture is then treated with bromocyclobutane (0.235 mL, 2.44 mmol) and the RM is heated to 80°C for 16h. The RM is allowed to cool to RT, water and Et_2O are then 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 to dryness under reduced pressure. Purification by FC (heptane/DCM = 2/1) affords methyl 4-bromo-2-cyclobutoxy-3-fluorobenzoate as a pale yellow oil (435 mg, 65%). LC-MS A: t_R = 0.95 min; no ionization.

C.1.29.2. methyl 4-bromo-3-fluoro-2-hydroxybenzoate

To a solution of 4-bromo-3-fluoro-2-hydroxybenzoic acid (800 mg, 3.40 mmol) in anh. DMF (6 mL) at RT is added potassium bicarbonate (409 mg, 4.08 mmol) and the mixture is stirred at RT for 5 min. The mixture is then treated with iodomethane (0.318 mL, 5.11 mmol) and the RM is heated to 40°C for 1.5h. The RM is allowed to cool to RT, 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 to dryness under reduced pressure affording methyl 4-bromo-3-fluoro-2-hydroxybenzoate (553 mg, 65%). LC-MS A: t_R = 0.88 min; no ionization.

C.1.30. methyl 2-cyclobutoxy-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The title compound is prepared according to the procedure described above in C.1.29. using methyl 4-bromo-2-cyclobutoxy-6-fluorobenzoate. LC-MS A: t_R = 1.02 min; $[M+H]^+$ = 351.18 .

C.1.30.1. methyl 4-bromo-2-cyclobutoxy-6-fluorobenzoate

The title compound is prepared according to the procedure described above in C.1.29.1. using methyl 4-bromo-2-fluoro-6-hydroxybenzoate. LC-MS A: t_R = 0.96 min; no ionization.

C.1.31. oxetan-3-yl 2-(oxetan-3-ylthio)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The title compound is prepared according to the procedure described above in C.1.4. using oxetan-3-yl 4-bromo-2-(oxetan-3-ylthio)benzoate. LC-MS A: t_R = 0.92 min; $[M+H]^+$ = 393.20 .

C.1.31.1. oxetan-3-yl 4-bromo-2-(oxetan-3-ylthio)benzoate

To a cooled (0°C) mixture of 4-bromo-2-mercaptobenzoic acid (500 mg, 2.04 mmol) in anh. DMF (20 mL) is added cesium carbonate (1.394 g, 4.28 mmol) and the mixture is stirred at RT for 15 min. The cooled (0°C) mixture is then treated with 3-bromooxetane (855 mg, 6.11 mmol) and the RM is heated to 85°C for 16h. The RM is allowed to cool to RT, water and EtOAc are then added, and the layers are separated. The aqueous layer is extracted twice with EtOAc and the combined organic layers are washed with brine, dried over anh. $MgSO_4$, filtered and concentrated to dryness under reduced pressure. Purification by FC (from heptane to tert-butyl methyl ether) affords oxetan-3-yl 4-bromo-2-(oxetan-3-ylthio)benzoate as a pale orange solid (229 mg, 33%). LC-MS A: t_R = 0.83 min; $[M+H]^+$ = 344.98.

C.1.32. 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 C.1.4., starting with ethyl 2-(4-bromo-2-ethoxyphenyl)-2-oxoacetate. LC-MS A: t_R = 0.98 min; $[M+H]^+$ = 349.19.

C.1.32.1. 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 20 h. 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.

C.1.33. 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.

C.1.34. 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.

C.1.34.1. 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 C.1.4., starting with propyl 2-(4-bromo-2-propoxyphenyl)acetate. LC-MS A: tR = 1.04 min; [M+H]+ = 363.12.

C.1.34.2. 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 over night, 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.

C.1.35. 2-(2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid

Following the synthesis of C.1.34., 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.

C.1.35.1. 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 C.1.4., starting with ethyl 2-(4-bromo-2-ethoxyphenyl)acetate. LC-MS A: t_R = 1.01 min; $[M+H]^+$ = 287.04.

C.1.35.2. Ethyl 2-(4-bromo-2-ethoxyphenyl)acetate

Following the synthesis of C.1.34.2., with 4-bromo-2-hydroxyphenylacetic acid and iodomethane, the title compound is obtained as a colorless oil. LC-MS B: t_R = 1.02 min; $[M+H]^+$ = 287.10.

C.1.36. 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 C.1.4., starting with 3-(4-Bromophenyl)-[1,2,4]oxadiazol-5(4H)-one. LC-MS B: t_R = 0.90 min; $[M+MeCN]^+$ = 330.12.

C.1.37. 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 C.1.4., starting with N-(4-bromo-2-ethoxyphenyl)formamide. LC-MS B: t_R = 0.94 min; $[M+H]^+$ = 292.23.

C.1.37.1. N-(4-bromo-2-ethoxyphenyl)formamide

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; $[M+H]^+$ = 285.06.

C.1.38. Isobutyl 2-(isobutylthio)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The title compound is prepared according to the procedure described for C.1.4., starting with isobutyl 4-bromo-2-(isobutylthio)benzoate. LC-MS A: t_R = 1.12 min; $[M+H]^+$ = 393.26.

C.1.38.1. Isobutyl 4-bromo-2-(isobutylthio)benzoate

The title compound is prepared according to the procedure described for C.1.4.1., using 4-bromo-2-sulfanylbenzoic acid and 1-iodo-2-methylproprane. LC-MS A: t_R = 1.09 min; $[M+H]^+$ = 345.06.

C.1.39. 5-(2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoxazol-3-ol

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 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.

C.1.39.1. 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.

C.1.39.2. 3-(4-Bromo-2-methoxyphenyl)-3-oxo-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide

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 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.

C.1.39.3. 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 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.

C.1.40. 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 a 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 40 min. 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 .

C.1.40.1. 5-(4-bromo-2-ethoxyphenyl)isoxazol-3-ol

To a solution of ethyl 3-(4-bromo-2-ethoxyphenyl)propiolate (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 .

C.1.40.2. Ethyl 3-(4-bromo-2-ethoxyphenyl)propiolate

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 .

C.1.40.3. ((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; ^{1}H NMR (400 MHz, d6-DMSO) δ: 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).

C.1.41. 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',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.432 g, 5.58 mmol), potassium acetate (2.192 g, 22.30 mmol) and $Pd(dppf)Cl_2$ (454 mg, 0.61 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 Et_2O. The filtrate is washed with water and the aqueous layer is extracted twice with Et_2O. The combined organic layers are then washed with brine, dried over $MgSO_4$, 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.

C.1.41.1. Methyl 2-(4-bromo-2-(trifluoromethoxy)phenyl)acetate

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 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 = 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.

C.1.42. 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 Pd(dppf)Cl_2 (573 mg, 0.77 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 dried over $MgSO_4$, 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_R = 1.04 min; $[M+H]^+$ = 333.25.

C.1.42.1. 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-(vinyloxy)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_4Cl 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. $MgSO_4$, 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_R = 0.99 min; no ionization.

C.1.42.2. Methyl 2-(4-bromo-2-(vinyloxy)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. $MgSO_4$, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(4-bromo-2-(vinyloxy)phenyl)acetate as a yellow oil (2.253 g, 64%). LC-MS B: t_R = 0.96 min; no ionization.

C.1.42.3. 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_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 = 1/1) affords methyl 2-(4-bromo-2-hydroxyphenyl)acetate as a colorless solid (2.733 g, 90%). LC-MS B: t_R = 0.80 min; no ionization.

C.1.43. Isopropyl 2-(2-isopropoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate

Bis(pinacolato)diboron (1618 mg, 6.31 mmol) followed by potassium acetate (2477 mg, 25.2 mmol) are added to a RT solution of isopropyl 2-(4-bromo-2-isopropoxyphenyl)acetate (2046 mg, 6.31 mmol) in DMF (25 mL). The RM is purged with N_2 and dichloro(1,1'-bis(diphenylphosphino)ferrocene) palladium (II) (513 mg, 0.694 mmol) is added. The RM is heated at 95°C overnight, then cooled to RT, filtered over a pad of celite and rinsed with Et_2O. Water and Et_2O are added, and the two layers are separated. The aqueous layer is extracted with Et_2O (3x). The combined organic layers are washed with water (2x), brine, dried over $MgSO_4$, filtered and evaporated in vacuum. The residue is purified by FC (Hept:EtOAc 100:0 to 70:30) to afford the title compound as a light green oil (1.604 g, 70%). LC-MS B: t_R = 1.14 min; $[M+H]^+$ = 363.25.

C.1.43.1. Isopropyl 2-(4-bromo-2-isopropoxyphenyl)acetate

To 4-bromo-2-hydroxyphenylacetic acid (2000 mg, 8.22 mmol) in DMF (25 mL) is added cesium carbonate (5359 mg, 16.4 mmol) and 2-bromopropane (2.73 mL, 28.8 mmol) at 0°C. The RM is warmed up to RT and stirred for 1 h, then heated to 45°C and stirred for 24h. Water is added and the resulting mixture is extracted with Et_2O (3x). Organic layers are mixed and washed with additional water (2x), brine, then dried over a phase separator and concentrated under vacuum. The residue is purified by FC (Hept:EtOAc 100:0 to 75:25) to yield the title compound as a light green oil (2.046 g, 79%). LC-MS B: t_R = 1.10 min; $[M+H]^+$ = 315.11.

C.1.44. 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 $Pd(dppf)Cl_2$ (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 $MgSO_4$, 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; $[M+H]^+$ = 339.21.

C.1.44.1. 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_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 = 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; $[M+H]^+$ = 290.99.

C.1.44.2. 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. $MgSO_4$, 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.

C.1.44.3. 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. $MgSO_4$, 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.

C.1.44.4. 5-Bromo-2-(chloromethyl)-1-ethoxy-3-fluorobenzene

A cooled (0°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°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.

C.1.44.5. (4-Bromo-2-ethoxy-6-fluorophenyl)methanol

To a cooled (-78°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°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 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. $MgSO_4$, 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.

C.1.44.6. 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 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 = 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; $[M+H]^+$ = 277.08.

C.1.45. 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_2 (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 $MgSO_4$, 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_R = 1.13 min; $[M+H]^+$ = 333.24.

C.1.45.1. 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_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 = 1/1) affords methyl 2-(4-bromo-2-isobutylphenyl)acetate as a clear oil (2.271 g, 92%). LC-MS B: t_R = 1.06 min; no ionization.

C.1.45.2. 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 anh. $MgSO_4$, 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.

C.1.45.3. 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 anh. $MgSO_4$, 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.

C.1.45.4. 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 anh. 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.

C.1.45.5. (4-Bromo-2-isobutylphenyl)methanol

To a cooled (-78°C) solution of methyl 4-bromo-2-isobutylbenzoate (2.712 g, 9.71 mmol) in anh. 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 anh. $MgSO_4$, 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.

C.1.45.6. Methyl 4-bromo-2-isobutylbenzoate

To a solution of 4-bromo-2-isobutylbenzoic acid (4.254 g, 14.30 mmol) in anh. 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_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 4-bromo-2-isobutylbenzoate as a light yellow oil (3.462 g, 89%). LC-MS B: t_R = 1.11 min; no ionization.

C.1.45.7. 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_2O, 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. $MgSO_4$, 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_R = 0.97 min; no ionization.

C.1.46. 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 $Pd(dppf)Cl_2$ (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 $MgSO_4$, 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_R = 1.08 min; $[M+H]^+$ = 319.28.

C.1.46.1. 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_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 2-(4-bromo-2-ethyl-6-methylphenyl)acetate as a yellow oil (1.176 g, 37%). LC-MS B: t_R = 1.03 min; no ionization.

C.1.46.2. 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. $MgSO_4$, 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.

C.1.46.3. 2-(4-Bromo-2-ethyl-6-methylphenyl)acetonitrile

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. $MgSO_4$, 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.

C.1.46.4. 5-Bromo-2-(chloromethyl)-1-ethyl-3-methylbenzene

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.

C.1.46.5. (4-Bromo-2-ethyl-6-methylphenyl)methanol

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. $MgSO_4$, 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.

C.1.46.6. Methyl 4-bromo-2-ethyl-6-methylbenzoate

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 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 = 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.

C.1.46.7. 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. $MgSO_4$, 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_R = 0.86 min; no ionization.

C.1.47. 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 $Pd(dppf)Cl_2$ (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 $MgSO_4$, 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.

C.1.47.1. 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_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 = 1/1) affords methyl 2-(4-bromo-2-propylphenyl)acetate as a yellow oil (2.380 g, 81%). LC-MS B: t_R = 1.04 min; no ionization.

C.1.47.2. 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. $MgSO_4$, 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_R = 0.91 min; no ionization.

C.1.47.3. 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. $MgSO_4$, 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_R = 1.02 min; no ionization.

C.1.47.4. 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_R = 1.10 min; no ionization.

C.1.47.5. (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.

C.1.47.6. Methyl 4-bromo-2-propylbenzoate

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_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 = 1/1) affords methyl 4-bromo-2-propylbenzoate as a colorless oil (3.300 g, 87%). LC-MS B: t_R = 1.05 min; no ionization.

C.1.47.7. 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 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. $MgSO_4$, filtered and concentrated under reduced pressure. Purification by FC (from 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.

C.1.48. 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, 13.00 mmol) and $Pd(dppf)Cl_2$ (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 $MgSO_4$, 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 light yellow oil (708 mg, 72%). LC-MS B: t_R = 1.05 min; $[M+H]^+$ = 305.22.

C.1.48.1. 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_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 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.

C.1.48.2. 2-(4-Bromo-2-ethylphenyl)acetic acid

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.

C.1.48.3. 2-(4-Bromo-2-ethylphenyl)acetonitrile

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.

C.1.48.4. 4-Bromo-1-(chloromethyl)-2-ethylbenzene

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.

C.1.48.5. (4-Bromo-2-ethylphenyl)methanol

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.

C.1.48.6. 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_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 4-bromo-2-ethylbenzoate as a clear oil (2.735 g, 88%). LC-MS B: t_R = 1.02 min; no ionization.

C.1.48.7. 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. $MgSO_4$, 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_R = 0.87 min; no ionization.

C.1.49. 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 $Pd(dppf)Cl_2$ (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 $MgSO_4$, 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_R = 1.08 min; $[M+H]^+$ = 325.19.

C.1.49.1. 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_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 2-(4-bromo-2-chloro-6-methylphenyl)acetate as a clear oil (2.614 g, 94%). LC-MS B: t_R = 1.00 min; no ionization.

C.1.49.2. 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. $MgSO_4$, 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_R = 0.86 min; no ionization.

C.1.49.3. 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 anh. $MgSO_4$, 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_R = 0.96 min; no ionization.

C.1.49.4. 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 anh. 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_R = 1.05 min; no ionization.

C.1.49.5. (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 anh. 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 anh. $MgSO_4$, 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_R = 0.90 min; no ionization.

C.1.49.6. 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 anh. 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_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 4-bromo-2-chloro-6-methylbenzoate as a dark orange oil (3.450 g, 98%). LC-MS B: t_R = 0.99 min; no ionization.

C.1.50. 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',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.

C.1.50.1. 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_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 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.

C.1.51. 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_2 (512 mg, 0.69 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 $MgSO_4$, 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_R = 1.02 min; $[M+H]^+$ = 294.33.

C.1.51.1. 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_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 4-bromo-1-propyl-1H-pyrrole-2-carboxylate as a clear oil (1.721 g, 97%). LC-MS B: t_R = 0.99 min; no ionization.

C.1.52. 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.

C.1.52.1. 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_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 = 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.

C.1.52.2. 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. $MgSO_4$, 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.

C.1.52.3. 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. $MgSO_4$, 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.

C.1.52.4. 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. $MgSO_4$, 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.

C.1.52.5. (3-Ethylthiophen-2-yl)methanol

To a cooled (-78°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°C, under nitrogen, for 10 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 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 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. $MgSO_4$, 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.

C.1.52.6. 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 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 affording methyl 3-ethylthiophene-2-carboxylate as a yellow oil (3.340 g, quantitative). LC-MS B: t_R = 0.89 min; $[M+H]^+$ = 171.04.

C.1.53. 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 $Pd(dppf)Cl_2$ (494 mg, 0.67 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 $MgSO_4$, 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_R = 0.96 min; $[M+H]^+$ = 280.24.

C.1.53.1. 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_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 4-bromo-1-ethyl-1H-pyrrole-2-carboxylate as a clear oil (1.567 g, 94%). LC-MS B: t_R = 0.94 min; no ionization.

C.1.54. Ethyl 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate

To a microwave vial under nitrogen are added (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (13 mg, 0.0192 mmol), 4,4'-di-tert-butyl-2,2'-dipyridyl (12.3 mg, 0.0448 mmol) and bis(pinacolato)diboron (164 mg, 0.64 mmol), followed by THF (2.5 mL), and 2-methyl-1H-pyrrole-3-carboxylic acid ethyl ester (200 mg, 1.28 mmol). The microwave tube is sealed and the RM is stirred at RT for 3h, then at 80°C overnight. Bis(pinacolato)diboron (164 mg, 0.64 mmol) is added and the RM stirred at RT for 3h. After concentration under reduced pressure, the residue is purified by FC (Hept:EtOAc 100:0 to 50:50), to yield the product as a clear oil (329 mg, 92%). LC-MS B: t_R = 0.93 min; $[M+H]^+$ = 280.37.

C.1.55. 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 C.1.4., starting with 1-(4-bromo-2-propylphenyl)cyclopropane-1-carboxylic acid. LC-MS B: t_R = 1.02 min; $[M+MeCN]^+$ = 372.47.

C.1.55.1. 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_2O (1.6 mL), AcOH (1.2 mL) and H_2SO_4 (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 $MgSO_4$, 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) δ: 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).

C.1.55.2. 1-(4-Bromo-2-propylphenyl)cyclopropane-1-carbonitrile

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 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.

C.1.56. 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 C.1.4., starting with 1-(4-bromo-2-ethoxylphenyl)cyclopropane-1-carboxylic acid. LC-MS B: t_R = 0.96 min; $[M+H]^+$ = 333.44.

C.1.56.1. 1-(4-Bromo-2-ethoxyphenyl)cyclopropane-1-carboxylic acid

The title compound is prepared according to the procedure described for C.1.55.1., starting with 1-(4-bromo-2-ethoxyphenyl)cyclopropane-1-carbonitrile. LC-MS B: tR = 0.90 min; [M+H]+ = 285.17.

C.1.56.2. 1-(4-Bromo-2-ethoxyphenyl)cyclopropane-1-carbonitrile

The title compound is prepared according to the procedure described for C.1.55.2., starting with 2-(4-bromo-2-ethoxyphenyl)acetonitrile(Example 282-d). LC-MS B: t_R = 1.00 min; $[M+H]^+$ = 265.94.

C.1.57. Methyl 2-(2-ethoxy-5-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-5-fluorophenyl)acetate (1.880 g, 6.41 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) (1.656 g, 6.46 mmol), potassium acetate (2.535 g, 25.80 mmol) and $Pd(dppf)Cl_2$ (0.525 g, 0.71 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. $MgSO_4$, filtered and concentrated under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords methyl 2-(2-ethoxy-5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a colorless solid (1.330 g, 61%). LC-MS B: t_R = 1.05 min; $[M+H]^+$ = 339.23.

C.1.57.1. Methyl 2-(4-bromo-2-ethoxy-5-fluorophenyl)acetate

To a solution of 2-(4-bromo-2-ethoxy-5-fluorophenyl)acetic acid (1.776 g, 6.41 mmol) in anh. DMF (20 mL) at RT are added cesium carbonate (3.132 g, 9.61 mmol) and iodomethane (0.60 mL, 9.61 mmol) and the mixture is stirred at RT, under nitrogen, for 30 min. 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 = 1/1) affords methyl 2-(4-bromo-2-ethoxy-5-fluorophenyl)acetate as a clear pink oil (1.880 g, quantitative). LC-MS B: t_R = 0.99 min; $[M+H]^+$ = 291.08.

C.1.57.2. 2-(4-Bromo-2-ethoxy-5-fluorophenyl)acetic acid

A mixture of 2-(4-bromo-2-ethoxy-5-fluorophenyl)acetonitrile (1.738 g, 6.74 mmol), water (6.5 mL), 95% sulfuric acid (7 mL) and acetic acid (8.5 mL) is heated to 110°C, under nitrogen, for 3h. The RM is 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 2-(4-bromo-2-ethoxy-5-fluorophenyl)acetic acid as a colorless solid (1.775 g, 95%). LC-MS B: t_R = 0.85 min; no ionization.

C.1.57.3. 2-(4-Bromo-2-ethoxy-5-fluorophenyl)acetonitrile

A solution of 1-bromo-4-(chloromethyl)-5-ethoxy-2-fluorobenzene (1.860 g, 6.95 mmol) in MeCN (18 mL) and water (2.5 mL) is treated with sodium cyanide (0.461 g, 9.04 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. $MgSO_4$, filtered and concentrated under reduced pressure. Purification by FC (from heptane to EtOAc) affords 2-(4-bromo-2-ethoxy-5-fluorophenyl)acetonitrile as a pale yellow solid (1.734 g, 97%). LC-MS B: t_R = 0.93 min; no ionization.

C.1.57.4. 1-Bromo-4-(chloromethyl)-5-ethoxy-2-fluorobenzene

A cooled (0°C) mixture of (4-bromo-2-ethoxy-5-fluorophenyl)methanol (1.780 g, 7.15 mmol) and zinc chloride (24.4 mg, 0.17 mmol) in anh. DCM (14 mL) is treated dropwise with thionyl chloride (1.04 mL, 14.30 mmol)

and the mixture is stirred at 0°C for 3h. The RM is concentrated under reduced pressure affording 1-bromo-4-(chloromethyl)-5-ethoxy-2-fluorobenzene as a colorless oil (1.860 g, 97%). LC-MS B: t_R = 1.03 min; no ionization.

C.1.57.5. (4-Bromo-2-ethoxy-5-fluorophenyl)methanol

To a cooled (-78°C) solution of methyl 4-bromo-2-ethoxy-5-fluorobenzoate (2.170 g, 7.83 mmol) in anh. THF (50 mL) is added dropwise a solution of diisobutylaluminum hydride (1 M in THF, 23.5 mL, 23.5 mmol) and the mixture is stirred at -78°C, under nitrogen, for 15 min, and then at 0°C for 45 min. The cooled RM is treated successively with water (1 mL), 2.8 N aq. NaOH (1 mL) and water (1 mL) and stirred at RT for 1h. The resulting mixture is filtered over celite and concentrated to dryness under reduced pressure. Purification by FC (from heptane to heptane/EtOAc = 1/1) affords (4-bromo-2-ethoxy-5-fluorophenyl)methanol as a colorless solid (1.780 g, 91%). LC-MS B: t_R = 0.84 min; no ionization.

C.1.57.6. Methyl 4-bromo-2-ethoxy-5-fluorobenzoate

To a solution of methyl 4-bromo-5-fluoro-2-hydroxybenzoate (1.763 g, 6.73 mmol) in anh. DMF (20 mL) at RT are added cesium carbonate (3.287 g, 10.10 mmol) and iodoethane (0.811 mL, 10.10 mmol) and the mixture is stirred at RT, under nitrogen, overnight. Water is added and the obtained solid is filtered, washed with water and dried under high vacuum to afford methyl 4-bromo-2-ethoxy-5-fluorobenzoate as a colorless solid (2.170 g, quantitative). LC-MS B: t_R = 0.94 min; $[M+H]^+$ = 277.09.

C.1.58. 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_2 (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. $MgSO_4$, 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_R = 1.05 min; $[M+H]^+$ = 339.23.

C.1.58.1. 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_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 2-(4-bromo-2-ethoxy-3-fluorophenyl)acetate as a clear oil (1.939 g, 91%). LC-MS B: t_R = 0.99 min; $[M+H]^+$ = 291.10.

C.1.58.2. 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. $MgSO_4$, 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_R = 0.85 min; no ionization.

C.1.58.3. 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. $MgSO_4$, 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_R = 0.97 min; no ionization.

C.1.58.4. 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.

C.1.58.5. (4-Bromo-2-ethoxy-3-fluorophenyl)methanol

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. $MgSO_4$, 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.

C.1.58.6. Ethyl 4-bromo-2-ethoxy-3-fluorobenzoate

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_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 = 3/1) affords ethyl 4-bromo-2-ethoxy-3-fluorobenzoate as a yellow oil (2.920 g, 79%). LC-MS B: t_R = 1.04 min; $[M+H]^+$ = 291.09.

C.1.59. 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',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 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; $[M+H]^+$ = 325.24.

C.1.59.1. Methyl 2-(3-propylthiophen-2-yl)acetate

A mixture of methyl 2-(3-bromothiophen-2-yl)acetate (1.655 g, 7.04 mmol), potassium n-propyltrifluorborate (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. $MgSO_4$, 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.

C.1.59.2. Methyl 2-(3-bromothiophen-2-yl)acetate

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_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 2-(3-bromothiophen-2-yl)acetate as a yellow oil (2.183 g, quantitative). LC-MS B: t_R = 0.86 min; no ionization.

C.1.60. 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 added at RT 4,4,4',4',5,5,5',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

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.

C.1.60.1. 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 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.

C.1.61. 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.

C.1.61.1. Methyl 2-(3-(difluoromethoxy)thiophen-2-yl)acetate

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_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 = 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.

C.1.61.2. 2-(3-(Difluoromethoxy)thiophen-2-yl)acetic acid

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. $MgSO_4$, 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.

C.1.61.3. 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_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 = 4/1) affords 2-(3-(difluoromethoxy)thiophen-2-yl)acetonitrile as a pale yellow oil (0.306 g, 75%). LC-MS B: t_R = 0.78 min; no ionization.

C.1.61.4. 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_R = 0.82 min; no ionization.

C.1.61.5. (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_R = 0.63 min; no ionization.

C.1.61.6. 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_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 = 1/1) affords methyl 3-(difluoromethoxy)thiophene-2-carboxylate as a colorless oil (0.495 g, 97%). LC-MS B: t_R = 0.81 min; no ionization.

D- Preparation of examples

General procedure A: Suzuki coupling with $Pd(PPh_3)_4$

A mixture of the respective pyrimidine halide derivative (A3) (0.15 mmol), the respective boronic acid derivative (A4) (0.18 mmol), and K_2CO_3 2M (0.3 mL, 0.6 mmol) in ethanol (3 mL) is purged with argon, $Pd(PPh_3)_4$ (0.0075 mmol) is added, and the RM is heated at 90°C overnight. Alternatively, the reaction can be performed in a MW apparatus, at 120°C for 15 - 30 min. The RM is filtered through a 0.45 um 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 ($MgSO_4$) and concentrated under reduced pressure. The residue is purified by preparative HPLC or by FC.

General procedure B: Suzuki coupling with $Pd(PPh_3)_4$ followed by ester hydrolysis

A mixture of the respective pyrimidine halide derivative (A3) (0.15 mmol), the respective boronic acid derivative (A4) (0.18 mmol), and K_2CO_3 2M (0.3 mL, 0.6 mmol) in EtOH (3 mL) is purged with argon, $Pd(PPh_3)_4$ (0.0075 mmol) is added, and the RM 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 RM is stirred at RT for 2 – 20h or at 90°C for 0.5 – 20h. It is then filtered through a 0.45 um 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 ($MgSO_4$) and concentrated under reduced pressure. The residue is purified by preparative HPLC or by FC.

General procedure C: Suzuki coupling with $PdCl_2$(dppf) followed by ester hydrolysis

A mixture of the respective pyrimidine halide derivative (A3) (0.15 mmol), the respective boronic acid derivative (A4) (0.18 – 0.3 mmol), and Cs_2CO_3 (0.75 mmol) in THF (4 mL) and water (0.5 mL) is purged with argon, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (0.015 mmol) is added, and the RM is heated at 80°C overnight. NaOH (32% solution, 0.5 mL) is added, and the RM is stirred at 80°C for 2 - 20 h. It is then filtered through a 0.45 um 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 ($MgSO_4$) and concentrated under reduced pressure. The residue is purified by preparative HPLC or by FC.

General procedure D: phosphonium-mediated SNAr

To a solution of 6-hydroxy-pyrimidine derivative (0.1 mmol) in DMF (1 mL) and TEA (0.4 mmol) is added PyBOP (0.16 mmol). The solution is stirred at RT for 15 min – 1h, then the respective aryl-ethylamine (0.125 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 $MgSO_4$, filtered and concentrated. The residue is purified by preparative HPLC or by FC if needed. Alternatively, a solution of 6-hydroxy-pyrimidine derivative (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

(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 $MgSO_4$, filtered and concentrated. The residue is purified by preparative HPLC or by FC if needed.

Compounds of Examples 1 - 155 listed in Table 4 below are prepared by applying either one of the above-mentioned procedures A, B or C to the pyrimidine halide derivatives A.1.1. – A.1.13., A.2.1. – A.2.3., B.1.1. – B.1.9. coupled with boronic acid derivatives or with boronic acid derivatives C.1.1. – C.1.31.

Table 4: Examples 1 - 155

Ex.	Compound	t_R [min] (LC-MS)	MS Data m/z $[M+H]^+$
1	5-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid	0.82 (A)	457.99
2	5-{6-[2-(5-Fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid	1.1 (C)	426.3
3	5-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid	1.1 (C)	424.2
4	5-{6-[2-(5-Chloro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid (*1)	1.2 (C)	442.2
5	5-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid	1.2 (C)	474
6	3-Methyl-5-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid	1.1 (C)	394.2
7	5-{6-[2-(2-Ethyl-5-fluoro-7-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid	1.2 (C)	440.2
8	4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	0.9 (C)	404.4
9	4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-hydroxy-benzoic acid	1.0 (C)	470.1
10	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-hydroxy-benzoic acid	1.0 (C)	438.1
11	4-{6-[2-(4,7-Dichloro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-hydroxy-benzoic acid	1.1 (C)	474.2

12	4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid	1.0 (C)	479
13	4-{6-[2-(2-Cyano-7-methoxy-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid	0.9 (C)	477.2
14	4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid	1.0 (C)	450.3
15	4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)	0.78 (A)	500.12
16	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid	0.77 (A)	452.02
17	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid	1.0 (C)	468.2
18	4-{6-[2-(2-Methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)	0.9 (C)	420.3
19	4-{6-[2-(4-Chloro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid	1.1 (C)	484.2
20	4-{6-[2-(4,7-Dichloro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid	1.1 (C)	504.2
21	4-{6-[2-(6-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)	1.0 (C)	468.2
22	4-{6-[2-(2-Ethyl-5-fluoro-7-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid	0.80 (A)	466.04
23	4-{6-[2-(7-Chloro-5-fluoro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)	1.1 (C)	488.2
24	4-{6-[2-(2-Methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)	0.9 (C)	436.2
25	3-Ethoxy-5-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid	1.2 (C)	472.2
26	5-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid	1.1 (C)	482.9
27	5-{6-[2-(2-Cyano-7-methoxy-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid	0.88 (A)	480.94
28	3-Ethoxy-5-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (*1)	1.1 (C)	488.2
29	5-{6-[2-(4-Chloro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid	1.2 (C)	488.4

30	5-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid (*1)	1.1 (C)	504.2
31	5-{6-[2-(4,5-Difluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid	1.1 (C)	490.3
32	3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid	1.2 (C)	472.2
33	5-[6-(2-Benzo[b]thiophen-3-yl-ethylamino)-pyrimidin-4-yl]-3-ethoxy-thiophene-2-carboxylic acid	1.0 (C)	426.1
34	3-Ethoxy-5-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid	1.0 (C)	472.1
35	5-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid (*1)	1.1 (C)	458.1
36	5-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid (*1)	1.1 (C)	454.1
37	3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (*1)	1.1 (C)	456.1
38	5-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid (*1)	1.1 (C)	488
39	3-Ethoxy-5-{6-[2-(2-ethyl-5-fluoro-7-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid	1.2 (C)	470.1
40	4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-benzoic acid	0.9 (C)	484.1
41	5-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-(2-hydroxy-ethoxy)-thiophene-2-carboxylic acid (*1)	1.0 (C)	488
42	4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethylsulfanyl-benzoic acid	1.0 (C)	464.1
43	2-Ethylsulfanyl-4-{6-[2-(2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.0 (C)	450
44	2-Ethylsulfanyl-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.0 (C)	434.3
45	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid	1.1 (C)	464.2
46	5-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophene-2-carboxylic acid	1.0 (C)	496.3
47	4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-fluoro-6-methylsulfanyl-benzoic acid	1.0 (C)	468.3

48	2-Fluoro-4-{6-[2-(2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methylsulfanyl-benzoic acid	1.0 (C)	454.1
49	2-Fluoro-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methylsulfanyl-benzoic acid	0.9 (C)	438.2
50	2-Chloro-4-{6-[2-(2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methylsulfanyl-benzoic acid	1.1 (C)	484.2
51	2-Chloro-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methylsulfanyl-benzoic acid	1.0 (C)	454.3
52	(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acetic acid	1.1 (C)	485.9
53	4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid	1.0 (C)	477.3
54	4-{6-[2-(2-Cyano-7-methoxy-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid	0.9 (C)	475.2
55	2-Ethoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)	1.0 (C)	482
56	2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	0.78 (A)	466.20
57	4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)	1.0 (C)	498
58	4-{6-[2-(2-Bromo-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)	1.1 (C)	529.3
59	4-{6-[2-(2-Chloro-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)	1.1 (C)	485.9
60	4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid	1.0 (C)	448.3
61	2-Ethoxy-4-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.0 (C)	466.4
62	2-Ethoxy-4-{6-[2-(6-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)	1.0 (C)	466.3
63	4-{6-[2-(4,7-Dichloro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid	1.1 (C)	502.4
64	4-{6-[2-(5-Chloro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)	1.1 (C)	465.9
65	4-{6-[2-(7-Chloro-5-fluoro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)	1.1 (C)	486.2

66	4-{6-[2-(4-Chloro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid	1.1 (C)	482.1
67	2-Ethoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	0.9 (C)	466.3
68	4-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)	1.0 (C)	452.3
69	2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.0 (C)	450.3
70	4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid	1.0 (C)	482.3
71	4-{6-[2-(5,7-Dichloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid	1.1 (C)	486.4
72	2-Ethoxy-4-{6-[2-(2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	0.9 (C)	434.3
73	2-Ethoxy-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)	0.9 (C)	418.3
74	4-{6-[2-(4-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-6-methyl-benzoic acid	0.9 (C)	466.3
75	4-{6-[2-(2-chloro-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid (*1)	1.0 (C)	454.2
76	6-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzofuran-3-carboxylic acid	0.80 (A)	444.15
77	6-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzofuran-2-carboxylic acid	0.9 (C)	444.4
78	5-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzofuran-2-carboxylic acid	0.9 (C)	444.2
79	5-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-3(2H)-one [tautomeric form: 5-(4-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)phenyl)-[1,2,4]oxadiazol-3-ol]	0.9 (C)	462.2
80	2-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-indole-6-carboxylic acid	1.1 (C)	461.3
81	5-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-isoxazol-3-ol [tautomeric form: 5-(4-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)phenyl)isoxazol-3(2H)-one]	1.0 (C)	461.3

82	2-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-indole-4-carboxylic acid	1.0 (C)	461.3
83	4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclopropoxy-benzoic acid	1.0 (C)	494
84	2-Cyclopropoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.0 (C)	494.4
85	2-Cyclopropoxy-4-{6-[2-(4,5-difluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.0 (C)	496
86	4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-(2-hydroxy-ethoxy)-benzoic acid (*1)	0.9 (C)	482
87	4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propylsulfanyl-benzoic acid	1.1 (C)	478.1
88	4-{6-[2-(2-Methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propylsulfanyl-benzoic acid	1.1 (C)	464
89	4-{6-[2-(2-Methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propylsulfanyl-benzoic acid	1.0 (C)	448.4
90	4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropylsulfanyl-benzoic acid	1.1 (C)	478.1
91	2-Isopropylsulfanyl-4-{6-[2-(2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)	1.1 (C)	464.2
92	2-Isopropylsulfanyl-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)	1.0 (C)	448.2
93	2-Fluoro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-propyl-benzoic acid	1.1 (C)	482
94	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isobutyl-benzoic acid	1.1 (C)	478
95	(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acetic acid methyl ester	1.2 (C)	500.3
96	*(E)*-3-(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acrylic acid	1.2 (C)	498.2
97	3-(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-propionic acid	1.1 (C)	500.3
98	4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-benzoic acid	1.1 (C)	512.3
99	4-{6-[2-(6-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid (*1)	1.1 (C)	480.3

100	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid	1.1 (C)	480
101	4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid	1.1 (C)	512.3
102	4-{6-[2-(4,7-Dichloro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid	1.2 (C)	516.4
103	2-Ethoxy-4-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methyl-benzoic acid	0.9 (C)	480
104	(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid	0.9 (C)	491.3
105	(2-Ethoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid	0.9 (C)	496
106	(4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid	0.9 (C)	496.1
107	(2-Ethoxy-4-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid	0.9 (C)	480.3
108	(4-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid	0.9 (C)	466
109	(4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid	0.9 (C)	462.3
110	(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid	0.9 (C)	480.1
111	(4-{6-[2-(4-Chloro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid (*1)	1.0 (C)	496.1
112	(2-Ethoxy-4-{6-[2-(6-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid	0.9 (C)	480.3
113	(4-{6-[2-(7-Chloro-5-fluoro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid (*1)	1.0 (C)	500
114	(4-{6-[2-(4,7-Dichloro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid (*1)	1.0 (C)	516.4
115	2-Difluoromethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.1 (C)	488
116	4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-difluoromethoxy-benzoic acid	1.1 (C)	520
117	(2-Ethoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-acetic acid	0.8 (C)	512.1

118	(2-Ethoxy-4-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-acetic acid (*1)	0.9 (C)	496.1
119	(2-Ethoxy-4-{6-[2-(6-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-acetic acid	0.9 (C)	496.3
120	(4-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-acetic acid	0.8 (C)	482.3
121	(4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-acetic acid	0.8 (C)	512
122	(4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-acetic acid (*1)	0.8 (C)	478.2
123	(4-{6-[2-(4,5-Difluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-acetic acid (*1)	0.8 (C)	513.2
124	(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-acetic acid (*1)	0.8 (C)	480.3
125	{4-[6-(2-Benzo[b]thiophen-3-yl-ethylamino)-pyrimidin-4-yl]-2-ethoxy-phenoxy}-acetic acid	0.8 (C)	450.3
126	rac-2-(4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-propionic acid	0.9 (C)	476
127	2-Butoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.2 (C)	494.3
128	(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenylamino)-acetic acid	0.8 (C)	495.2
129	2-Cyclobutylsulfanyl-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.1 (C)	460.3
130	2-Cyclobutylsulfanyl-4-{6-[2-(2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.2 (C)	490.2
131	4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-(oxetan-3-ylsulfanyl)-benzoic acid	1.0 (C)	492.4
132	4-[6-(2-Benzo[b]thiophen-3-yl-ethylamino)-pyrimidin-4-yl]-2-cyclobutoxy-benzoic acid	1.0 (C)	446.3
133	4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-benzoic acid	0.81 (A)	508.01
134	2-Cyclobutoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.1 (C)	508.1
135	4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-benzoic acid	1.1 (C)	524.4

136	2-Cyclobutoxy-4-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.1 (C)	492.3
137	4-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-benzoic acid (*1)	1.1 (C)	478.3
138	2-Cyclobutoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.1 (C)	492
139	2-Cyclobutoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.0 (C)	492
140	2-Cyclobutoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.1 (C)	476.3
141	2-Cyclobutoxy-4-{6-[2-(4,5-difluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.1 (C)	510
142	{6-[3-Ethoxy-4-(1H-tetrazol-5-yl)-phenyl]-pyrimidin-4-yl}-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethyl]-amine	1.0 (C)	490
143	3-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-propionic acid (*1)	0.9 (C)	510.3
144	2-Butoxy-6-fluoro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.2 (C)	512.3
145	N-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-oxalamic acid	1.0 (C)	509.4
146	2-Cyclobutoxy-3-fluoro-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.1 (C)	526.3
147	4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-3-fluoro-benzoic acid	1.1 (C)	526.3
148	2-Cyclobutoxy-6-fluoro-4-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.2 (C)	510
149	2-Cyclobutoxy-6-fluoro-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.1 (C)	526.1
150	2-Cyclobutoxy-4-{6-[2-(4,5-difluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-6-fluoro-benzoic acid	1.1 (C)	528.3
151	4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-6-fluoro-benzoic acid	1.1 (C)	526.1
152	2-Cyclopentyloxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.2 (C)	506
153	4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclopentyloxy-benzoic acid	1.2 (C)	538.1

154	2-Cyclopentyloxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid	1.2 (C)	490.2
155	3-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(2-ethoxy-4-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)phenyl)-[1,2,4]oxadiazol-5-ol]	1.1 (C)	506.3

Example 156: 3-Ethoxy-5-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)-N-sulfamoylthiophene-2-carboxamide

3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid (Example 32, 75 mg, 0.159 mmol) is dissolved in DMSO/THF (2:1) (3.3 mL) and CDI (38.7 mg, 0.239 mmol) is added. The RM is heated at 60°C for 1h, cooled to RT and treated with sulfamide (33.6 mg, 0.35 mmol) and DBU (0.0594 mL, 0.398 mmol). The RM is stirred at RT for 2h. HCl 2M (5 mL) is added, the precipitate is filtered, then purified by prep HPLC to yield the title compound as a white solid (29 mg, 33%). LC-MS B: t_R = 0.96 min; $[M+H]^+$ = 550.11.

Example 157: N-(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carbonyl)-methanesulfonamide

Following the procedure described for the synthesis of Example 156, with 3-ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid and methanesulfonamide, the title compound is obtained as a white solid. LC-MS B: t_R = 1.04 min; $[M+H]^+$ = 549.13.

Example 158: {6-[4-Ethoxy-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-pyrimidin-4-yl}-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethyl]-amine

Following the general procedure D with 2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine (A.1.4.1.) and 6-(4-ethoxy-5-(1H-tetrazol-5-yl)thiophen-2-yl)pyrimidin-4-ol, the title compound is obtained as a brown solid. LC-MS B: t_R = 0.96 min; $[M+H]^+$ = 496.11.

a) 6-(4-Ethoxy-5-(1H-tetrazol-5-yl)thiophen-2-yl)pyrimidin-4-ol

4-(4-Ethoxy-5-(1H-tetrazol-5-yl)thiophen-2-yl)-6-methoxypyrimidine (30 mg, 0.0986 mmol) is treated with HCl 4M in dioxane (0.5 mL) and the RM is stirred at 55-60 °C overnight. It is then concentrated under reduced pressure and purified by prep. HPLC to afford the title compound as a white solid (12 mg, 42%). LC-MS B: t_R = 0.59 min; $[M+H]^+$ = 291.04.

b) 4-(4-Ethoxy-5-(1H-tetrazol-5-yl)thiophen-2-yl)-6-methoxypyrimidine

To a solution of 3-ethoxy-5-(6-methoxypyrimidin-4-yl)thiophene-2-carbonitrile (72 mg, 0.276 mmol) in toluene (2.1 mL), trimethylsilylazide (0.0544 mL, 0.413 mmol) and dibutyltin oxide (6.86 mg, 0.0276 mmol) are added. The RM is stirred at 110°C overnight in a sealed tube. The solvent is evaporated, then the residue is dissolved in MeOH and adjusted to pH = 10 with NaOH 2M. The solution is loaded onto a PE_AX cartridge for standard

catch&release protocol, which affords the title compound as a yellow solid (43 mg, 51%). LC-MS B: t_R = 0.78 min; $[M+H]^+$ = 305.06.

c) 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 B: t_R = 1.00 min; $[M+H]^+$ = 262.26.

d) 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 NH4OH (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 B: t_R = 0.79 min; $[M+H]^+$ = 280.22.

e) 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 24.5% (8N) (60mL), MeOH is removed under vacuum and the slury is filtered, to afford the title compound as a yellow solid (7.41 g, 99%). LC-MS B: t_R = 0.77 min; $[M+H]^+$ = 281.19.

f) 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), dichloro(1,1'-bis(diphenylphosphino) ferrocene) palladium (II) dichloromethane adduct) (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 $MgSO_4$, filtered and concentrated. Purification by FC (heptane/EtOAc, from 1:0 to 0:1) affords the title compound as a yellow solid (7.87 g, 89%). LC-MS B: t_R = 0.93 min; $[M+H]^+$ = 295.18.

f) 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 C.1.1. using methyl 3-ethoxythiophene-2-carboxylate, and obtained as a white solid; LC-MS B: t_R = 0.63 min; $[M+H]^+$ = 313.13.

Example 159: 3-(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(3-ethoxy-5-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol] (*1)

Following the general procedure D with 2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine (A.1.4.1.) and 3-(3-ethoxy-5-(6-hydroxypyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol, the title compound is obtained as a light brown solid. LC-MS B: t_R = 1.03 min; $[M+H]^+$ = 512.12.

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 affords 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 (Example 158-c, 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.

Example 160: 4-Ethoxy-2-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-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 (0.14 mL, 1.0 mmol) and PyBop (156 mg, 0.3 mmol). The RM is stirred at RT for a few minutes until complete dissolution and 2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine (A.1.4.1.) (56 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 affords the title compound as a yellow solid. LC-MS B: t_R = 1.01 min; $[M+H]^+$ = 473.11.

a) Ethyl 4-ethoxy-2-(6-hydroxypyrimidin-4-yl)thiazole-5-carboxylate

Following the procedure described for the synthesis of Example 159-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 161: 4-Ethyl-2-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiazole-5-carboxylic acid

Following the procedure described for the synthesis of Example 160, using 2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine (A.1.4.1.) and ethyl 4-ethyl-2-(6-hydroxypyrimidin-4-yl)thiazole-5-carboxylate, the title compound is obtained as a yellow solid. LC-MS B: t_R = 1.01 min; $[M+H]^+$ = 457.02.

a) Ethyl 4-ethyl-2-(6-hydroxypyrimidin-4-yl)thiazole-5-carboxylate

Following the procedure described for the synthesis of Example 159-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 162: 3-(4-Ethoxy-2-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiazol-5-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-ethoxy-2-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol] (*1)

Following the general procedure D with 2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine (A.1.4.1.) and 3-(4-ethoxy-2-(6-hydroxypyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol, the title compound is obtained as a yellow solid. LC-MS B: t_R = 1.14 min; $[M+H]^+$ = 513.02.

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 159-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 159-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 159-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_4OH (25%, 4.05 mL, 26.3 mmol) and I2 (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 $NaHSO_3$ 40% (15 mL) and extracted with EtOAc, dried over $MgSO_4$ 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 147-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 rinced with EtOAc. The filtrate is dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue is dissolved in DCM (20 mL) and MnO2 (2701 mg, 26.4 mmol) is added. The mixture is stirred 5h at RT, then filtered over a pad of Celite and rinced 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 163: 3-(4-Ethyl-2-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiazol-5-yl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-ethyl-2-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol]

Following the general procedure D, using 3-(4-ethyl-2-(6-hydroxypyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol and 2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethan-1-amine (A.1.4.1.), the title compound is obtained as a yellow solid. LC-MS B: t_R = 1.09 min; $[M+H]^+$ = 497.00.

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 159-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 159-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 159-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 158-c with 2-(6-ethoxypyrimidin-4-yl)-4-ethylthiazole-5-carboxamide, the title compound is obtained as a beige solid. LC-MS A: 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 158-d 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 161-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_2O.The aqueous phase is then acidified with 2N HCl and extracted with EtOAc (3 x). The combined organic extracts are dried over $MgSO_4$, fitlered 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.

Compounds of Examples 164 - 205 listed in Table 5 below are prepared by applying either one of the above-mentioned procedures A, B or C to the pyrimidine halide derivatives A.1.1. – A.1.15. coupled with boronic acid derivatives or with boronic acid derivatives C.1.1. – C.1.54.

Table 5: Examples 164 - 205

Ex.	Compound	t_R [min] (LC-MS C)	MS Data m/z $[M+H]^+$
164	(4-{6-[2-(2-Cyano-7-methoxy-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid	0.854	489.3
165	(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-6-fluoro-phenyl)-acetic acid	1.047	509.3
166	4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isobutylsulfanyl-benzoic acid	1.202	492.3

167	4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid (*1)	1.076	473
168	(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-acetic acid (*1)	0.858	475
169	(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-phenyl)-acetic acid (*1)	0.965	503.3
170	(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-phenyl)-acetic acid (*1)	0.951	487.3
171	(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-phenyl)-acetic acid (*1)	0.945	503.2
172	4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-benzoic acid (*1)	1.09	489.1
173	4-{6-[2-(2-Cyano-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid (*1)	0.916	445
174	(4-{6-[2-(2-Cyano-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-acetic acid (*1)	0.771	443.1
175	(4-{6-[2-(2-Cyano-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid (*1)	0.82	457.1
176	3-(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-propionic acid (*1)	0.863	519.2
177	3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5(4H)-one [tautomeric form: 3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5-ol]	1.023	462.3
178	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzamide	0.84	421.4
179	2-Ethylsulfanyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)	1.1	482.3
180	3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-4-hydroxy-cyclobut-3-ene-1,2-dione	0.849	474.1
181	2-Ethyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid methyl ester	1.202	464.3
182	(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isobutyl-phenyl)-acetic acid (*1)	1.014	492.2
183	[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethyl]-[6-(1H-indol-5-yl)-pyrimidin-4-yl]-amine	0.858	417

184	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isobutoxy-benzoic acid (*1)	1.168	494
185	(2-Ethyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid (*1)	0.911	464.3
186	(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-phenyl)-acetic acid (*1)	0.965	478.3
187	(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-trifluoromethoxy-phenyl)-acetic acid (*1)	1.134	520.3
188	N-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-formamide	0.82	421.3
189	(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-oxo-acetic acid	0.984	494.1
190	(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-phenyl)-acetic acid (*1)	0.974	494.1
191	N-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-formamide	0.922	465.3
192	(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-phenyl)-acetic acid (*1)	0.959	494.1
193	2-Ethyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)	1.018	450.3
194	(2-Ethyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methyl-phenyl)-acetic acid (*1)	0.926	478.3
195	2-Cyclopropoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (*1)	1.046	478.2
196	(2-Cyclopropoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid (*1)	0.95	492.3
197	(3-Ethyl-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acetic acid (*1)	1.067	470.3
198	(2-Chloro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methyl-phenyl)-acetic acid (*1)	1.018	484
199	3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid (*1)	0.994	455.3
200	1-Ethyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-pyrrole-2-carboxylic acid (*1)	0.824	439.3
201	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1-propyl-1H-pyrrole-2-carboxylic acid (*1)	0.868	453.3

202	5-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-isoxazol-3-ol [tautomeric form: 5-(2-ethoxy-4-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)phenyl)isoxazol-3(2H)-one]	1.098	505.3
203	5-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-isoxazol-3-ol [tautomeric form: 5-(4-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)-2-methoxyphenyl)isoxazol-3(2H)-one]	1.028	491.3
204	(E)-3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acrylic acid (*1)	0.945	448
205	5-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methyl-1H-pyrrole-3-carboxylic acid (*1)	0.815	425

Example 206: 4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzamide

To a solution of 4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid (Example 45, 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 (15 mg, 40%). LC-MS C: t_R = 0.926 min; $[M+H]^+$ = 463.3.

Following the procedure described for Example 206, with 4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid (Example 45) and the corresponding commercially available amines, the following examples are synthesized:

Table 6

Ex.	Compound	t_R [min] (LC-MS C)	MS Data m/z $[M+H]^+$
207	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-2-methyl-propyl)-2-propyl-benzamide	0.974	535
208	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-(2-methoxy-ethyl)-2-propyl-benzamide	1.003	521.2
209	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-ethyl)-2-propyl-benzamide	0.897	507.3
210	4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-methyl-2-propyl-benzamide	0.965	477.2

Following the procedure described for Example 206, with 2-ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid (Example 56) and the corresponding commercially available amines, the following examples are synthesized:

Table 7

Ex.	Compound	t_R [min] (LC-MS C)	MS Data m/z $[M+H]^+$
211	2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-ethyl)-benzamide	0.922	509.1
212	2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-methyl-benzamide	1.003	479.3
213	2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzamide	0.951	465.3

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By applying either one of the above-mentioned General Procedures A, B or C to the pyrimidine halide derivatives A.1.1. – A.1.15. coupled with commercial boronic acid derivatives or with boronic acid derivatives C.1.1. – C.1.XX, the following examples are synthesized:

Ex.	Compound	t_R [min] (LC-MS method)	MS Data m/z $[M+H]^+$
214	2-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-pyrazol-1-yl)-2-methyl-propionic acid (*1)	0.824 (C)	454.3
215	1-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-cyclopropanecarboxylic acid (*1)	0.97 (C)	506.2
216	(2-Ethoxy-3-fluoro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid (*1)	0.985 (C)	498.3
217	(2-Ethoxy-5-fluoro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid (*1)	1.01 (C)	498.3
218	1-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-phenyl)-cyclopropanecarboxylic acid (*1)	1.015 (C)	504.1
219	(5-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-propyl-thiophen-2-yl)-acetic acid (*1)	1.126 (C)	484.3
220	(3-Difluoromethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acetic acid (*1)	1.187 (C)	508.2
221	2-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-indole-7-carboxylic acid (*1)	1.197 (C)	461.3

222	2-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzo[b]thiophene-7-carboxylic acid (*1)	1.262 (C)	478.2
223	3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-propionic acid (*1)	0.62 (B)	480.24

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 bioavailablility 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.

Tumor growth inhibition assay

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% CO2, 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 $1x10^6$ EMT-6 cells in 200 µL of RPMI 1640 into the right flank or by injection of $2.5x10^5$ 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 crinerce 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 = ($width^2$ x length)/2.

When tumors reach between 60 and $100mm^3$ (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.

Biological 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 PathHunterTM 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 ProLinkTM 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 µl 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 ± STDEV. (each concentration is measured in duplicate)

IC_{50} 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% 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: 100uM in DMSO) is used as agonist at 20nM 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. 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 μl 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 ± STDEV. (each concentration is measured in duplicate)

IC_{50} 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 EP2 and EP4 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_2 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_2 (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_2 (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_{50} 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_2 (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_2 (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 ± STDEV (each concentration is measured in duplicate) is calculated.

IC_{50} 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 of exemplified compounds are displayed in *Table 8* (in cAMP assays, except for compounds marked with * measured in beta-arrestin):

Table 8

Ex.	hEP2 b-arr IC_{50}	hEP4 b-arr IC_{50}	hEP2 cAMP IC_{50}	hEP4 cAMP IC_{50}	Ex.	hEP2 b-arr IC_{50}	hEP4 b-arr IC_{50}	hEP2 cAMP IC_{50}	hEP4 cAMP IC_{50}
1	59	142		22	**113**		209	284	765
2	25	189	23	117	**114**		246	477	781
3	18	202	18	222	**115**	16	208	8	60
4	11	262	33	394	**116**	30	297	35	223
5	106	247	177	479	**117**	20	23	101	54
6	5	673	4	549	**118**	16	29	112	87
7	283	577	198	624	**119**	21	143	119	110
8	16	1170	8	369	**120**	29	290	59	123
9	118	1650	44	550	**121**	27	75	155	129
10	58	1040	32	860	**122**	14	83	40	136
11	99	3090	71		**123**		142	359	219
12	4	112	4	20	**124**	26		115	310
13	51	114	32	27	**125**			359	426
14	4	195	6	105	**126**	104	423	233	425
15	6	168	21	134	**127**	16	225	106	873

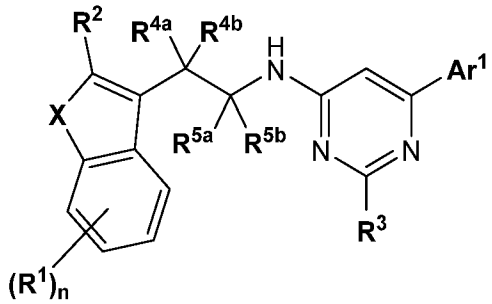
16	13	391	21	189	**128**			37	82
17	5	248	9	243	**129**	6	1410	15	795
18	1	1200	1	414	**130**	12	193	20	980
19	12	414	83	468	**131**	12	1220	22	625
20	30	762	26	532	**132**	58	561	167	166
21	4	283	24	564	**133**	25	74	68	170
22	101	493	172	661	**134**	27	893	46	194
23	9	488	27	667	**135**	14	235	30	198
24	3	3420	4	795	**136**	13	155	91	411
25	2	7	8	1	**137**	15	258	49	423
26			1	2	**138**	14	269	75	478
27		2	11	4	**139**	51	209	245	481
28	2	5	11	5	**140**	37	1420	72	580
29	14	25	14	9	**141**	140	340	111	582
30	10	18	8	11	**142**	12	41	38	105
31	11	27	10	13	**143**	52	63	86	115
32	2	16	2	13	**144**	26	92	26	112
33	19	168	17	18	**145**	13		76	271
34	6	12	6	22	**146**	47	357	47	243
35	3	35	2	36	**147**	213	873	117	889
36	1	26	4	44	**148**	30	43	109	238
37	2	42	2	49	**149**	13	67	114	241
38	9	12	12	80	**150**	109	363	97	450
39	31	50	28	112	**151**	60	163	95	631
40	48	680	94	433	**152**	27	337	84	581
41			13	42	**153**	46	157	212	827
42	4	328	14	224	**154**	47	911	70	901
43	3	1080	4	497	**155**	18	47	87	108
44	1	1020	4	1380	**156**	5	26	10	163
45	20	57	48	147	**157**	8	42	18	69
46	46	93	31	30	**158**	6	7	4	20
47	10	807	12	989	**159**		3	11	5
48	5	3380	2		**160**	15	16	10	18
49	2	3620	1		**161**	61	256	27	363
50	18	432	13	605	**162**	6	5	35	51

51	10	3490	1		**163**	26	17	20	429
52	46	133	95	231	**164**	504	50	348	17
53	9	34	7	44	**165**	28	54	129	40
54	194	60	77	47	**166**	31	254	183	1130
55	15	117	40	138	**167**	5	34	11	29
56	13	47	19	186	**168**	65	66	3030	2990
57	17	287	44	220	**169**	30	100	142	30
58	12	454	17	278	**170**	19	19	116	13
59	15	625	12	285	**171**	59	57	275	42
60	7	372	15	344	**172**	40	166	50	70
61	22	245	60	356	**173**	8	757		
62	12	499	14	393	**174**	135	723		
63	27	461	64	445	**175**	89	492		
64	11	522	7	546	**176**	9	19	37	12
65	16	428	15	565	**177**	47	212		
66	27	407	101	607	**178**	48	331		
67	73	369	142	635	**179**	8	184		
68	14	659	39	714	**180**	20	120		
69	24	668	74	760	**181**	126	423		
70	37	394	80	985	**182**	41	164	617	378
71	7	958	10	1030	**183**	40	210		
72	3	2250	8	1590	**184**	7	311	39	553
73	5	3500	4		**185**	50	134		
74			273	644	**186**	22	242	309	252
75	8	4300	9	1160	**187**	79	425		
76	10	1140	39	523	**188**	98	694		
77	6	1310	8	130	**189**	20	92	27	121
78			7	87	**190**	28	200	274	219
79	26	263	106	91	**191**	45	135		
80	13		20	306	**192**	72	261		
81		202	392	323	**193**	18	667		
82	13	155	21	138	**194**	47	96	326	71
83	22	101	44	111	**195**	4	111	6	48
84	21	80	21	117	**196**	16	99	50	100
85	68	374	49	258	**197**	85	146		

86	19	4520	11	289	**198**	77	175		
87	5	318	15	451	**199**	5	363		
88	21	1030	11	695	**200**	63	550		
89	10	1030	5	1140	**201**	34	351		
90	11	247	35	338	**202**	17	100	75	297
91	20	843	10	539	**203**	16	239		
92	6	816	6	672	**204**	108	1030		
93	36		35	362	**205**	74	771		
94	45		92	302	**206**	10	288		
95		484	647	855	**207**	26	335		
96	20	16	121	42	**208**	62	837		
97	49	84	120	105	**209**	8	280		
98	55	340	53	216	**210**	19	469		
99	5	238	30	450	**211**	30	367		
100	12	299	20	457	**212**	11	667		
101	22	505	85	482	**213**	10	405		
102	26	810	54	867	**214**	237	388		
103	79	521	111	331	**215**	143	151		
104	36	161	48	30	**216**	41	234		
105	33	58	157	125	**217**	126	847		
106		159	396	247	**218**	95	143		
107	38	167	249	255	**219**	41	211		
108	31		107	264	**220**	44	407		
109	24	405	95	290	**221**	24	908		
110	25	403	160	296	**222**	14	453		
111		197	561	433	**223**	35	487		
112	42	665	188	450					

Claims

1. A compound of formula (I)



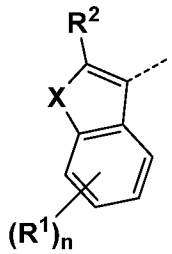
Formula (I)

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 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)

the fragment



is substituted with R^2, wherein R^2 represents hydrogen, (C_{1-4})alkyl, halogen, or cyano; and

is optionally substituted with $(R^1)_n$; wherein $(R^1)_n$ represents one, two or three optional substituents, wherein said substituents R^1 are independently selected from (C_{1-3})alkyl, (C_{1-3})alkoxy, halogen, (C_{1-3})fluoroalkyl, (C_{1-3})fluoroalkoxy, or cyano;

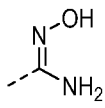
X represents S or O;

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;

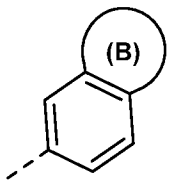
R^{5a} and R^{5b} independently represent hydrogen, methyl, or R^{5a} and R^{5b} together with the carbon atom to which they are attached represent a cycloprop-1,1-diyl group;

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;
  - (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_{4-6})cycloalkyl containing a ring oxygen atom, wherein said (C_{4-6})cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy;
  - (C_{3-6})cycloalkyl-oxy;
  - hydroxy;
  - -**X**^{1}-CO-**R**^{O1}, wherein
    - **X**^{1} represents a direct bond, (C_{1-3})alkylene, -O-(C_{1-3})alkylene-*, -NH-(C_{1-3})alkylene-*, -S-CH_2-*, -CF_2-, –CH=CH-, –CH≡CH-, -NH-CO-*, -CO-, or (C_{3-5})cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-**R**^{O1} group; and
    - **R**^{O1} represents
      - -OH;
      - -O-(C_{1-4})alkyl;
      - -NH-SO_2-**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})alkylene wherein the (C_{3-6})cycloalkyl optionally contains a ring oxygen atom, (C_{1-3})fluoroalkyl, or -NH_2;
      - -O-CH_2-CO-**R**^{O4}, wherein **R**^{O4} repesents hydroxy, or (C_{1-4})alkoxy, or -N[(C_{1-4})alkyl]$_2$;
      - -O-CH_2-O-CO-**R**^{O5}, wherein **R**^{O5} repesents (C_{1-4})alkyl or (C_{1-4})alkoxy;
      - -O-CH_2-CH_2-N[(C_{1-4})alkyl]$_2$; or
      - (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyloxy-;
  - -CO-CH_2-OH;
  -  ;
  - 2-hydroxy-3,4-dioxo-cyclobut-1-enyl;
  - hydroxy-(C_{1-4})alkyl;
  - dihydroxy-(C_{2-4})alkyl;

- hydroxy-(C_{2-4})alkoxy;
- (C_{1-4})alkoxy-(C_{2-4})alkoxy;
- -(CH_2)$_r$-CO-N$R^{N3}R^{N4}$ wherein **r** represents the integer 0 or 1; and wherein R^{N3} and R^{N4} independently represent hydrogen, (C_{1-4})alkyl, hydroxy-(C_{2-4})alkyl, (C_{1-3})alkoxy-(C_{2-4})alkyl, or hydroxy;
- -X^2-N$R^{N1}R^{N2}$, wherein X^2 represents -(CH_2)$_m$-, wherein **m** represents the integer 0 or 1; or X^2 represents -O-CH_2-CH_2-*,wherein the asterisk indicates the bond that is linked to the -N$R^{N1}R^{N2}$ group; and wherein
  - R^{N1} and R^{N2} independently represent hydrogen, (C_{1-4})alkyl, (C_{1-4})alkoxy-(C_{2-4})alkyl, (C_{3-6})cycloalkyl, or (C_{2-3})fluoroalkyl;
  - or R^{N1} independently represents hydrogen or (C_{1-4})alkyl, and R^{N2} independently represents –CO-H, –CO-(C_{1-3})alkyl, –CO-(C_{1-3})alkylene-OH, or –CO-O-(C_{1-3})alkyl;
  - or R^{N1} and R^{N2} 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-N$R^{N5}R^{N6}$ wherein R^{N5} and R^{N6} independently represent hydrogen or (C_{1-4})alkyl;
- -SO_2-R^{S1} wherein R^{S1} represents hydroxy, (C_{1-4})alkyl, or -N$R^{N7}R^{N8}$ wherein R^{N7} and R^{N8} independently represent hydrogen or (C_{1-3})alkyl;
- -S-R^{S2} wherein R^{S2} represents (C_{1-4})alkyl, or (C_{3-6})cycloalkyl optionally containing one ring oxygen atom;
- -(CH_2)$_q$-HET^1, wherein **q** represents the integer 0, 1 or 2; and wherein HET^1 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;
- -(CH_2)$_p$-**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_{1-4})alkyl, (C_{1-4})alkoxy, -COOH, hydroxy, hydroxy-(C_{1-3})alkyl, (C_{3-5})cycloalkyl optionally containing one ring oxygen atom, or -N$R^{N9}R^{N10}$ wherein R^{N9} and R^{N10} independently represent hydrogen, (C_{1-3})alkyl, or hydroxy-(C_{2-4})alkyl;
- or Ar^1 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_{1-4})alkyl; (C_{1-4})alkoxy; (C_{1-3})fluoroalkyl; (C_{1-3})fluoroalkoxy; halogen; cyano; hydroxy, or -(C_{0-3})alkylene-COOR^{O2} wherein R^{O2} repesents hydrogen or (C_{1-4})alkyl;

- or **Ar**^{1} represents a group of the structure (Ar-III):

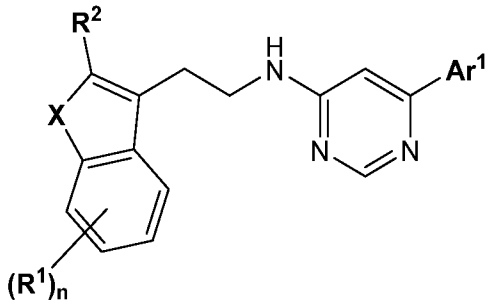


(Ar-III)

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; wherein said ring (B) independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from oxo, (C_{1-6})alkyl and -(C_{0-3})alkylene-COO**R**^{O3} wherein **R**^{O3} repesents hydrogen or (C_{1-3})alkyl;

or a pharmaceutically acceptable salt thereof.

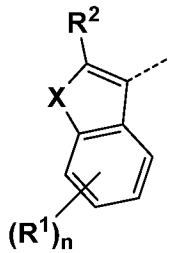
2. A compound of formula (II)



Formula (II)

wherein in compounds of the formula (II)

the fragment



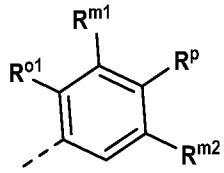
is substituted with **R**^{2}, wherein **R**^{2} represents hydrogen, (C_{1-4})alkyl, halogen, or cyano; and

is optionally substituted with (**R**^{1})$_n$; wherein (**R**^{1})$_n$ represents one, two or three optional substituents, wherein said substituents **R**^{1} are independently selected from (C_{1-3})alkyl, (C_{1-3})alkoxy, halogen, (C_{1-3})fluoroalkyl, (C_{1-3})fluoroalkoxy, or cyano;

X represents S or O;

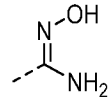
Ar^1 represents

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



(Ar-I)

wherein

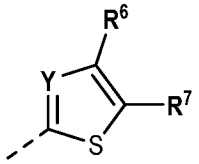
- **R^p** represents
  - (C_{4-6})cycloalkyl containing a ring oxygen atom, wherein said (C_{4-6})cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy;
  - hydroxy;
  - -**X^1**-CO-**R^{O1}**, wherein
    - **X^1** represents a direct bond, (C_{1-3})alkylene, -O-(C_{1-3})alkylene-*, -NH-(C_{1-3})alkylene-*, -S-CH_2-*, -CF_2-, –CH=CH-, –CH≡CH-, -NH-CO-*, -CO-, or (C_{3-5})cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-**R^{O1}** group; and
    - **R^{O1}** represents
      - -OH;
      - -O-(C_{1-4})alkyl;
      - -NH-SO_2-**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})alkylene wherein the (C_{3-6})cycloalkyl optionally contains a ring oxygen atom, (C_{1-3})fluoroalkyl, or -NH_2;
      - -O-CH_2-CO-**R^{O4}**, wherein **R^{O4}** repesents hydroxy, or (C_{1-4})alkoxy, or -N[(C_{1-4})alkyl]$_2$;
      - -O-CH_2-O-CO-**R^{O5}**, wherein **R^{O5}** repesents (C_{1-4})alkyl or (C_{1-4})alkoxy;
      - -O-CH_2-CH_2-N[(C_{1-4})alkyl]$_2$; or
      - (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyloxy-;
  - 

;
  - 2-hydroxy-3,4-dioxo-cyclobut-1-enyl;
  - hydroxy-(C_{1-4})alkyl;
  - hydroxy-(C_{2-4})alkoxy;

- $-(CH_2)_r-CO-NR^{N3}R^{N4}$ wherein **r** represents the integer 0 or 1; and wherein R^{N3} and R^{N4} independently represent hydrogen, (C_{1-4})alkyl, hydroxy-(C_{2-4})alkyl, (C_{1-3})alkoxy-(C_{2-4})alkyl, or hydroxy;
- $-NR^{N1}R^{N2}$, 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;
- -NH-CO-$NR^{N5}R^{N6}$ wherein R^{N5} and R^{N6} independently represent hydrogen or (C_{1-4})alkyl;
- $-SO_2-R^{S1}$ wherein R^{S1} represents (C_{1-4})alkyl, or $-NR^{N7}R^{N8}$ wherein R^{N7} and R^{N8} independently represent hydrogen or (C_{1-3})alkyl;
- $-(CH_2)_q$-**HET**^{1}, wherein **q** represents the integer 0, 1 or 2; and wherein **HET**^{1} 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;
- $-(CH_2)_p$-**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_{1-4})alkyl, (C_{1-4})alkoxy, -COOH, hydroxy, hydroxy-(C_{1-3})alkyl, (C_{3-5})cycloalkyl optionally containing one ring oxygen atom, or $-NR^{N9}R^{N10}$ wherein R^{N9} and R^{N10} independently represent hydrogen, (C_{1-3})alkyl, or hydroxy-(C_{2-4})alkyl;

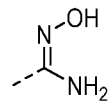
- R^{m1} represents
  - hydrogen;
  - (C_{1-6})alkyl;
  - (C_{1-4})alkoxy;
  - (C_{1-3})fluoroalkyl;
  - (C_{1-3})fluoroalkoxy;
  - halogen;
  - (C_{3-6})cycloalkyl;
  - (C_{3-6})cycloalkyl-oxy;
  - hydroxy;
  - hydroxy-(C_{2-4})alkoxy;
  - $-X^2-NR^{N1}R^{N2}$, wherein X^2 represents a direkt bond; or X^2 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^{N1} and R^{N2} independently represent hydrogen, (C_{1-4})alkyl, or (C_{3-6})cycloalkyl;
  - $-S-R^{S2}$ wherein R^{S2} represents (C_{1-4})alkyl, or (C_{3-6})cycloalkyl optionally containing one ring oxygen atom;
- R^{m2} represents hydrogen, methyl, fluoro, or chloro; and
- R^{o1} represents hydrogen; or, in case R^{m2} represents hydrogen, R^{o1} represents hydrogen or fluoro;

- or **Ar**[1] represents a 5-membered heteroaryl group of the structure (Ar-II):



(Ar-II)

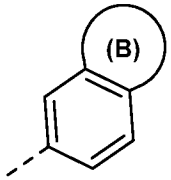
wherein

- **Y** represents C**R**[8] wherein **R**[8] represents hydrogen or halogen; or **Y** represents N;
- **R**[7] represents
  - (C_{4-6})cycloalkyl containing a ring oxygen atom, wherein said (C_{4-6})cycloalkyl containing a ring oxygen atom is unsubstituted or mono-substituted with hydroxy;
  - -**X**[1]-CO-**R**[O1], wherein
    - **X**[1] represents a direct bond, (C_{1-3})alkylene, -O-(C_{1-3})alkylene-*, -NH-(C_{1-3})alkylene-*, -S-CH_2-*, -CF_2-, –CH=CH-, –CH≡CH-, -NH-CO-*, -CO-, or (C_{3-5})cycloalkylene; wherein the asterisks indicate the bond that is linked to the -CO-**R**[O1] group; and
    - **R**[O1] represents
      - -OH;
      - -O-(C_{1-4})alkyl;
      - -NH-SO_2-**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})alkylene wherein the (C_{3-6})cycloalkyl optionally contains a ring oxygen atom, (C_{1-3})fluoroalkyl, or -NH_2;
      - -O-CH_2-CO-**R**[O4], wherein **R**[O4] repesents hydroxy, or (C_{1-4})alkoxy, or -N[(C_{1-4})alkyl]$_2$;
      - -O-CH_2-O-CO-**R**[O5], wherein **R**[O5] repesents (C_{1-4})alkyl or (C_{1-4})alkoxy; or
      - -O-CH_2-CH_2-N[(C_{1-4})alkyl]$_2$;
      - (5-methyl-2-oxo-[1,3]dioxol-4-yl)-methyloxy-;
    -  ;
  - 2-hydroxy-3,4-dioxo-cyclobut-1-enyl;
  - hydroxy-(C_{1-4})alkyl;
  - hydroxy-(C_{2-4})alkoxy;
  - -(CH_2)$_r$-CO-N**R**[N3]**R**[N4] wherein **r** represents the integer 0 or 1; and wherein **R**[N3] and **R**[N4] independently represent hydrogen, (C_{1-4})alkyl, hydroxy-(C_{2-4})alkyl, (C_{1-3})alkoxy-(C_{2-4})alkyl, or hydroxy;
  - -N**R**[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;

- -NH-CO-N$R^{N5}R^{N6}$ wherein R^{N5} and R^{N6} independently represent hydrogen or (C_{1-4})alkyl;
- -SO_2-R^{S1} wherein R^{S1} represents (C_{1-4})alkyl, or -N$R^{N7}R^{N8}$ wherein R^{N7} and R^{N8} independently represent hydrogen or (C_{1-3})alkyl;
- -(CH_2)$_q$-**HET**^{1}, wherein **q** represents the integer 0, 1 or 2; and wherein **HET**^{1} 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;
- -(CH_2)$_p$-**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_{1-4})alkyl, (C_{1-4})alkoxy, -COOH, hydroxy, hydroxy-(C_{1-3})alkyl, (C_{3-5})cycloalkyl optionally containing one ring oxygen atom, or -N$R^{N9}R^{N10}$ wherein R^{N9} and R^{N10} independently represent hydrogen, (C_{1-3})alkyl, or hydroxy-(C_{2-4})alkyl;

- R^6 represents
  - (C_{1-6})alkyl;
  - (C_{1-4})alkoxy;
  - (C_{1-3})fluoroalkyl;
  - (C_{1-3})fluoroalkoxy;
  - halogen;
  - hydroxy;
  - (C_{3-6})cycloalkyl;
  - (C_{3-6})cycloalkyl-oxy;
  - hydroxy-(C_{2-4})alkoxy;
  - -X^2-N$R^{N1}R^{N2}$, wherein X^2 represents a direkt bond; or X^2 represents -O-CH_2-CH_2-*, wherein the asterisk indicates the bond that is linked to the -N$R^{N1}R^{N2}$ group; and wherein R^{N1} and R^{N2} independently represent hydrogen, (C_{1-4})alkyl, or (C_{3-6})cycloalkyl;
  - -S-R^{S2} wherein R^{S2} represents (C_{1-4})alkyl, or (C_{3-6})cycloalkyl optionally containing one ring oxygen atom;

- or Ar^1 represents 8- to 10-membered bicyclic heteroaryl; wherein said 8- to 10-membered bicyclic heteroaryl independently is mono-substituted with -(C_{0-3})alkylene-COOR^{O2} wherein R^{O2} repesents hydrogen or (C_{1-4})alkyl;
- or Ar^1 represents a group of the structure (Ar-III):

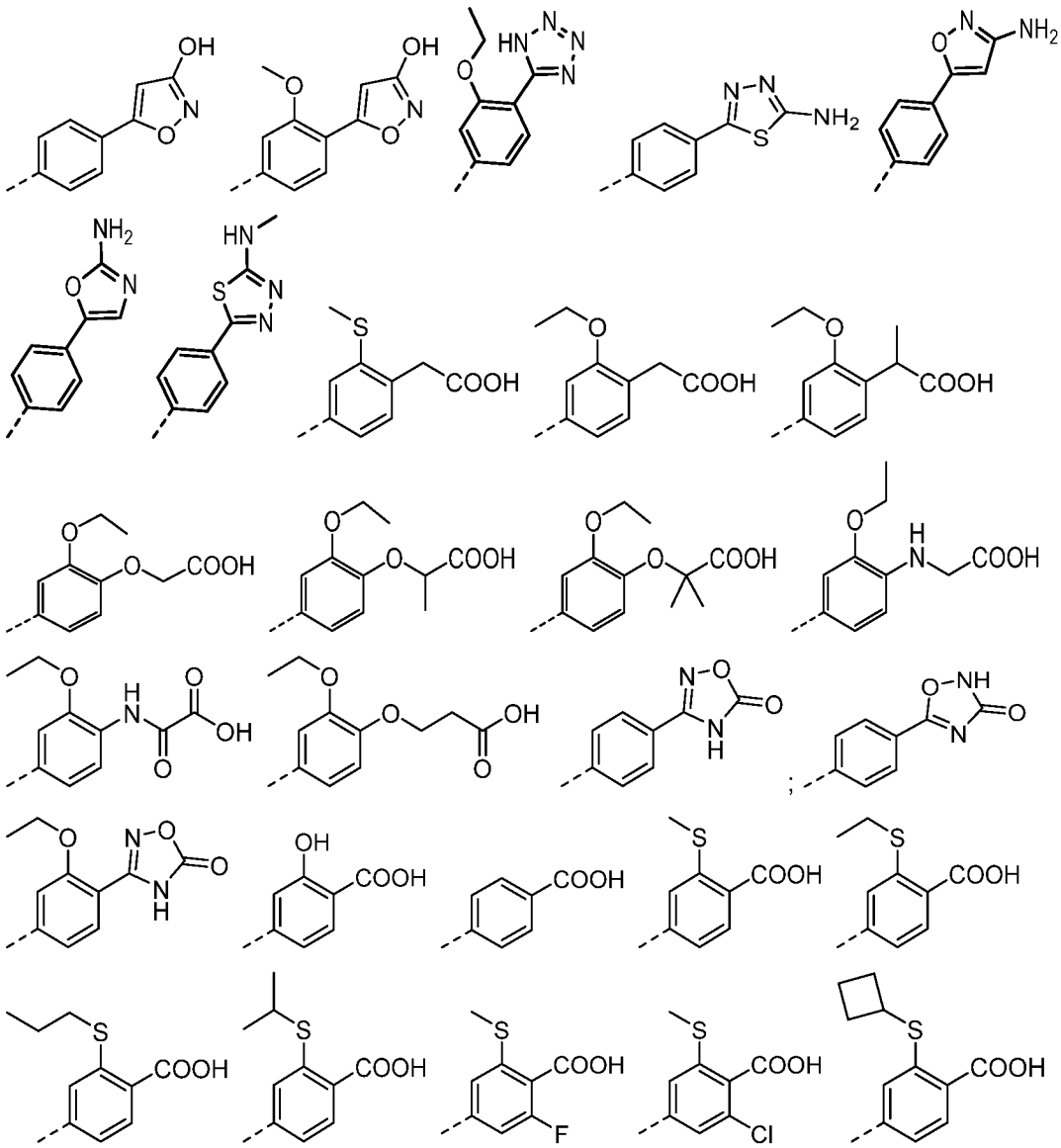


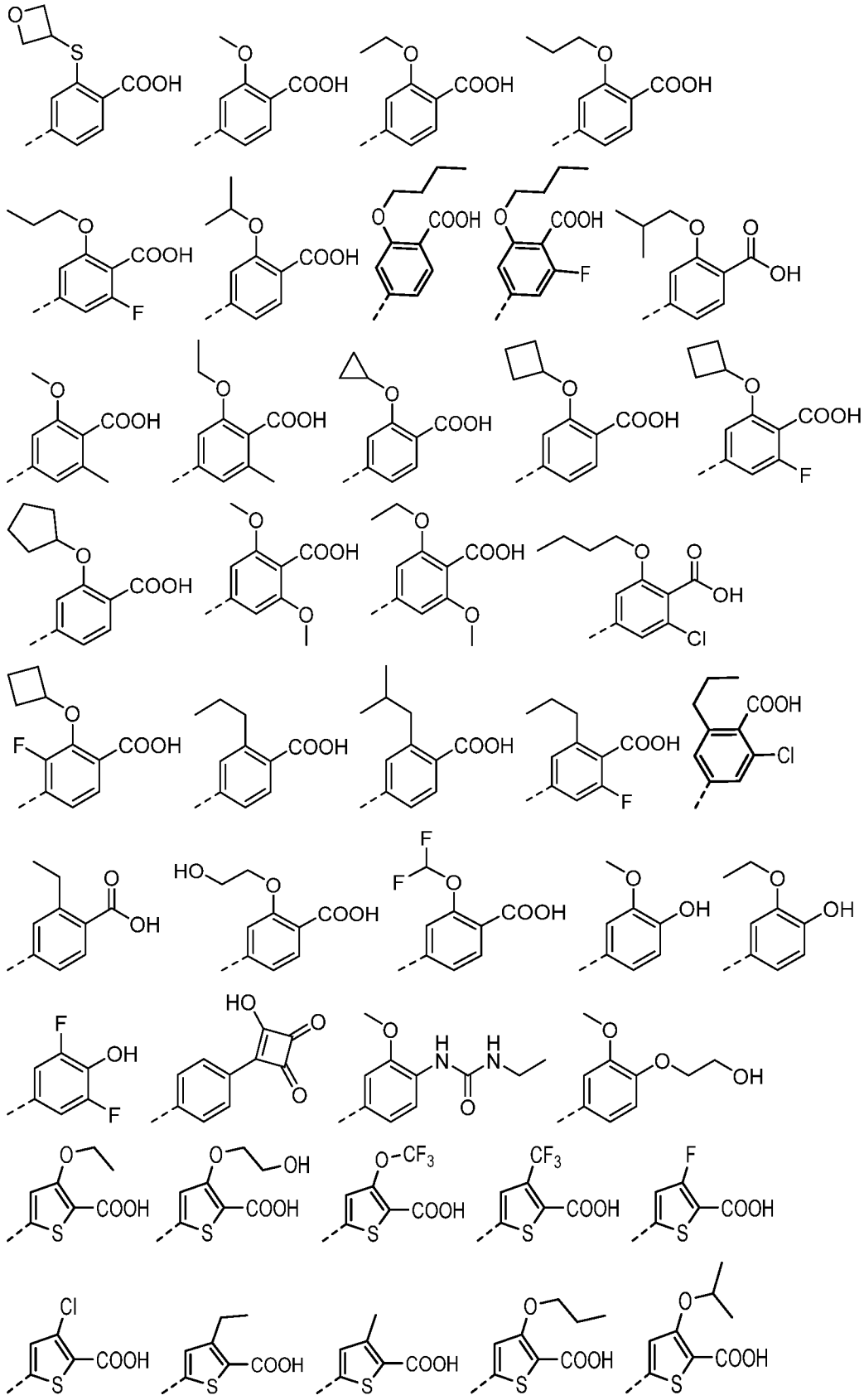
(Ar-III)

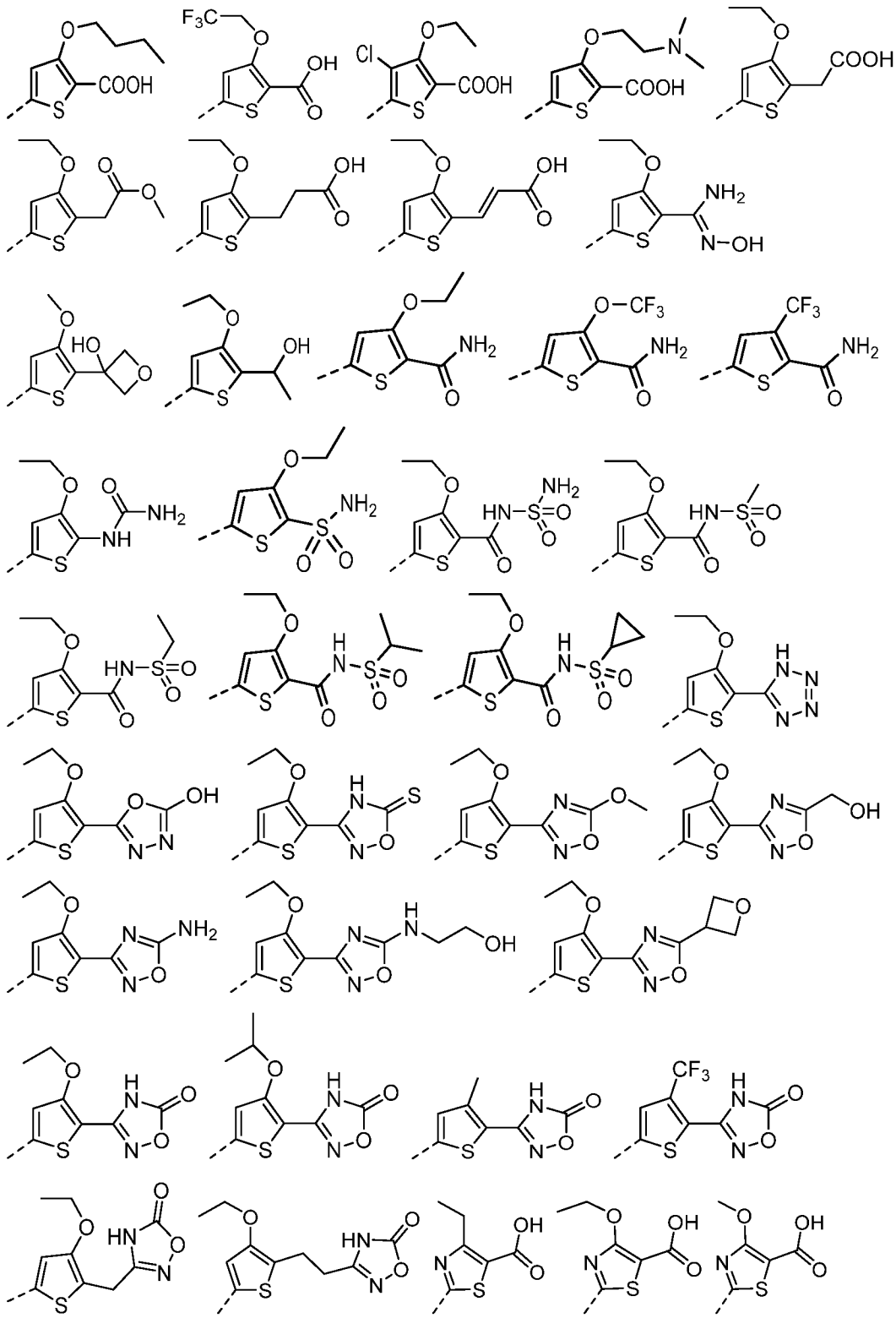
which is selected from 2-oxo-2,3-dihydro-benzooxazol-6-yl, 3-methyl-2-oxo-2,3-dihydro-benzooxazol-5-yl, 1-methyl-3-oxo-2,3-dihydro-1H-indazol-6-yl, 2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-6-yl, 1-oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydro-quinazolin-7-yl,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

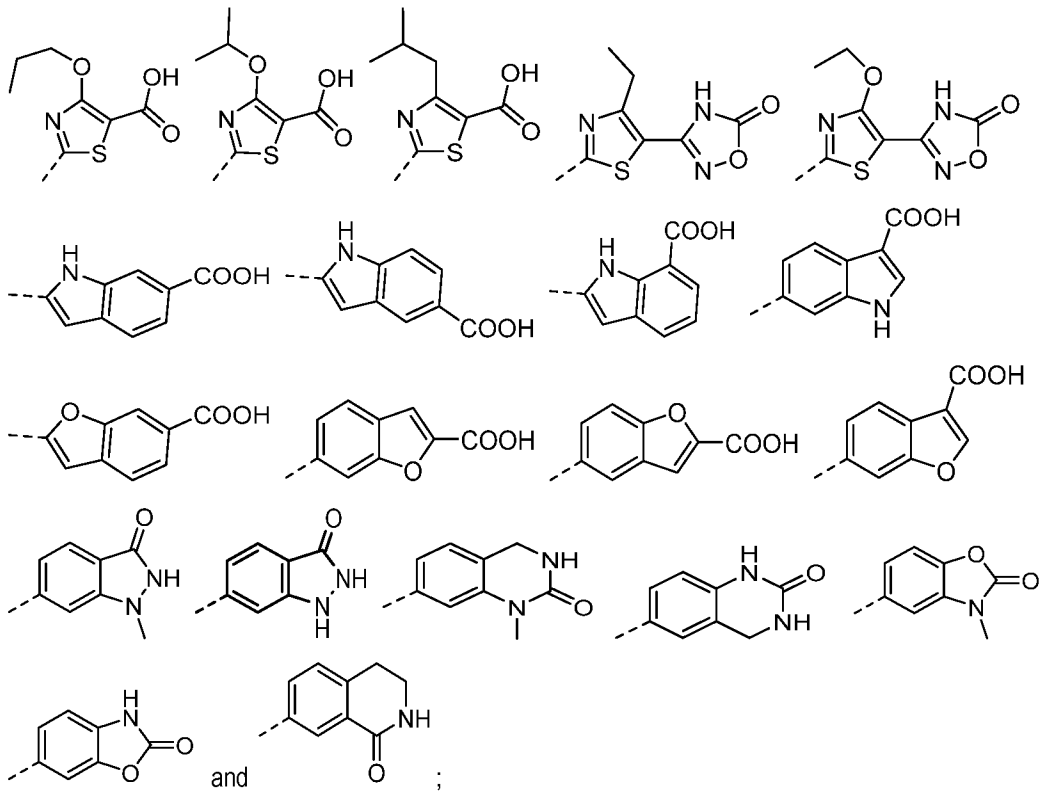
or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2; wherein **Ar**[1] represents a group selected from:





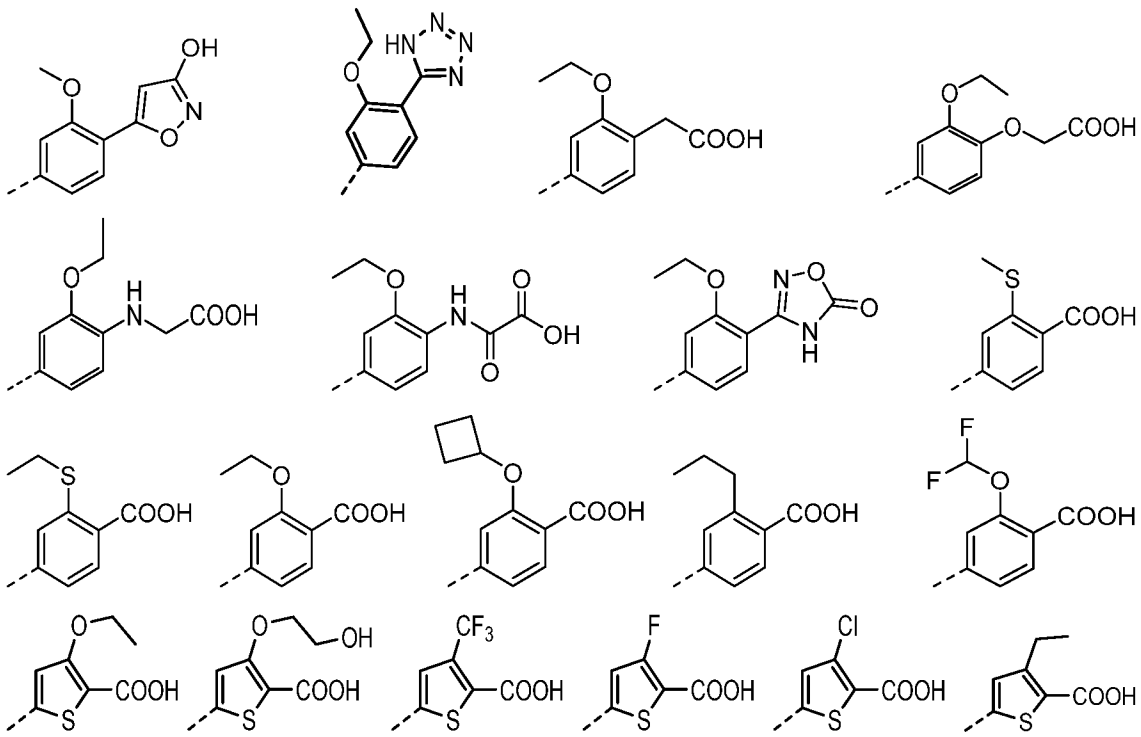


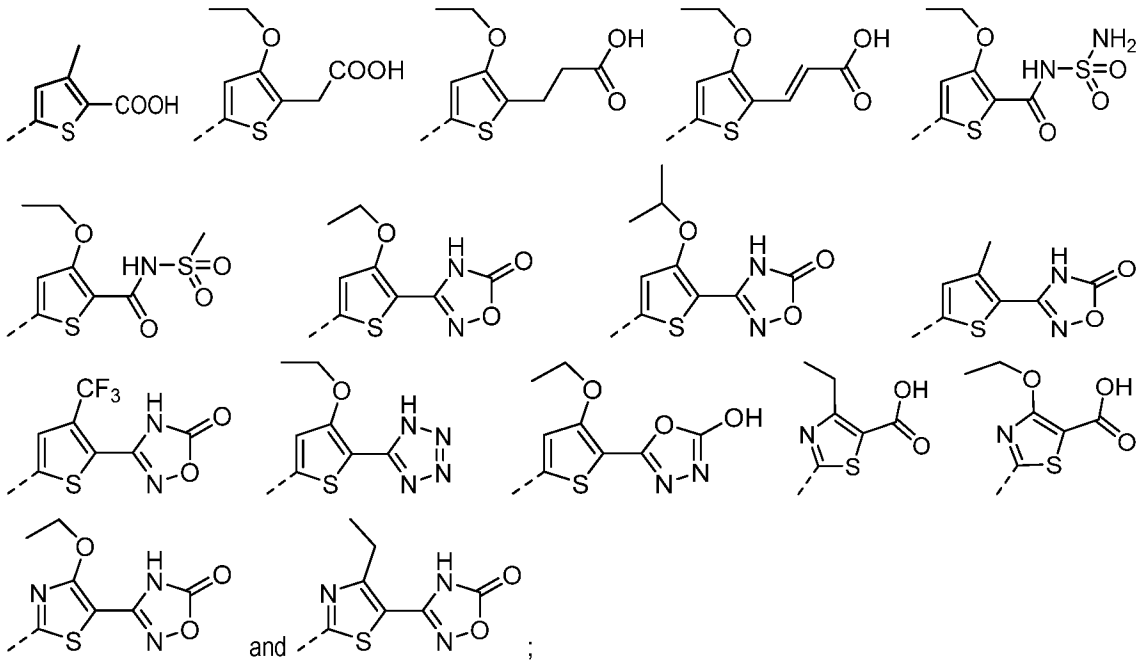


and ;

or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 2; wherein **Ar**[1] represents a group selected from





and ;

or a pharmaceutically acceptable salt thereof.

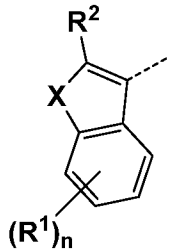
5. A compound according to any one of claims 2 to 4; wherein **X** represents S;

or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 2 to 5; wherein R^2 represents (C_{1-4})alkyl, halogen, or cyano;

or a pharmaceutically acceptable salt thereof.

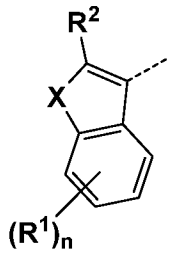
7. A compound according to any one of claims 2 to 6; wherein in the fragment



$(R^1)_n$ represents one, two or three substituents, wherein said substituents R^1 are independently selected from (C_{1-3})alkyl, (C_{1-3})alkoxy, halogen, (C_{1-3})fluoroalkyl, (C_{1-3})fluoroalkoxy, or cyano;

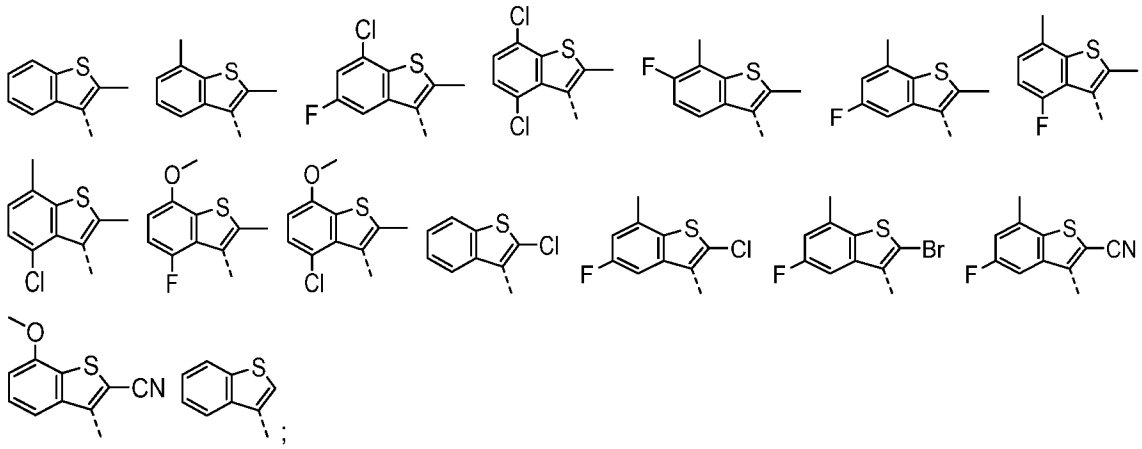
or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 2 to 4; wherein the fragment

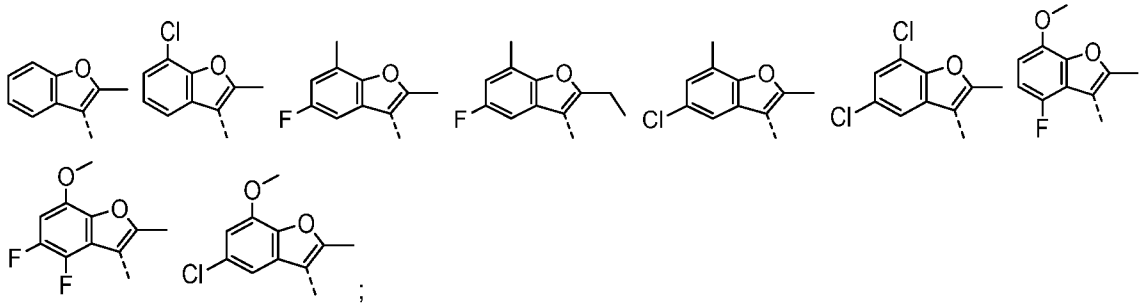


represents

- a benzothiophene selected from:

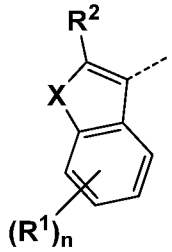


- or a benzofurane selected from:

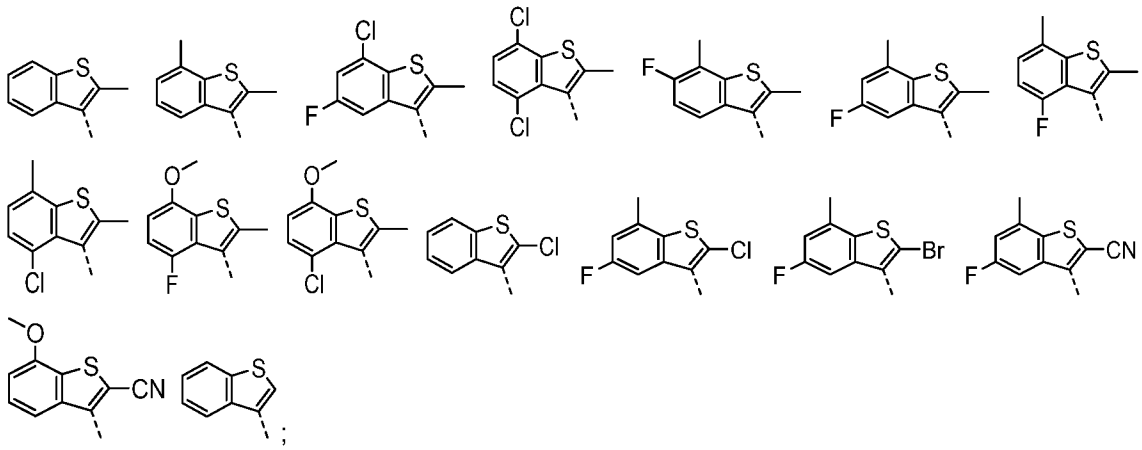


or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 2 to 4; wherein the fragment



represents a benzothiophene selected from:



or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 2 selected from the group consisting of:

5-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid;

4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

4-{6-[2-(2-Cyano-7-methoxy-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

3-Ethoxy-5-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

5-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

5-{6-[2-(2-Cyano-7-methoxy-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

3-Ethoxy-5-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

5-{6-[2-(4-Chloro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

5-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

5-{6-[2-(4,5-Difluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

5-[6-(2-Benzo[b]thiophen-3-yl-ethylamino)-pyrimidin-4-yl]-3-ethoxy-thiophene-2-carboxylic acid;

3-Ethoxy-5-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

5-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

5-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

5-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-ethoxy-thiophene-2-carboxylic acid;

5-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-(2-hydroxy-ethoxy)-thiophene-2-carboxylic acid;

5-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-trifluoromethyl-thiophene-2-carboxylic acid;

4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

4-{6-[2-(2-Cyano-7-methoxy-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

6-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzofuran-2-carboxylic acid;

5-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzofuran-2-carboxylic acid;

5-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-3(2H)-one;

5-(4-(6-((2-(5-Fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)phenyl)-[1,2,4]oxadiazol-3-ol;

2-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-indole-4-carboxylic acid;

(E)-3-(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acrylic acid;

(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid;

2-Difluoromethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

(2-Ethoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-acetic acid;

(2-Ethoxy-4-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-acetic acid;

(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenylamino)-acetic acid;

N-(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carbonyl)-methanesulfonamide;

{6-[4-Ethoxy-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-pyrimidin-4-yl}-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethyl]-amine;

3-(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-[1,2,4]oxadiazol-5(4H)-one;

3-(3-Ethoxy-5-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)thiophen-2-yl)-[1,2,4]oxadiazol-5-ol;

4-Ethoxy-2-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiazole-5-carboxylic acid;

3-(4-Ethoxy-2-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiazol-5-yl)-[1,2,4]oxadiazol-5(4H)-one;

3-(4-Ethoxy-2-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol;

5-{6-[2-(5-Fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid;

5-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid;

5-{6-[2-(5-Chloro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-3-methyl-thiophene-2-carboxylic acid;

3-Methyl-5-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-hydroxy-benzoic acid;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-hydroxy-benzoic acid;

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

4-{6-[2-(2-Methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

4-{6-[2-(4-Chloro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

4-{6-[2-(4,7-Dichloro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

4-{6-[2-(6-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

4-{6-[2-(7-Chloro-5-fluoro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

4-{6-[2-(2-Methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

3-Ethoxy-5-{6-[2-(2-ethyl-5-fluoro-7-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid;

4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-benzoic acid;

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethylsulfanyl-benzoic acid;

2-Ethylsulfanyl-4-{6-[2-(2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Ethylsulfanyl-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid;

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-fluoro-6-methylsulfanyl-benzoic acid;

2-Chloro-4-{6-[2-(2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methylsulfanyl-benzoic acid;

(3-Ethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acetic acid;

2-Ethoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

4-{6-[2-(2-Bromo-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

4-{6-[2-(2-Chloro-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

2-Ethoxy-4-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Ethoxy-4-{6-[2-(6-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(4,7-Dichloro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

4-{6-[2-(5-Chloro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

4-{6-[2-(7-Chloro-5-fluoro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

4-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

4-{6-[2-(5,7-Dichloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

2-Ethoxy-4-{6-[2-(2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Ethoxy-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(2-chloro-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-benzoic acid;

2-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-indole-6-carboxylic acid;

4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclopropoxy-benzoic acid;

2-Cyclopropoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Cyclopropoxy-4-{6-[2-(4,5-difluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-(2-hydroxy-ethoxy)-benzoic acid;

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propylsulfanyl-benzoic acid;

4-{6-[2-(2-Methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propylsulfanyl-benzoic acid;

4-{6-[2-(2-Methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propylsulfanyl-benzoic acid;

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropylsulfanyl-benzoic acid;

2-Isopropylsulfanyl-4-{6-[2-(2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Isopropylsulfanyl-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Fluoro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-propyl-benzoic acid;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isobutyl-benzoic acid;

4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-benzoic acid;

4-{6-[2-(6-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid;

4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid;

4-{6-[2-(4,7-Dichloro-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-benzoic acid;

(4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid;

4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-difluoromethoxy-benzoic acid;

(4-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-acetic acid;

(4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-acetic acid;

2-Cyclobutylsulfanyl-4-{6-[2-(2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Cyclobutylsulfanyl-4-{6-[2-(2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-(oxetan-3-ylsulfanyl)-benzoic acid;

4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-benzoic acid;

2-Cyclobutoxy-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(4-Chloro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-benzoic acid;

2-Cyclobutoxy-4-{6-[2-(4-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

4-{6-[2-(7-Chloro-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-benzoic acid;

2-Cyclobutoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Cyclobutoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

{6-[3-Ethoxy-4-(1H-tetrazol-5-yl)-phenyl]-pyrimidin-4-yl}-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethyl]-amine;

3-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenoxy)-propionic acid;

2-Butoxy-6-fluoro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

N-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-oxalamic acid;

2-Cyclobutoxy-3-fluoro-4-{6-[2-(4-fluoro-7-methoxy-2-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Cyclobutoxy-4-{6-[2-(4,5-difluoro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-6-fluoro-benzoic acid;

4-{6-[2-(5-Chloro-7-methoxy-2-methyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-2-cyclobutoxy-6-fluoro-benzoic acid;

2-Cyclopentyloxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

2-Cyclopentyloxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzofuran-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

3-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5(4H)-one;

3-(2-Ethoxy-4-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)phenyl)-[1,2,4]oxadiazol-5-ol;

3-Ethoxy-5-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)-N-sulfamoylthiophene-2-carboxamide;

4-Ethyl-2-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiazole-5-carboxylic acid;

3-(4-Ethyl-2-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiazol-5-yl)-[1,2,4]oxadiazol-5(4H)-one; and

3-(4-Ethyl-2-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)thiazol-5-yl)-[1,2,4]oxadiazol-5-ol;

or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 2 selected from the group consisting of:

(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-6-fluoro-phenyl)-acetic acid;

4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzoic acid;

(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-acetic acid;

(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-phenyl)-acetic acid;

(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-phenyl)-acetic acid;

(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-phenyl)-acetic acid;

4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-benzoic acid;

3-(4-{6-[2-(2-Cyano-5-fluoro-7-methyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenoxy)-propionic acid;

2-Ethylsulfanyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-4-hydroxy-cyclobut-3-ene-1,2-dione;

(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isobutyl-phenyl)-acetic acid;

(2-Ethyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid;

(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-oxo-acetic acid;

(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propoxy-phenyl)-acetic acid;

N-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-formamide;

(2-Ethyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methyl-phenyl)-acetic acid;

2-Cyclopropoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

(2-Cyclopropoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid;

(3-Ethyl-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acetic acid;

(2-Chloro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-6-methyl-phenyl)-acetic acid;

5-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-isoxazol-3-ol;

5-(2-ethoxy-4-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)phenyl)isoxazol-3(2H)-one;

1-(2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-cyclopropanecarboxylic acid;

1-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-phenyl)-cyclopropanecarboxylic acid;

4-{6-[2-(2,7-Dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isobutylsulfanyl-benzoic acid;

4-{6-[2-(2-Cyano-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methylsulfanyl-benzoic acid;

(4-{6-[2-(2-Cyano-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid;

3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5(4H)-one;

3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-[1,2,4]oxadiazol-5-ol;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzamide;

[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethyl]-[6-(1H-indol-5-yl)-pyrimidin-4-yl]-amine;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isobutoxy-benzoic acid;

(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-phenyl)-acetic acid;

(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-trifluoromethoxy-phenyl)-acetic acid;

N-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-formamide;

(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-isopropoxy-phenyl)-acetic acid;

2-Ethyl-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzoic acid;

5-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-isoxazol-3-ol;

5-(4-(6-((2-(5-fluoro-2,7-dimethylbenzo[b]thiophen-3-yl)ethyl)amino)pyrimidin-4-yl)-2-methoxyphenyl)isoxazol-3(2H)-one;

5-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methyl-1H-pyrrole-3-carboxylic acid;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-propyl-benzamide;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-2-methyl-propyl)-2-propyl-benzamide;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-(2-methoxy-ethyl)-2-propyl-benzamide;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-ethyl)-2-propyl-benzamide;

4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-methyl-2-propyl-benzamide;

2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-(2-hydroxy-ethyl)-benzamide;

2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-N-methyl-benzamide;

2-Ethoxy-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzamide;

(2-Ethoxy-3-fluoro-4-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-phenyl)-acetic acid;

(5-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-3-propyl-thiophen-2-yl)-acetic acid;

(3-Difluoromethoxy-5-{6-[2-(5-fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-thiophen-2-yl)-acetic acid;

2-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-1H-indole-7-carboxylic acid;

2-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-benzo[b]thiophene-7-carboxylic acid;

3-(4-{6-[2-(5-Fluoro-2,7-dimethyl-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-methoxy-phenyl)-propionic acid;

(4-{6-[2-(2-Cyano-7-methoxy-benzo[b]thiophen-3-yl)-ethylamino]-pyrimidin-4-yl}-2-ethoxy-phenyl)-acetic acid.

12. A pharmaceutical composition comprising, as active principle, a compound according to any one of claims 2 to 11, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

13. A compound according to any one of claims 2 to 11, or a pharmaceutically acceptable salt thereof, for use as a medicament.

14. A compound according to any one of claims 2 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; or for use in the control of female fertility.

15. A compound according to any one of claims 2 to 11, or a pharmaceutically acceptable salt thereof, for use in 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.

16. Use of a compound according to any one of claims 2 to 11, or of a 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; or for the control of female fertility.

17. A compound according to any one of claims 2 to 11, or a pharmaceutically acceptable salt thereof, 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 compound is optionally used in combination with one or more chemotherapy agents and / or radiotherapy and / or targeted therapy.

18. A method of modulating an immune response in a subject having a tumor, comprising the administration of an effective amount of a compound of formula (I) as defined in claim 1, or of a compound of formula (II) according to any one of claims 2 to 11, or of a pharmaceutically acceptable salt thereof; wherein said effective amount reactivates the immune system in the tumor of said subject.

19. A method of prophylaxis or treatment of cancer; pain; endometriosis; autosomal dominant polycystic kidney disease; acute ischemic syndromes in atherosclerotic patients; pneumonia; and neurodegenerative diseases; or for the control of female fertility; comprising administering to a subject in need thereof a compound of formula (II) according to any one of claims 2 to 11, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/062843

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 C07D405/12 C07D409/12 C07D409/14 C07D417/14
A61P35/00 A61K31/506
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008/152093 A2 (BAYER SCHERING PHARMA AG [DE]; BUCHMANN BERND [DE]; BRAEUER NICO [DE];) 18 December 2008 (2008-12-18) claims 1, 8, 16 page 30, lines 11-24	1,18

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Y	claims 1, 40 page 158	1,18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 2018	26/06/2018

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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