



(51) International Patent Classification:

C07D 403/04 (2006.01) A61P 25/00 (2006.01)

C07D 487/04 (2006.01) A61P 35/00 (2006.01)

A61K 31/4439 (2006.01) A61P 37/00 (2006.01)

A61K 31/437 (2006.01)

(21) International Application Number:

PCT/EP2019/051230

(22) International Filing Date:

18 January 2019 (18.01.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

PCT/EP2018/051278

19 January 2018 (19.01.2018) EP

(71) Applicant: IDORSIA PHARMACEUTICALS LTD
[CH/CH]; Hegenheimermattweg 91, 4123 Allschwil (CH).

(72) Inventors: FROIDEVAUX, Sylvie; c/o Idorsia Pharmaceuticals Ltd, Hegenheimermattweg 91, 4123 Allschwil (CH). HUBLER, Francis; c/o Idorsia Pharmaceuticals Ltd, Hegenheimermattweg 91, 4123 Allschwil (CH). MURPHY, Mark; c/o Idorsia Pharmaceuticals Ltd, Hegenheimermattweg 91, 4123 Allschwil (CH). RENNEBERG, Dorte; c/o Idorsia Pharmaceuticals Ltd, Hegenheimermattweg 91, 4123 Allschwil (CH). STAMM, Simon; c/o Idorsia Pharmaceuticals Ltd, Hegenheimermattweg 91, 4123 Allschwil (CH).

(74) Agent: VELKER, Jörg; c/o Idorsia Pharmaceuticals Ltd, Hegenheimermattweg 91, 4123 Allschwil (CH).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,

MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

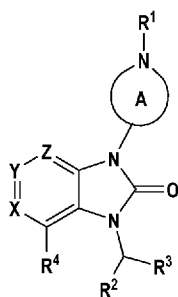
Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))

(54) Title: C5A RECEPTOR MODULATORS



Formula (I)

(57) Abstract: The present invention relates to derivatives of formula (I) wherein ring A, X, Y, Z, R¹, R², R³ and R⁴ are as described in the description, 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 C5a receptor modulators.



C5a receptor modulators

The present invention relates to novel C5a receptor modulators of formula (I) 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), and their use as C5a receptor modulators, especially in the treatment of vasculitic diseases or disorders, inflammatory diseases or disorders involving intravascular microvesicle release, immune complex (IC) diseases or disorders, neurodegenerative diseases or disorders, complement related inflammatory diseases or disorders, bullous diseases or disorders, diseases or disorders related to ischemia and/or ischemic reperfusion injury, inflammatory bowel diseases or disorders, and autoimmune diseases or disorders; as well as in contact sensitivity or an inflammation caused by contact with artificial surfaces; increased leukocyte and platelet activation (and infiltration to tissues thereof); pathologic sequelae associated to an intoxication or an injury such as a trauma, an hemorrhage, a shock, or surgery including transplantation, such sequelae including multiple organ failure (MOF), septic shock, shock due to intoxication, or acute lung inflammatory injury; pathologic sequelae associated with insulin-dependent diabetes mellitus; myocardial infarction or thrombosis; edema or an increased capillary permeability; reduction of coronary endothelial dysfunction induced by cardiopulmonary bypass and/or cardioplegia; or cancer.

C5aR1 (CD88) is a seven transmembrane bound G protein coupled receptor (GPCR) belonging to the rhodopsin like family, the gene of which is located on chromosome 19. It couples to pertussis toxin sensitive G α 2, G α 3 or pertussis toxin insensitive G α 16 and initiates several downstream signaling pathways. C5aR1 is expressed on a number of immune cell types including monocytes, neutrophils, mast cells, basophils and eosinophils. In addition, it is expressed on many other cell types including hepatocytes, pulmonary and endothelial cells, microglia, neurons and renal glomerular cells. There are a number of ligands described which bind to the C5aR. These include C5a, C5adesArg and C5a +1kDa. C5a is a central effector molecule of the complement system which itself is a complex enzymatic cascade evolved to crucially complement the immune system against invading pathogens, however, a significant body of evidence shows that inadvertent complement activation leads to many acute inflammatory disorders and autoimmune diseases (Ricklin, D., et al. (2010) "Complement: a key system for immune surveillance and homeostasis." Nat Immunol 11(9): 785-797) and specifically C5a has been shown to be elevated in a number of these inflammatory and autoimmune disorders. The complement system is activated through four pathways: The classical pathway, and the mannose binding lectin (MBL) pathway which is similar to the classical pathway except for the initial recognition and activation steps which recognize pathogens or antibody complexes. The alternative pathway is activated by binding of spontaneously activated complement C3 protein (C3b fragment) to pathogen surface. These three pathways all lead to the eventual formation of C3 convertases, which is the point where the 3 pathways converge (Guo, R. F. and P. A. Ward (2005) Annu Rev Immunol 23: 821-852). Subsequently C3 convertases lead to the formation of the anaphalatoxins C3a and C5a, together with other complement proteins required to produce the membrane attack complex. A fourth pathway, the extrinsic pathway involves plasma proteases (eg. elastase, thrombin) which act directly on C3 or C5 leading to the

subsequent production of C3a and C5a. The anaphylatoxin C5a leads to the recruitment and activation of inflammatory cells of the innate and adaptive system, partly through the enhancement of cell adhesion molecule expression, the release of granule-based enzymes, delayed or enhanced apoptosis, phagocytosis, oxidative burst, histamine secretion and release and chemotaxis. In addition, it elicits the release of other pro inflammatory mediators, such as TNF- α , IL-1, IL-6, IL-8, prostaglandins, and leukotrienes) (N.S. Merle et al. (2015) "Complement System Part II: Role in Immunity." *Front Immunol* 6: 257), activation of endothelial cells and vascular permeability which may lead to events in which at the end thrombotic microangiopathy can occur. Therefore, C5a represents one of the most potent inflammatory molecules produced during immune responses and because of its fundamental biology it is potentially implicated in a very wide range of pathologies (Janeway's Immunobiology, 8th edition (2012), Kenneth Murphy, Garland Science, p. 48-72).

C5a is central to the immune system and as such is important in key aspects of inflammation and tissue injury. In addition, there is considerable experimental evidence in the literature that implicates increased levels of C5a with a number of diseases and disorders, in particular in autoimmune and inflammatory diseases and disorders (Ricklin, D., et al. (2010) *Nat Immunol* 11(9): 785-797).

There is a large body of evidence about C5a and its receptor C5aR in contributing to vasculitic diseases, which demonstrate that C5a levels are elevated and give rise to leukocyte migration and subsequent inflammation which then leads to the eventual destruction of vessel walls (Charles J., et al (2013) *Semin Nephrol* 33(6): 557-564; Vasculitis, 2nd Edition (2008), Edited by Ball and Bridges, Oxford University Press, pp 47-53; Huang, Y. M., et al. (2015) *Arthritis Rheumatol* 67(10): 2780-2790; Kallenberg, C. G. and P. Heeringa (2015) *Mol Immunol* 68(1): 53-56). Inhibition of the C5aR with a C5aR antagonist was effective at ameliorated anti-myeloperoxidase (MPO)-induced NCGN in mice expressing the human C5a receptor (Xiao, H. et al (2014) *J Am Soc Nephrol* 25(2): 225-231) and was confirmed to be effective in a phase II trial of patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (ClinicalTrials.gov Identifier NCT02222155). Therefore, a C5a antagonist may be useful to treat vasculitic diseases such as ANCA associated vasculitis, leukoclastic vasculitis, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, Henoch-Schönlein purpura, polyarteritis nodosa, rapidly progressive glomerulonephritis (RPGN), cryoglobulinaemia, giant cell arteritis (GCA), Behcet's disease and Takayasu's arteritis (TAK).

C5a is generated when human blood makes contact with artificial surfaces, such as in cardiopulmonary bypass and hemodialysis procedures for instance on the artificial surface of the heart - lung machine in association with vascular surgery such as coronary artery bypass grafting or heart valve replacement or on surfaces of a kidney dialysis machine (Howard, R. J., et al. (1988) *Arch Surg* 123(12): 1496-1501; Kirklin, J. K., et al. (1983) *J Thorac Cardiovasc Surg* 86(6): 845-857; Craddock, P. R., et al. (1977) *J Clin Invest* 60(1): 260-264; Craddock, P. R., et al. (1977) *N Engl J Med* 296(14): 769-774) or in association with contact with other artificial vessels or container surfaces (e.g. ventricular assist devices, artificial heart machines, transfusion tubing, blood storage bags, plasmapheresis, plateletpheresis, and the like). As such C5aR antagonists could prove useful in preventing

deleterious consequences of contact sensitivity and/or inflammation caused by contact with artificial surfaces. In addition, it may be useful in treating inflammatory disorders involving intravascular microvesicle release such as for example thrombotic microangiopathy and sickle cell disease (Zecher, D., et al. (2014) *Arterioscler Thromb Vasc Biol* 34(2): 313-320). A C5aR antagonist could also prove useful in certain hemotological diseases which are associated with activation of coagulation and fibrinolytic systems, disseminated intravascular coagulation (DIC), pernicious anemia, warm and cold autoimmune hemolytic anemia (AIHA), anti-phospholipid syndrome and its associated complications, arterial and venous thrombosis, pregnancy complications such as recurrent miscarriage and fetal death, preeclampsia, placental insufficiency, fetal growth restriction, cervical remodeling and preterm birth, idiopathic thrombocytopenic purpura (ITP), atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH) and allergic transfusion reactions. The C5-specific humanized antibody, eculizumab is approved for paroxysmal nocturnal hemoglobinuria and atypical haemolytic uraemic syndrome (aHUS) (Wong EK, Kavanagh D, *Transl Res.* (2015) 165(2):306-20) and has been shown to be efficacious in renal transplant such as acute antibody-mediated kidney allograft rejection and cold agglutinin disease further supporting a potential role for C5aR antagonists in these diseases.

In myocardial ischemia-reperfusion injury C5a has been described to have an important function. Complement depletion reduced myocardial infarct size in mice (Weisman, H. F., T. et al. (1990) *Science* 249(4965): 146-151; De Hoog, V. C., et al. (2014) *Cardiovasc Res* 103(4): 521-529) and treatment with anti-C5a antibodies reduced injury in a rat model of hindlimb ischemia-reperfusion (Bless, N. M., et al. (1999) *Am J Physiol* 276(1 Pt 1): L57-63). Reperfusion injury during myocardial infarction was also markedly reduced in pigs that were re-treated with a monoclonal anti-C5a IgG (Amsterdam, E. A., et al. (1995) *Am J Physiol* 268(1 Pt 2): H448-457). A recombinant human C5aR antagonist reduces infarct size in a porcine model of surgical revascularization (Riley, R. D., et al. (2000) *J Thorac Cardiovasc Surg* 120(2): 350-358) providing evidence for the utility of a C5aR antagonist in these diseases. In addition, diseases related to ischemia / reperfusion injury, such as those resulting from transplants, including solid organ transplant, where C5a has been shown to play an important role (Farrar, C. A. and S. H. Sacks (2014) *Curr Opin Organ Transplant* 19(1): 8-13), could benefit from a C5aR antagonist as could related syndromes such as ischemic reperfusion injury, ischemic colitis and cardiac ischemia (Mueller, M., et al. (2013) *Immunobiology* 218(9): 1131-1138).

Furthermore, diseases where complement plays a role such as coronary thrombosis (Distelmaier, K., et al. (2009) *Thromb Haemost* 102(3): 564-572), vascular occlusion, post-surgical vascular reocclusion, atherosclerosis, traumatic central nervous system injury, arrhythmogenic cardiomyopathy (Mavroidis, M., et al. (2015) *Basic Res Cardiol* 110(3): 27) and Gaucher disease (Pandey et al. (2017) *Nature* 543: 108-112) could also benefit from a C5aR antagonist. Thus, C5aR modulators may be used preventatively in a patient at risk for myocardial infarction or thrombosis (i.e. a patient who has one or more recognized risk factors for myocardial infarction or thrombosis, such as, but not limited to, obesity, smoking, high blood pressure, hypercholesterolemia, previous or genetic history of myocardial infarction or thrombosis) in order to reduce the risk of myocardial infarction or thrombosis.

C5a causes increased capillary permeability and edema, leukocyte and platelet activation and infiltration to tissues, as well as bronchoconstriction (Sarma, J. V. and P. A. Ward (2012) *Cell Health Cytoskeleton* 4: 73-82; Czernak, B. J., et al. (1998) *J Leukoc Biol* 64(1): 40-48). Administration of an anti-C5a monoclonal antibody was shown to reduce cardiopulmonary bypass and cardioplegia-induced coronary endothelial dysfunction (Tofukuji, M., et al. (1998) *J Thorac Cardiovasc Surg* 116(6): 1060-1068).

C5a and its receptor are also involved in the pathogenesis of acute respiratory distress syndrome (ARDS) (Hammerschmidt, D. E., et al. (1980) *Lancet* 1(8175): 947-949), Chronic Obstructive Pulmonary Disorder (COPD) (Marc, M. M., et al. (2004) *Am J Respir Cell Mol Biol* 31(2): 216-219), and multiple organ failure (MOF) (Huber-Lang, M., et al. (2001) "Role of C5a in multiorgan failure during sepsis." *J Immunol* 166(2): 1193-1199; Heideman, M. and T. E. Hugli (1984) *J Trauma* 24(12): 1038-1043;). C5a increases monocyte production of two important proinflammatory cytokines TNF- α and IL-1 which contribute to pathology in these diseases. C5a has also been shown to play an important role in the development of tissue injury, and particularly pulmonary injury, in animal models of septic shock (Smedegard, G., et al. (1989) *Am J Pathol* 135(3): 489-497; Unnewehr, H., et al. (2013) *J Immunol* 190(8): 4215-4225). In sepsis models using rats, pigs and non-human primates, anti-C5a antibodies administered to the animals before treatment with endotoxin or *E. coli* resulted in decreased tissue injury, as well as decreased production of IL-6 (Hopken, U., et al. (1996) *Eur J Immunol* 26(5): 1103-1109; Stevens, J. H., et al. (1986) *J Clin Invest* 77(6): 1812-1816). Inhibition of C5a with anti-C5a polyclonal antibodies has been shown to significantly improve survival rates in a caecal ligation/puncture model of sepsis in rats (Czernak, B. J., et al. (1999) *Nat Med* 5(7): 788-792). In the same sepsis model, anti-C5a antibodies were shown to inhibit apoptosis of thymocytes (Guo, R. F., et al. (2000) *J Clin Invest* 106(10): 1271-1280). Anti-C5a antibodies were also protective in a cobra venom factor model of lung injury in rats, and in immune complex-induced lung injury (Mulligan, M. S., et al. (1996) *J Clin Invest* 98(2): 503-512). The importance of C5a in immune complex-mediated lung injury was also shown in mouse (Bozic, C. R., et al. (1996) *Science* 273(5282): 1722-1725). Therefore, a C5aR antagonist could be of benefit in many inflammatory disorders and related conditions including neutropenia, sepsis, septic shock, stroke, inflammation associated with severe burns (Hoesel, L. M., et al. (2007) *J Immunol* 178(12): 7902-7910), osteoarthritis (Yuan, G., et al. (2003) *Chin Med J (Engl)* 116(9): 1408-1412), as well as acute (adult) respiratory distress syndrome (ARDS), chronic pulmonary obstructive disorder (COPD), bronchial asthma (Pandey, M. K. (2013) *Curr Allergy Asthma Rep* 13(6): 596-606), systemic inflammatory response syndrome (SIRS), tissue graft rejection, hyperacute rejection of transplanted organs, and the like, and multiple organ dysfunction syndrome (MODS). In addition, C5aR antagonists may be beneficial in treating pathologic sequelae associated with insulin-dependent diabetes mellitus such as diabetic kidney disease (Li, L., et al. (2015) *Metabolism* 64(5): 597-610), diabetic retinopathy (Cheng, L., et al. (2013). *Invest Ophthalmol Vis Sci* 54(13): 8191-8198), lupus nephropathy (Bao, L., et al. (2005) *Eur J Immunol* 35(8): 2496-2506), Heyman nephritis, membranous nephritis, and other forms of glomerulonephritis such as C3 glomerulopathy including dense deposit disease (DDD) (Zhang et al., *Clin J Am Soc Nephrol* (2014) 9: 1876-1882). Furthermore, the compound eculizumab has been shown to have potential utility for the treatment of neuromyelitis optica.

C5aR antagonists substantially reduced ovalbumin (OVA)-induced total cell (60%), neutrophil (66%) and eosinophil (65%) influxes in lavage fluid sampling suggesting that C5aR blockage might represent a novel therapeutic agent for reducing asthmatic outcomes (Staab, E. B., et al. (2014) *Int Immunopharmacol* 21(2): 293-300).

The complement system and in particular C5a contribute to the development of many bullous diseases among other things through activation of innate cells including mast cells and neutrophils (e.g. bullous pemphigoid, bullous
5
acquisita, pemphigus foliaceus and pemphigus vulgaris). The detachment of epidermal basal keratinocytes from the underlying basement membrane is thought to be caused by autoantibodies to keratinocytes at the cutaneous basement membrane leading to blisters and a high influx of neutrophils in both the upper dermal layers and within the blister cavities. In experimental models a reduction of neutrophils or absence of complement (total or C5-
10
selective) can inhibit formation of sub-epidermal blisters (Heimbach, L., et al. (2011) *J Biol Chem* 286(17): 15003-15009; Gammon, W. R. (1989) *Immunol Ser* 46: 509-525). Recent evidence has emerged to suggest that inhibition of C5a may prove beneficial in the treatment of the skin disorder hidradenitis suppurativa where an antibody against human C5a was shown to improve patient outcome in an open label phase II clinical trial. A C5a receptor antagonist may therefore be useful in bullous diseases.

Complement is believed to be important in inflammatory bowel disease (IBD) pathology and the C5aR is found to be expressed in the epithelial cells of the colon. (Cao, Q., et al. (2012) *Am J Physiol Cell Physiol* 302(12): C1731-1740). In addition, pharmacological inhibition of C5a activity by PMX205 a peptidic C5aR antagonist is efficacious in preventing DSS-induced colitis, providing further evidence that targeting CD88 in patients with IBD irritable bowel
15
syndrome, ulcerative colitis, Crohn's disease, inflammatory bowel disease (IBD) (Johswich, K., et al. (2009) *Inflamm Bowel Dis* 15(12): 1812-1823) could be of therapeutic benefit (Woodruff, T. M., et al. (2003) *J Immunol* 171(10): 5514-5520; Jain, U., et al. (2013) *Br J Pharmacol* 168(2): 488-501).

There is a body of evidence suggesting a role for C5a and its receptor in pathologies of the CNS. C5aR expression is upregulated on reactive astrocytes, microglia, and endothelial cells in an inflamed human central nervous system (O'Barr, S. A., et al. (2001) *J Immunol* 166(6): 4154-4162; Gasque, P., et al. (1997) *Am J Pathol* 150(1): 31-41) and
25
C5a has been reported to be involved in the pathogenesis of many neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) (Mantovani, S., et al. (2014) *J Neuroimmunol* 276(1-2): 213-218; Humayun, S., et al. (2009) *J Neuroimmunol* 210(1-2): 52-62; Woodruff, T. M., et al. (2008) *J Immunol* 181(12): 8727-8734), Alzheimer disease (Fonseca, M. I., et al. (2013) *J Neuroinflammation* 10: 25; Ager, R. R., et al. (2010) *J Neurochem* 113(2): 389-401), Parkinson's disease (Wang, X. J., et al. (2007) *Neurochem Int* 50(1): 39-50) and
30
Huntington's disease (Singhrao et al. (1999) *Experimental Neurology* 159, 362-376). Furthermore C5a is found to be elevated in the CSF of Guillain-Barre syndrome patients (Hartung, H. P., et al. (1987) *Neurology* 37(6): 1006-1009; Wakerley, B. R. and N. Yuki (2015) *Expert Rev Neurother* 15(8): 847-849) and an anti C5 antibody was found to be effective in reducing neuropathy in the mouse (Halstead, S. K., et al. (2008) *Brain* 131 (Pt 5): 1197-1208; Basta, M. and D. R. Branch (2014) *Clin Exp Immunol* 178 Suppl 1: 87-88). Also, inhibition of the C5a
35
receptor alleviates experimental CNS lupus (Zwirner, J., et al. (1999) *Mol Immunol* 36(13-14): 877-884; Jacob, A., B. Hack, et al. (2010) *J Neuroimmunol* 221(1-2): 46-52). Therefore, C5aR antagonists provided herein may be to

treat ALS, Alzheimer's disease, multiple sclerosis, Guillain-Barre syndrome, Parkinson's disease, Huntington's disease and also cognitive function decline associated with cardiopulmonary bypass surgery and related procedures in addition to central nervous system involvement in diseases such as SLE, Sjögren's syndrome and associated immunological profiles.

- 5 In many autoimmune diseases Immunoglobulin G-containing immune complex (IC) depositions are found. These contribute to the pathophysiology of the diseases which frequently manifest in different organs of the body including the kidneys, heart, lungs, liver, blood vessels, the nervous system and the skin. There are numerous such IC diseases and examples are systemic lupus erythematosus (SLE), cryoglobulinemia, rheumatoid arthritis, Sjögren's syndrome (Lawley, T. J., et al. (1979) *J Immunol* 123(3): 1382-1387), Goodpasture syndrome (antiglomerular
10 basement antibody disease), and hypersensitivity. Immune complexes are known to induce C5 convertases leading to C5a production which subsequently contributes to these diseases (Karsten, C. M. and J. Kohl (2012) *Immunobiology* 217(11): 1067-1079). In animal models reproducing the mechanisms of IC activation of complement, C5aR has been shown to play an important role. Studies show that C5aR deficient mice and the use of a peptidic C5aR antagonist result in protection from tissue injury induced by ICs. (Strachan, A. J., et al. (2000) *J Immunol* 164(12): 6560-6565; Kohl, J. and J. E. Gessner (1999) *Mol Immunol* 36(13-14): 893-903; Baumann, U., et al. (2000) *J Immunol* 164(2): 1065-1070). Therefore, inhibitors of C5aR could be useful to treat IC diseases including the autoimmune diseases rheumatoid arthritis (Jose, P. J., et al. (1990) *Ann Rheum Dis* 49(10): 747-752; Grant, E. P., et al. (2002) *J Exp Med* 196(11): 1461-1471; Yuan, G., et al. (2003) *Chin Med J (Engl)* 116(9): 1408-1412)), osteoarthritis, systemic lupus erythematosus (Porcel, J. M., et al. (1995) *Clin Immunol Immunopathol* 74(3):
20 283-288; Pawaria, S., et al. (2014) *J Immunol* 193(7): 3288-3295), lupus nephritis (Bao, L., et al. (2005) *Eur J Immunol* 35(8): 2496-2506), lupus glomerulonephritis and IgA nephropathy (Liu, L., et al. (2014) *J Clin Immunol* 34(2): 224-232), Heyman nephritis, membranous nephritis and other forms of glomerulonephritis, vasculitis, dermatomyositis (Fiebiger, E., et al. (1998) *J Clin Invest* 101(1): 243-251), pemphigus, systemic sclerosis (scleroderma) (Sprott, H., et al. (2000) *J Rheumatol* 27(2): 402-404), bronchial asthma, autoimmune hemolytic and
25 thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage) (Ma, R., et al. (2013) *J Clin Immunol* 33(1): 172-178), immunovascularitis, and complement mediated thrombotic microangiopathies including atypical haemolytic uremic syndrome (Song, D., et al. (2015) *Am J Reprod Immunol* 74(4): 345-356; Davin, J. C., N. C. van de Kar (2015) *Ther Adv Hematol* 6(4): 171-185), mixed cryoglobulinemia, atopic dermatitis (Neuber, K., R. et al. (1991) *Immunology* 73(1): 83-87; Dang, L., et al. (2015) *Mol Med Rep* 11(6): 4183-4189), and chronic urticaria (Kaplan, A. P. (2004) *J Allergy Clin Immunol* 114(3): 465-474; Yan, S., et al. (2014) *J Dermatol Sci* 76(3): 240-245). Furthermore, the compound eculizumab has been shown to have potential utility for the treatment of myasthenia gravis, and anti-phospholipid syndrome.

C5a is present in psoriatic plaques and C5aR expression has also been reported in psoriasis where T cells, neutrophils mast cells and dendritic cells are involved in pathogenesis of the disease and are chemotactic to C5a
35 (Diani, M., G. Altomare and E. Reali (2015) *Autoimmun Rev* 14(4): 286-292). Neutrophil accumulation under the stratum corneum is observed in the highly inflamed areas of psoriatic plaques, and psoriatic lesion (scale) extracts

contain highly elevated levels of C5a and exhibit potent chemotactic activity towards neutrophils, an effect that can be inhibited by addition of a C5a antibody. Furthermore, T cells and neutrophils are chemo-attracted by C5a under certain conditions (Nataf, S., et al. (1999) J Immunol 162(7): 4018-4023; Tsuji, R. F., et al. (2000) J Immunol 165(3): 1588-1598; Werfel, T., et al. (1997) Arch Dermatol Res 289(2): 83-86; Mrowietz, U., et al. (2001) Exp Dermatol 10(4): 238-245) meaning C5aR antagonists may be of benefit in treating psoriasis. Furthermore, complement has been implicated in the pathogenesis of glaucoma (Howell et al. (2011), J. Clin. Invest. 121(4): 1429-1444). In addition, there is experimental evidence to suggest a beneficial role of C5aR antagonists in treating cancer with checkpoint blockers. For example, an antibody against the C5aR receptor (IPH5401) has been reported to be efficacious in murine models of cancer (web page Innate Pharma – IPH5401, 2018; <https://www.innate-pharma.com/en/pipeline/iph5401-first-class-anti-c5ar-mab>; Zah H., et al. (2017) Oncoimmunology 6(10): e1349587; Wang Y., et al., (2016) Cancer Discovery 6(9) 1022-1035).

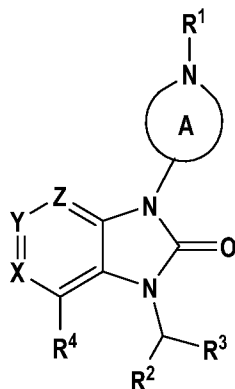
Thus, C5a and C5aR are believed to be clinically implicated in vasculitic diseases or disorders, inflammatory diseases or disorders involving intravascular microvesicle release, immune complex (IC) diseases or disorders, neurodegenerative diseases or disorders, complement related inflammatory diseases or disorders, bullous diseases or disorders, diseases or disorders related to ischemia and/or ischemic reperfusion injury, inflammatory bowel diseases or disorders, and autoimmune diseases or disorders; as well as in contact sensitivity or an inflammation caused by contact with artificial surfaces; increased leukocyte and platelet activation (and infiltration to tissues thereof); pathologic sequelae associated to an intoxication or an injury such as a trauma, an hemorrhage, a shock, or surgery including transplantation, including multiple organ failure (MOF), septic shock, shock due to intoxication, or acute lung inflammatory injury; pathologic sequelae associated with insulin-dependent diabetes mellitus; myocardial infarction or thrombosis; edema or an increased capillary permeability; reduction of coronary endothelial dysfunction induced by cardiopulmonary bypass and/or cardioplegia, or cancer.

There is therefore a requirement for new small organic molecule modulators of the C5a receptor (C5aR), especially antagonists of the C5aR, that could be useful for inhibiting pathogenic events associated with elevated levels of C5a and/or with C5aR activation.

Certain benzimidazolone derivatives as chymase inhibitors are disclosed in WO2008/147697. 4-(Benzimidazol-1-yl)-piperidines as sodium channel inhibitors are disclosed in WO2003/037890. Certain 3-substituted piperidines comprising urea functionality are disclosed as analgesics in WO2001/068604. Benzimidazolone derivatives as phosphodiesterase inhibitors are disclosed in WO2001/005770. 1-Benzyl-1,3-dihydro-2H-benzimidazol-2-one derivatives as vasopressin and/or oxytocin receptor ligands are disclosed in US 5,661,169. D. R. Owen et al., Bioorg. Med. Chem. Lett. 19 (2009) 1702–1706 discloses the compound 3-(1-(4-aminopyridin-2-yl)piperidin-4-yl)-1-benzyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one in a series of 2,4-diaminopyridine δ -opioid receptor agonists, which however had pronounced activity in the hERG binding assay.

The present invention provides cyclic urea derivatives of formula (I) which are modulators of the C5a receptor, and are useful for the prevention or treatment of diseases which respond to the C5a receptor.

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



Formula (I)

wherein

- 5 • ring **A** represents a saturated 4- to 7-membered mono-cyclic carbocyclic ring containing the ring nitrogen atom to which **R**¹ is attached, wherein said ring independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from (C₁₋₃)alkyl (especially methyl), fluoro, or (C₁₋₄)alkoxy-carbonyl (especially ethoxy-carbonyl) [especially such ring **A** is azetidin-1,3-diyl, pyrrolidin-1,3-diyl, 4-methyl-pyrrolidin-1,3-diyl, piperidin-1,3-diyl, piperidin-1,4-diyl, 3-fluoro-piperidin-1,4-diyl, 2-methyl-piperidin-1,4-diyl, 3-methyl-piperidin-1,4-diyl, 3-(ethoxycarbonyl)-piperidin-1,4-diyl, 3,3-dimethyl-piperidin-1,4-diyl, azepan-1,4-diyl]; or
- 10 • ring **A** represents a saturated 7- or 8-membered bridged bi-cyclic carbocyclic ring containing the ring nitrogen atom to which **R**¹ is attached, wherein said ring is unsubstituted [especially such ring is 2-aza-bicyclo[2.2.1]heptane-2,5-diyl, 3-aza-bicyclo[3.1.1]heptane-3,6-diyl];

X and **Z** independently represent CR⁵ or N; and **Y** represents CR⁵; or, in case both **X** and **Z** represent CH, **Y** may in addition represent N; wherein each **R**⁵ independently represents hydrogen, or (C₁₋₃)alkyl (especially methyl) [notably one of **X** and **Z** represents CH or N; the other represents CH; and **Y** represents CR⁵, wherein especially **R**⁵ represents hydrogen];

R¹ represents

- (C₁₋₄)alkyl (especially methyl, isopropyl);
- 20 • -CO-**R**¹¹ wherein **R**¹¹ represents (C₁₋₄)alkyl; (C₁₋₄)alkoxy; phenyl, phenoxy; (C₃₋₆)cycloalkyl; or (C₃₋₆)cycloalkoxy optionally containing one ring oxygen and optionally mono-substituted with methyl or trifluoromethyl [especially such group -CO-**R**¹¹ is tert.-butyl-carbonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, tert.-butoxycarbonyl, oxetan-3-yl-oxy-carbonyl, (3-methyl-oxetan-3-yl)-oxy-carbonyl, (3-trifluoromethyl-oxetan-3-yl)-oxy-carbonyl, phenylcarbonyl, phenoxycarbonyl, cyclopropylcarbonyl];
- 25 • benzyl wherein the phenyl ring of said benzyl is optionally mono- or di-substituted with halogen [especially 2,4-dichlorobenzyl]; or

- phenyl, or 5- or 6-membered heteroaryl (especially pyrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl); wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from
 - (C₁₋₄)alkyl (especially methyl, isopropyl);
 - (C₁₋₄)alkoxy (especially methoxy, n-butyloxy);
 - (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
 - (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy);
 - halogen (especially fluoro, chloro, bromo);
 - cyano;
 - nitro;
 - hydroxy;
 - hydroxy-(C₁₋₃)alkyl (especially 1-hydroxyethyl, hydroxymethyl, 1-hydroxy-1-methyl-ethyl);
 - (C₁₋₄)alkoxy-(C₁₋₃)alkyl (especially 1-methoxyethyl);
 - hydroxy-(C₂₋₃)alkoxy (especially 2-hydroxy-ethoxy);
 - (C₁₋₄)alkoxy-(C₂₋₃)alkoxy (especially 2-methoxy-ethoxy);
 - (C₃₋₆)cycloalkyl-**X**¹², wherein **X**¹² represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen [especially such group (C₃₋₆)cycloalkyl-**X**¹² is cyclopropyl, cyclopropyl-oxy, cyclobutyl-oxy, oxetan-3-yl-oxy, cyclopropyl-methoxy, or tetrahydropyran-4-yl-oxy];
 - **R**¹³-CO-**X**¹³, wherein **X**¹³ represents a direct bond or (C₁₋₃)alkylene, and **R**¹³ represents hydrogen or (C₁₋₄)alkyl (especially such group **R**¹³-CO-**X**¹³ is formyl, acetyl, 2-oxo-ethyl);
 - 3-(morpholin-4-yl)-prop-1-ynyl;
 - **R**^{14a}**R**^{14b}N-**X**¹⁴, wherein **X**¹⁴ represents a direct bond or (C₁₋₃)alkylene; and wherein **R**^{14a} and **R**^{14b} independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R**^{14a} and **R**^{14b} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl (especially methyl), hydroxy, (C₁₋₄)alkoxy (especially methoxy), or dimethylamino, [especially such group **R**^{14a}**R**^{14b}N-**X**¹⁴ is amino, methylamino-methyl, dimethylamino-methyl, [(2-hydroxyethyl)-methylamino]-methyl, [(2-hydroxyethyl)-ethylamino]-methyl, [(2-methoxy-1-methyl-ethyl)-amino]-methyl, [(2-methoxyethyl)-methylamino]-methyl, [di-(2-hydroxyethyl)-amino]-methyl, (azetidin-1-yl)-methyl, (pyrrolidin-1-yl)-methyl, (piperidin-1-yl)-methyl, morpholin-4-yl, piperazin-1-ylmethyl, (morpholin-4-yl)-methyl, 2-(morpholin-4-yl)-ethyl, 3-(morpholin-4-yl)-propyl, (3-methoxy-azetidin-1-yl)-methyl, 1-(3-methoxy-azetidin-1-yl)-ethyl, (1-methyl-piperazin-4-yl)-methyl, (4-hydroxypiperidin-1-yl)-methyl, (4-methoxypiperidin-1-yl)-methyl, (3-methoxy-pyrrolidin-1-yl)-methyl, (4-dimethylamino-piperidin-1-yl)-methyl];
- or

- benzyloxy, wherein the phenylring of benzyloxy is optionally mono- or di-substituted with halogen or methyl;

R² represents phenyl, or 5- or 6-membered heteroaryl (notably 6-membered heteroaryl; in particular thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl); wherein said phenyl or 5- or 6-membered heteroaryl independently is

5

mono-, di- or tri-substituted (especially mono-substituted, in particular in *ortho* position with regard to the point of attachment of the rest of the molecule), wherein the substituents are independently selected from

- (C₁₋₄)alkyl (especially methyl, isopropyl);
- (C₁₋₄)alkoxy (especially methoxy, isopropoxy);
- (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
- 10 ➤ (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy);
- halogen (especially chloro, fluoro); or
- (C₃₋₆)cycloalkyl-**X²¹**-, wherein **X²¹** represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen [especially such group (C₃₋₆)cycloalkyl-**X²¹**- is cyclopropyl, cyclopropyl-oxy, cyclobutyl-oxy, oxetan-3-yl-oxy, cyclopropyl-methoxy;

15 **R³** represents hydrogen, or (C₁₋₃)alkyl (especially methyl); and

R⁴ represents

- (C₁₋₄)alkyl (especially methyl);
- hydroxy-(C₁₋₃)alkyl (especially hydroxymethyl);
- -O-**R⁴¹**, wherein **R⁴¹** represents

20

- hydrogen;
- (C₁₋₄)alkyl (especially methyl);
- (C₂₋₄)alkyl which is substituted with one or two hydroxy (especially 2-hydroxyethyl, 2,3-dihydroxypropyl);
- **R^{41a}R^{41b}N**-(C₂₋₃)alkylene-, wherein **R^{41a}** and **R^{41b}** independently represent hydrogen or (C₁₋₄)alkyl (especially such group is 2-dimethylamino-ethyl); or

25

- (C₄₋₇)heterocyclyl-**X⁴¹**-, wherein **X⁴¹** represents a direct bond or (C₁₋₃)alkylene, and wherein the (C₄₋₇)heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen and oxygen; wherein said (C₄₋₇)heterocyclyl independently is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from:

- (C₁₋₄)alkyl (especially methyl); and/or
- 30 ▪ (C₁₋₄)alkoxy-carbonyl attached to a ring nitrogen atom having a free valency;

[especially such (C₄₋₇)heterocyclyl-**X⁴¹**- group is oxetan-3-yl, 1-methyl-pyrrolidin-3-yl, 2,2-dimethyldioxolan-4-yl-methyl, 2-morpholin-4-yl-ethyl, 1-tert-butoxy-carbonyl-piperidin-4-yl, piperidin-4-yl];

- -**NR^{42a}R^{42b}** wherein **R^{42a}** and **R^{42b}** independently represent hydrogen, (C₁₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₃)alkyl, hydroxy-(C₂₋₃)alkyl, or **R^{42a}** and **R^{42b}** together with the nitrogen to which they are attached form a 4- to 7-
- 35 membered saturated ring optionally containing one further ring heteroatom selected from oxygen and nitrogen, wherein said ring is unsubstituted or mono-substituted with (C₁₋₃)alkyl (especially methyl), or (C₁₋₃)alkoxy

(especially methoxy) [especially such group $-\text{NR}^{42a}\text{R}^{42b}$ is (2-hydroxyethyl)-amino, (2-hydroxyethyl)-methyl-amino, (2-methoxyethyl)-amino, morpholin-4-yl, 3-methoxy-azetidyl, or 4-methyl-piperazin-1-yl]; or

- $-\text{CO}-\text{R}^{43}$ wherein R^{43} represents (C_{1-4}) alkoxy (especially methoxy); or $-\text{NR}^{43a}\text{R}^{43b}$ wherein R^{43a} and R^{43b} independently represent hydrogen, (C_{1-4}) alkyl (especially methyl), (C_{1-3}) alkoxy- (C_{2-3}) alkyl (especially 2-methoxy-ethyl), or hydroxy- (C_{2-3}) alkyl (especially 2-hydroxy-ethyl); [especially such group $-\text{CO}-\text{R}^{43}$ is methoxycarbonyl, carbamoyl, methyl-carbamoyl, dimethylcarbamoyl, hydroxyethylcarbamoyl, methoxyethylcarbamoyl].

The compounds of formula (I) may contain one or more further stereogenic or asymmetric centers, such as one or more additional asymmetric carbon atoms. The compounds of formula (I) 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 / as having an absolute (R)- or (S)-configuration, 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 (or (R^*, R^*) designations) are to be understood as referring to the respective stereoisomer of the respective relative configuration in enriched form, especially in essentially pure form.

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.

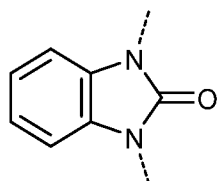
The term "essentially pure", when used in the context of stereoisomers, is to be understood in the context of the present invention to mean that the respective stereoisomer is present in a purity of at least 95% by weight, especially of at least 99% by weight, with regard to the respective other stereoisomer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

In some instances, the compounds of formula (I) may contain tautomeric forms. Such tautomeric forms are encompassed in the scope of the present invention. For example, in case the present compounds may contain heteroaromatic aromatic rings containing unsubstituted ring nitrogen atoms having a free valency such as pyrazolyl, such rings may be present in tautomeric forms. For example, the group pyrazol-3-yl represents the tautomeric forms 1*H*-pyrazol-3-yl and 2*H*-pyrazol-3-yl.

The present invention also includes isotopically labelled, especially ^2H (deuterium) labelled compounds of formula (I), which compounds are identical to the compounds of formula (I) except that one or more atoms have each been

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

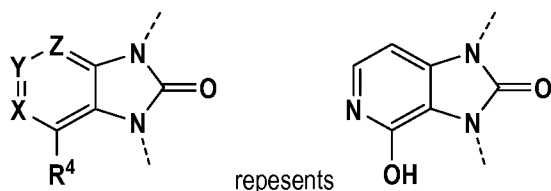
- 10 In this patent application, a bond drawn as a dotted line shows the point of attachment of the radical drawn. For example, the radical drawn below



is the 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1,3-diyl group.

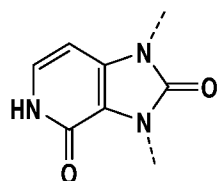
- In addition, it is well understood that in certain instances the drawn structure of the present compounds may represent several tautomers and such tautomers are comprised in the scope of the present invention:

For example compounds of formula (I) wherein Z and Y are CH, X is N, and R⁴ is hydroxy: i.e. compounds wherein the fragment:



represents

- are understood as being one of two possible tautomeric forms. Such compounds, thus, also comprise the compounds wherein said fragment represents the corresponding tautomer:



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) according to embodiments 1) to 25) is to be understood as referring also to the salts (and especially the pharmaceutically acceptable salts) of such compounds, as appropriate and expedient.

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

Definitions provided herein are intended to apply uniformly to the compounds of formula (I), as defined in any one of embodiments 1) to 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.

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

The term "alkyl", used alone or in combination, refers to a saturated straight or branched chain hydrocarbon group containing one to six carbon atoms. The term "(C_{x-y})alkyl" (x and y each being an integer), refers to an alkyl group as defined before, containing x to y carbon atoms. For example a (C₁₋₆)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 example a (C₁₋₄)alkyl group contains from one to four carbon atoms. Examples of alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert.-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, ethyl and isopropyl. Most preferred is methyl. Examples of (C₁₋₃)alkyl groups as used for the substituents at ring **A** (without R¹) is methyl. Examples of (C₁₋₄)alkyl groups as used for R¹ are methyl and isopropyl. An example of R¹¹ in -CO-R¹¹ is tert-butyl, an example of a (C₁₋₄)alkyl substituent at phenyl in R¹ is methyl, an example of (C₁₋₄)alkyl of R^{14a} or R^{14b} is methyl and ethyl. Examples of (C₁₋₄)alkyl groups as used for R² are methyl and isopropyl. Examples of (C₁₋₃)alkyl groups as used for R³ is methyl. An example of (C₁₋₄)alkyl groups as used for R⁴, R⁴¹, R^{41a}, R^{41b}, R^{43a} and R^{43b} is methyl.

The term "-(C_{x-y})alkylene-", used alone or in combination, refers to bivalently bound alkyl group as defined before containing x to y carbon atoms. Preferably, the points of attachment of a -(C_{1-y})alkylene group are in 1,1-diyl, in 1,2-diyl, or in 1,3-diyl arrangement. Preferably, the points of attachment of a -(C_{2-y})alkylene group are in 1,2-diyl or in 1,3-diyl arrangement. Preferred alkylene groups are methylene, ethylene and propylene. A -(C₀)alkylene- group is absent and refers to a direct bond.

Alkylene-oxy linker groups -(C₁₋₃)alkylene-O- as used for example in the substituents (C₃₋₆)cycloalkyl-X¹²- or (C₃₋₆)cycloalkyl-X²¹- are to be read from left to right, i.e. they refer to the respective (C₃₋₆)cycloalkyl-(C₁₋₃)alkylene-O-groups. An example for (C₃₋₆)cycloalkyl-(C₁₋₃)alkylene-O- is cyclopropyl-methoxy.

Alkylene-amino linker groups R^{14a}R^{14b}N-X¹⁴-, wherein X¹⁴ represents (C₁₋₃)alkylene, are used for example in the substituents methylamino-methyl, dimethylamino-methyl, (2-hydroxy-ethyl)-methyl-amino-methyl, (2-methoxy-1-

methyl-ethylamino)-methyl, (2-methoxy-ethyl)-methyl-amino]-methyl, [ethyl-(2-hydroxy-ethyl)-amino]-methyl, and [bis-(2-hydroxy-ethyl)-amino]-methyl. Further, alkylene-amino linker groups $R^{14a}R^{14b}N-X^{14}$ -, wherein X^{14} represents (C₁₋₃)alkylene and R^{14a} and R^{14b} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen, are used for example in the substituents azetidin-1-ylmethyl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, piperazin-1-ylmethyl, morpholin-4-ylmethyl, morpholin-4-yl-ethyl, morpholin-4-yl-propyl, 1-methyl-piperazin-4-yl)-methyl, 3-methoxy-azetidin-1-ylmethyl, 4-hydroxy-piperidin-1-ylmethyl, 3-methoxy-pyrrolidin-1-ylmethyl, 4-methoxy-piperidin-1-ylmethyl, and 4-dimethylamino-piperidin-1-ylmethyl.

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 (C₁₋₄)alkoxy group means a group of the formula (C₁₋₄)alkyl-O- in which the term "(C₁₋₄)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. Examples of (C₁₋₄)alkoxy groups as used for R¹¹ in -CO-R¹¹ are methoxy, ethoxy, isopropoxy, n-butyloxy and tert-butoxy. An example of a (C₁₋₄)alkoxy substituent at phenyl in R¹ is methoxy and n-butyloxy. Examples of (C₁₋₄)alkoxy groups as used for R² are methoxy and isopropoxy. An example of a (C₁₋₄)alkoxy group as used for R⁴³ is methoxy.

The term "hydroxy-(C₁₋₃)alkyl" relates to an alkyl group wherein a hydroxyl group can be attached to any of the carbon atoms of the alkyl group, for instance 1-hydroxyethyl, 2-hydroxyethyl, hydroxymethyl, 1-hydroxy-1-methyl-ethyl. An example for "hydroxy-(C₂₋₄)alkyl" is 2-hydroxyethyl.

The term "(C₁₋₄)alkoxy-(C₁₋₃)alkyl" relates to an alkyl group wherein an alkoxy group can be attached to any of the carbon atoms of the alkyl group, for instance 1-methoxyethyl, 2-methoxy-1-methyl-ethyl and 2-methoxyethyl.

The term "hydroxyl-(C₂₋₃)alkoxy" relates to an alkoxy group wherein a hydroxyl group can be attached to any of the carbon atoms of the alkoxy group, for instance 2-hydroxy-ethoxy.

The term "(C₁₋₄)alkoxy-(C₂₋₃)alkoxy" relates to a first alkoxy group wherein a second alkoxy group can be attached to any of the carbon atoms of the first alkoxy group, for instance 2-methoxy-ethoxy.

The term "alkynyl", used alone or in combination, refers to a straight or branched hydrocarbon chain containing two to five carbon atoms and one carbon-carbon triple bond. The term "(C_{x-y})alkynyl" (x and y each being an integer), refers to an alkynyl group as defined before containing x to y carbon atoms. For example a (C₂₋₅)alkynyl group contains from two to five carbon atoms. An example of an alkynyl group is prop-2-yn-1-yl. An example for an alkynyl group as used for the phenyl substituent in R¹ is 3-morpholin-4-yl-prop-1-ynyl.

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 (C₁₋₃)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 (C₁)fluoroalkyl groups, especially trifluoromethyl.

The term "fluoroalkoxy", used alone or in combination, refers to an alkoxy group as defined before containing one to three carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. The term "(C_{x-y})fluoroalkoxy" (x and y each being an integer) refers to a fluoroalkoxy group as defined before containing x to y carbon atoms. For example a (C₁₋₃)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 (C₁)fluoroalkoxy groups, especially trifluoromethoxy.

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

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 (C₃₋₆)cycloalkyl group contains from three to six carbon atoms. Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Preferred are cyclopropyl, cyclopentyl and cyclohexyl; especially cyclopropyl. An example of (C₃₋₆)cycloalkyl groups as used for the group R¹¹ is cyclopropyl. An example for a (C₃₋₆)cycloalkyl group as used for the phenyl substituent in (C₃₋₆)cycloalkyl-X¹²- is cyclopropyl, examples for a (C₃₋₆)cycloalkyl group as used for the phenyl or heteroaryl substituent in (C₃₋₆)cycloalkyl-X²¹- are cyclopropyl and cyclobutyl.

The term "(C_{x-y})cycloalkyl-(C_{x-y})alkyl-O-" refers to a (C_{x-y})cycloalkyl group as defined before, which is linked through a (C_{x-y})alkylene-O- group as defined before to the rest of the molecule. A particular example of such groups is cyclopropyl-methoxy.

The term "(C₃₋₆)cycloalkyl optionally containing one ring oxygen atom", used alone or in combination, refers to a cycloalkyl group as defined before. In addition, one ring carbon atom of said cycloalkyl may be replaced by an oxygen atom. Examples of such groups are especially cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl; as well as oxygen containing groups such as oxetanyl, tetrahydrofuranyl, and tetrahydro-2H-pyranyl.

The term "heterocyclyl", used alone or in combination, and if not explicitly defined in a more narrow way, refers to a saturated monocyclic hydrocarbon ring containing one or two ring heteroatoms independently selected from nitrogen and oxygen (especially one nitrogen atom, two nitrogen atoms, one nitrogen atom and one oxygen atom, one oxygen atom, or two oxygen atoms; preferably such heterocyclyl contains one or two ring oxygen atoms, or one nitrogen atom). The term "(C_{x-y})heterocyclyl" refers to such a heterocyclyl group containing x to y ring atoms. Heterocyclyl groups are unsubstituted or substituted as explicitly defined. Examples of heterocyclyl groups as used for the group R⁴¹ wherein R⁴¹ represents (C₄₋₇)heterocyclyl-X⁴¹- are oxetan-3-yl, 1-methyl-pyrrolidin-3-yl, piperidin-4-

yl, 2,2-dimethyl-dioxolan-4-yl (notably 2,2-dimethyl-dioxolan-4-yl-methyl), morpholin-4-yl (notably morpholin-4-yl-ethyl) and 1-tert-butoxy-carbonyl-piperidin-4-yl.

The term "(C_{x-y}) heterocyclyl-(C_{x-y})alkyl" refers to a (C_{x-y})heterocyclyl group as defined before, which is linked through a (C_{x-y})alkylene group as defined before to the rest of the molecule. For the (C₄₋₇)heterocyclyl-(C₁₋₃)alkyl groups as used for **R**⁴¹ examples of -(C₁₋₃)alkylene- groups are methylene, and ethylene. Examples of heterocyclyl groups part of such (C₄₋₇)heterocyclyl-(C₁₋₃)alkylene groups as used for the group **R**⁴¹ wherein **R**⁴¹ represents (C₄₋₇)heterocyclyl-X⁴¹- are 2,2-dimethyl-dioxolan-4-yl-methylene and morpholin-4-yl-ethylene.

The substituent phenyl of **R**¹ independently is unsubstituted, mono-, di or trisubstituted. Examples for mono-, di or trisubstituted phenyl as **R**¹ are 2,6-di-methyl-phenyl, 2-methoxy-phenyl, 2-n-butyloxy-phenyl, 2,6-di-methoxy-phenyl, 2-methoxy-ethoxy-phenyl, 2-methoxy-6-methyl-phenyl, 2-bromo-6-fluoro-phenyl, 2,6-di-fluoro-phenyl, 2-fluoro-phenyl, 2-fluoro-6-methoxy-phenyl, 2-fluoro-6-(1-methoxy-ethyl)-phenyl, 2-fluoro-6-methyl-phenyl, 2-Fluoro-6-(3-morpholin-4-yl-prop-1-ynyl)-phenyl, 2-fluoro-6-formyl-phenyl, 2-fluoro-6-cyano-phenyl, 2-fluoro-6-hydroxymethyl-phenyl, 2-fluoro-6-(1-hydroxyethyl)-phenyl, 2-fluoro-6-(1-hydroxy-1-methyl-ethyl)-phenyl, 2-fluoro-6-nitro-phenyl, 2-fluoro-6-acetyl-phenyl, 2-amino-6-fluoro-phenyl, 2-fluoro-6-methylaminomethyl-phenyl, 2-dimethylaminomethyl-6-fluoro-phenyl, 2-fluoro-6-[[2-hydroxy-ethyl)-methyl-amino]-methyl]-phenyl, 2-fluoro-6-[(2-methoxy-1-methyl-ethylamino)-methyl]-phenyl, 2-Fluoro-6-[[2-methoxy-ethyl)-methyl-amino]-methyl]-phenyl, 2-[[Ethyl-(2-hydroxy-ethyl)-amino]-methyl]-6-fluoro-phenyl, 2-[[bis-(2-hydroxy-ethyl)-amino]-methyl]-6-fluoro-phenyl, 2-azetidin-1-ylmethyl-5-fluoro-phenyl, 2-fluoro-6-pyrrolidin-1-ylmethyl-phenyl, 2-Fluoro-6-piperidin-1-ylmethyl-phenyl, 2-fluoro-6-morpholin-4-yl-phenyl, 2-Fluoro-6-piperazin-1-ylmethyl-phenyl, 2-Fluoro-6-morpholin-4-ylmethyl-phenyl, 2-Fluoro-6-(2-morpholin-4-yl-ethyl)-phenyl, 2-Fluoro-6-(3-morpholin-4-yl-propyl)-phenyl, 2-Fluoro-6-(1-methyl-piperazin-4-yl)-methyl-phenyl, 2-Fluoro-6-(3-methoxy-azetidin-1-ylmethyl)-phenyl, 2-Fluoro-6-(4-hydroxy-piperidin-1-ylmethyl)-phenyl, 2-Fluoro-6-(3-methoxy-pyrrolidin-1-ylmethyl)-phenyl, 2-Fluoro-6-[1-(3-methoxy-azetidin-1-yl)-ethyl]-phenyl, 2-Fluoro-6-(4-methoxy-piperidin-1-ylmethyl)-phenyl, 2-(4-Dimethylamino-piperidin-1-ylmethyl)-6-fluoro-phenyl, 1-hydroxy-phenyl, 2-hydroxy-ethoxy-phenyl, oxetan-3-yl-oxy-phenyl, cyclopropyl-methoxy-phenyl, cyclobutyl-oxy-,phenyl, 2-(tetrahydro-pyran-4-yloxy)-phenyl, 1-benzyloxy-phenyl or 1-trifluoromethoxy-phenyl.

The substituent phenyl of **R**² independently is unsubstituted, mono-, di or trisubstituted, especially mono- or trisubstituted. Examples for mono or trisubstituted phenyl as **R**² are 2-trifluoromethoxy-phenyl, 2-trifluoromethyl-phenyl, 2-methoxy-phenyl, 2-isopropoxy-phenyl, 2-cyclopropyl-phenyl, 2-cyclopropyl-oxy-phenyl, 2-oxetan-3-yl-oxy-phenyl, 2-cyclopropylmethoxy-phenyl, 2-cyclobutyl-oxy-phenyl or 2,4-difluoro-6-isopropoxy-phenyl.

The term "heteroaryl", used alone or in combination, means a 5- or 6-membered monocyclic aromatic ring containing one to a maximum of three heteroatoms, each independently selected from oxygen, nitrogen and sulfur. Examples of such heteroaryl groups are furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl. Preferred 5- or 6-membered heteroaryl groups are pyrazolyl, oxodiazolyl, thiazolyl, pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl. The above-mentioned heteroaryl groups are unsubstituted or substituted as explicitly defined. In case 5- or 6-

membered heteroaryl group is substituted in *ortho*-position with regard to the point of attachment of the rest of the molecule, it is understood that such substituent is attached in direct neighbourhood with regard to the point of attachment of the rest of the molecule, i.e. in a relative 1,2-arrangement. In case **R**¹ represents "5- or 6-membered heteroaryl", the term means the above-mentioned 5- or 6-membered groups, especially pyrazolyl, oxodiazolyl, pyridinyl, pyrimidinyl or pyridazinyl. For the substituent **R**¹, such 5- or 6-membered heteroaryl group is unsubstituted or mono-, di- or tri-substituted (especially mono-, or di-substituted, in particular di-substituted) wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, cyano, or halogen (especially fluoro or chloro, in particular fluoro). Examples for the 5-membered heteroaryl containing at least one nitrogen atom and optionally one or two further heteroatoms selected from nitrogen or oxygen are 2,5-dimethyl-2H-pyrazol-3-yl, 4-chloro-2,5-dimethyl-2H-pyrazol-3-yl, 2,4,5-trimethyl-2H-pyrazol-3-yl, 5-cyclopropyl-2-methyl-2H-pyrazol-3-yl, 4-formyl-2,5-dimethyl-2H-pyrazol-3-yl, 4-cyano-2,5-dimethyl-2H-pyrazol-3-yl, 4-chloro-5-cyclopropyl-2-methyl-2H-pyrazol-3-yl, 5-cyclopropyl-2,4-dimethyl-2H-pyrazol-3-yl, 5-cyclopropyl-4-formyl-2-methyl-2H-pyrazol-3-yl, 5-isopropyl-[1,3,4]oxodiazol-2-yl, 5-trifluoromethyl-[1,3,4]oxodiazol-2-yl. Examples for the 6-membered heteroaryl group containing one or two nitrogen atoms are 3-methoxy-pyridin-2-yl, 3,5-dimethoxy-pyridin-4-yl, 2,4-dimethoxy-pyridin-3-yl, 3-methyl-pyridin-2-yl, 4-methyl-2-methoxy-pyridin-3-yl, 2-methyl-4-methoxy-pyridin-3-yl, 2-cyano-4-methyl-pyridin-3-yl, 2,4-dimethyl-pyridin-3-yl, 3,5-dimethyl-pyridin-4-yl, 3-fluoro-pyridin-2-yl, 2-fluoro-pyridin-3-yl, 4-fluoro-pyridin-3-yl, 3,5-difluoro-pyridin-4-yl, 3,5-dichloro-pyridazin-4-yl, 3,4-dichloro-pyridazin-2-yl, 4,6-dimethoxy-pyrimidin-5-yl or 4-methyl-6-methoxy-pyrimidin-5-yl.

For the substituent **R**², such 5- or 6-membered heteroaryl group is unsubstituted or mono-, di- or tri-substituted (especially mono-substituted) pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl, wherein the substituents are independently selected from (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), (C₁₋₄)alkyl (especially methyl and isopropyl), (C₁₋₄)alkoxy (especially methoxy and isopropoxy), halogen (especially chloro). Examples for the 5-membered heteroaryl containing at least one nitrogen atom and optionally one or two further heteroatoms selected from nitrogen or oxygen are 2-trifluoromethyl-thiazol-4-yl and 2-methyl-4-trifluoromethyl-thiazol-5-yl. Examples for the 6-membered heteroaryl group containing one or two nitrogen atoms are 3-methoxy-pyridin-2-yl, 3-isopropoxy-pyridin-2-yl, 4-trifluoromethyl-pyridin-3-yl, 2-trifluoro-pyridin-3-yl, 4-isopropyl-pyridin-3-yl, 3-trifluoromethyl-pyridin-4-yl, 4-methoxy-pyridazin-3-yl, 4-isopropoxy-pyridazin-3-yl, 4-methyl-pyridazin-3-yl, 6-chloro-4-methoxy-pyridazin-3-yl, 6-chloro-4-isopropoxy-pyridazin-3-yl, 4-methoxy-pyrimidin-5-yl, 4-trifluoromethyl-pyrimidin-5-yl, 3-trifluoromethyl-pyrazin-2-yl, 3-methoxy-pyrazin-2-yl, 3-isopropoxy-pyrazin-2-yl or 3-isopropyl-pyrazin-2-yl.

Further embodiments of the invention are presented hereinafter:

2) A second embodiment relates to compounds according to embodiment 1), wherein

- ring **A** represents a saturated 4- to 7-membered mono-cyclic carbocyclic ring containing the ring nitrogen atom to which **R**¹ is attached, wherein said ring independently is unsubstituted, or mono-substituted with (C₁₋₃)alkyl (especially methyl), fluoro, or (C₁₋₄)alkoxy-carbonyl (especially ethoxy-carbonyl), or di-substituted wherein the substituents are two (C₁₋₃)alkyl (especially methyl) substituents, or two fluoro substituents [especially such ring

A is azetidin-1,3-diyl, pyrrolidin-1,3-diyl, 4-methyl-pyrrolidin-1,3-diyl, piperidin-1,3-diyl, piperidin-1,4-diyl, 3-fluoro-piperidin-1,4-diyl, 2-methyl-piperidin-1,4-diyl, 3-methyl-piperidin-1,4-diyl, 3-(ethoxycarbonyl)-piperidin-1,4-diyl, 3,3-dimethyl-piperidin-1,4-diyl, azepan-1,4-diyl]; or

- ring **A** represents a saturated 7- or 8-membered bridged bi-cyclic carbocyclic ring containing the ring nitrogen atom to which **R**¹ is attached, wherein said ring is unsubstituted [especially such ring is 2-aza-bicyclo[2.2.1]heptane-2,5-diyl, 3-aza-bicyclo[3.1.1]heptane-3,6-diyl].

3) Another embodiment relates to compounds according to embodiment 1), wherein ring **A** represents a saturated 4- to 7-membered mono-cyclic carbocyclic ring containing the ring nitrogen atom to which **R**¹ is attached, wherein said ring independently is unsubstituted, or mono-substituted with (C₁₋₃)alkyl (especially methyl), fluoro, or (C₁₋₄)alkoxy-carbonyl (especially ethoxy-carbonyl), or di-substituted wherein the substituents are two (C₁₋₃)alkyl (especially methyl) substituents, or two fluoro substituents [especially such ring **A** is azetidin-1,3-diyl, pyrrolidin-1,3-diyl, 4-methyl-pyrrolidin-1,3-diyl, piperidin-1,3-diyl, piperidin-1,4-diyl, 3-fluoro-piperidin-1,4-diyl, 2-methyl-piperidin-1,4-diyl, 3-methyl-piperidin-1,4-diyl, 3-(ethoxycarbonyl)-piperidin-1,4-diyl, 3,3-dimethyl-piperidin-1,4-diyl, azepan-1,4-diyl].

4) Another embodiment relates to compounds according to embodiment 1), wherein ring **A** represents unsubstituted, mono- or di-substituted azetidin-1,3-diyl, pyrrolidin-1,3-diyl, piperidin-1,3-diyl, piperidin-1,4-diyl, azepan-1,4-diyl, 2-aza-bicyclo[2.2.1]heptane-2,5-diyl, 3-aza-bicyclo[3.1.1]heptane-3,6-diyl, wherein the substituents are selected from the group of (C₁₋₃)alkyl (especially methyl), fluoro, or (C₁₋₄)alkoxy-carbonyl (especially ethoxy-carbonyl) [especially such ring **A** is azetidin-1,3-diyl, pyrrolidin-1,3-diyl, 4-methyl-pyrrolidin-1,3-diyl, piperidin-1,3-diyl, piperidin-1,4-diyl, 3-fluoro-piperidin-1,4-diyl, 2-methyl-piperidin-1,4-diyl, 3-methyl-piperidin-1,4-diyl, 3-(ethoxycarbonyl)-piperidin-1,4-diyl, 3,3-dimethyl-piperidin-1,4-diyl, azepan-1,4-diyl, 2-aza-bicyclo[2.2.1]heptane-2,5-diyl, 3-aza-bicyclo[3.1.1]heptane-3,6-diyl].

5) Another embodiment relates to compounds according to embodiment 1), wherein ring **A** represents

- azetidin-1,3-diyl, pyrrolidin-1,3-diyl, 4-methyl-pyrrolidin-1,3-diyl, piperidin-1,3-diyl, piperidin-1,4-diyl, 3-fluoro-piperidin-1,4-diyl, 2-methyl-piperidin-1,4-diyl, 3-methyl-piperidin-1,4-diyl, 3-(ethoxycarbonyl)-piperidin-1,4-diyl, 3,3-dimethyl-piperidin-1,4-diyl, or azepan-1,4-diyl; or
- 2-aza-bicyclo[2.2.1]heptane-2,5-diyl, 3-aza-bicyclo[3.1.1]heptane-3,6-diyl;

wherein in a sub-embodiment ring **A** represents pyrrolidin-1,3-diyl, or piperidin-1,4-diyl (especially piperidin-1,4-diyl).

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

- **X** represents CR⁵; **Z** represents CR⁵; and **Y** represents CR⁵; wherein each **R**⁵ independently represents hydrogen, or (C₁₋₃)alkyl (especially methyl); wherein preferably at maximum one **R**⁵ is different from hydrogen [especially all **R**⁵ represent hydrogen];
- **X** represents CH; **Z** represents N; and **Y** represents CR⁵; wherein each **R**⁵ independently represents hydrogen, or (C₁₋₃)alkyl (especially methyl); [especially **R**⁵ represents hydrogen];

- **X** represents N; **Z** represents CR⁵; and **Y** represents CR⁵; wherein each **R**⁵ independently represents hydrogen, or (C₁₋₃)alkyl (especially methyl); wherein preferably at maximum one **R**⁵ is different from hydrogen; [especially all **R**⁵ represent hydrogen];
- **X** represents N; **Z** represents N; and **Y** represents CR⁵; wherein **R**⁵ represents hydrogen, or (C₁₋₃)alkyl (especially methyl); [especially **R**⁵ represents hydrogen].

7) Another embodiment relates to compounds according to any one of embodiments 1) to 5), wherein one of **X** and **Z** represents CH or N; the other represents CH; and **Y** represents CR⁵, wherein **R**⁵ represents hydrogen or (C₁₋₃)alkyl (especially **R**⁵ represents hydrogen).

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

- (C₁₋₄)alkyl (especially methyl, isopropyl);
- -CO-**R**¹¹ wherein **R**¹¹ represents (C₁₋₄)alkyl (especially tert-butyl); (C₁₋₄)alkoxy (especially methoxy, ethoxy, isopropoxy, n-butoxy, tert-butoxy); phenyl, phenoxy; (C₃₋₆)cycloalkyl (especially cyclopropyl); or (C₃₋₆)cycloalkoxy optionally containing one ring oxygen (especially oxetan-3-yloxy) and optionally mono-substituted with methyl or trifluoromethyl (especially 3-methyl-oxetan-3-yloxy, 3-trifluoromethyl-oxetan-3-yloxy); [especially such group -CO-**R**¹¹ is tert.-butyl-carbonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, tert.-butoxycarbonyl, oxetan-3-yl-oxy-carbonyl, (3-methyl-oxetan-3-yl)-oxy-carbonyl, (3-trifluoromethyl-oxetan-3-yl)-oxy-carbonyl, phenylcarbonyl, phenoxy carbonyl, cyclopropylcarbonyl];
- benzyl wherein the phenyl ring of said benzyl is optionally mono- or di-substituted with halogen [especially 2,4-dichlorobenzyl];
- phenyl which is unsubstituted, mono-, di- or tri-substituted (notably mono- or di-substituted, wherein at least one substituent is attached in *ortho* position with regard to the point of attachment of the rest of the molecule; especially di-substituted in *ortho* position), wherein the substituents are independently selected from
 - (C₁₋₄)alkyl (especially methyl, isopropyl);
 - (C₁₋₄)alkoxy (especially methoxy, n-butoxy);
 - (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
 - (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy);
 - halogen (especially fluoro, bromo);
 - cyano;
 - nitro;
 - hydroxy;
 - hydroxy-(C₁₋₃)alkyl (especially 1-hydroxyethyl, hydroxymethyl, 1-hydroxy-1-methyl-ethyl);
 - (C₁₋₄)alkoxy-(C₁₋₃)alkyl (especially 1-methoxyethyl);
 - hydroxy-(C₂₋₃)alkoxy (especially 2-hydroxy-ethoxy);
 - (C₁₋₄)alkoxy-(C₂₋₃)alkoxy (especially 2-methoxy-ethoxy);

- (C₃₋₆)cycloalkyl-**X**¹²-, wherein **X**¹² represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen [especially such group (C₃₋₆)cycloalkyl-**X**¹²- is cyclopropyl, cyclopropyl-oxy, cyclobutyl-oxy, oxetan-3-yl-oxy, cyclopropyl-methoxy or tetrahydropyran-4-yl-oxy];
- 5 ➤ **R**¹³-CO-**X**¹³-, wherein **X**¹³ represents a direct bond or (C₁₋₃)alkylene, and **R**¹³ represents hydrogen or (C₁₋₄)alkyl (especially such group **R**¹³-CO-**X**¹³ is formyl, acetyl, 2-oxo-ethyl);
- 3-(morpholin-4-yl)-prop-1-ynyl;
- **R**^{14a}**R**^{14b}N-**X**¹⁴-, wherein **X**¹⁴ represents a direct bond or (C₁₋₃)alkylene; and wherein **R**^{14a} and **R**^{14b} independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R**^{14a} and **R**^{14b} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl (especially methyl), hydroxy, (C₁₋₄)alkoxy (especially methoxy), or dimethylamino;
- 10 [especially such group **R**^{14a}**R**^{14b}N-**X**¹⁴- is amino, methylamino-methyl, dimethylamino-methyl, [(2-hydroxyethyl)-methylamino]-methyl, [(2-hydroxyethyl)-ethylamino]-methyl, [(2-methoxy-1-methyl-ethyl)-amino]-methyl, [(2-methoxyethyl)-methylamino]-methyl, [di-(2-hydroxyethyl)-amino]-methyl, (azetidin-1-yl)-methyl, (pyrrolidin-1-yl)-methyl, (piperidin-1-yl)-methyl, morpholin-4-yl, piperazin-1-ylmethyl (morpholin-4-yl)-methyl, 2-(morpholin-4-yl)-ethyl, 3-(morpholin-4-yl)-propyl, (3-methoxy-azetidin-1-yl)-methyl, 1-(3-methoxy-azetidin-1-yl)-ethyl, (1-methyl-piperazin-4-yl)-methyl, (4-hydroxypiperidin-1-yl)-methyl, (4-methoxypiperidin-1-yl)-methyl, (3-methoxy-pyrrolidin-1-yl)-methyl, (4-dimethylamino-piperidin-1-yl)-methyl];
- 20 or
- benzyloxy; or
- 5- or 6-membered heteroaryl (especially pyrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl); wherein said 5- or 6-membered heteroaryl independently is mono-, di- or tri-substituted (notably mono-, di-, or tri-substituted
- 25 wherein at least one substituent is attached in *ortho* position with regard to the point of attachment of the rest of the molecule; especially di-substituted in *ortho* position), wherein the substituents are independently selected from
- (C₁₋₄)alkyl (especially methyl, isopropyl);
- (C₁₋₄)alkoxy (especially methoxy);
- 30 ➤ (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
- (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy);
- halogen (especially fluoro, chloro);
- cyano;
- (C₃₋₆)cycloalkyl-**X**¹²-, wherein **X**¹² represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-; [especially such group (C₃₋₆)cycloalkyl-**X**¹²- is cyclopropyl,]; or
- 35 ➤ **R**¹³-CO-**X**¹³-, wherein **X**¹³ represents a direct bond or (C₁₋₃)alkylene, and **R**¹³ represents hydrogen or (C₁₋₄)alkyl (especially such group **R**¹³-CO-**X**¹³ is formyl).

wherein in a sub-embodiment **R**¹ represents phenyl, or 5- or 6-membered heteroaryl (especially pyrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl); wherein said phenyl or 5- or 6-membered heteroaryl are substituted as defined herein before.

9) Another embodiment relates to compounds according to any one of embodiments 1) to 7), wherein

5 **R**¹ represents

- -CO-**R**¹¹ wherein **R**¹¹ represents (C₁₋₄)alkyl (especially tert-butyl); or (C₁₋₄)alkoxy (especially methoxy, ethoxy, isopropoxy, n-butoxy, tert-butoxy); [especially such group -CO-**R**¹¹ is tert-butyl-carbonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, tert-butoxycarbonyl];
 - phenyl which is mono-, or di- or tri-substituted (notably mono- or di-substituted wherein at least one substituent is attached in *ortho* position with regard to the point of attachment of the rest of the molecule; especially di-substituted in *ortho* position), wherein the substituents are independently selected from
 - (C₁₋₄)alkyl (especially methyl, isopropyl);
 - (C₁₋₄)alkoxy (especially methoxy);
 - (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
 - (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy);
 - halogen (especially fluoro, bromo);
 - cyano;
 - nitro;
 - hydroxy-(C₁₋₃)alkyl (especially 1-hydroxyethyl, hydroxymethyl, 1-hydroxy-1-methyl-ethyl);
 - (C₁₋₄)alkoxy-(C₁₋₃)alkyl (especially 1-methoxyethyl);
 - hydroxy-(C₂₋₃)alkoxy (especially 2-hydroxy-ethoxy);
 - (C₁₋₄)alkoxy-(C₂₋₃)alkoxy (especially 2-methoxy-ethoxy);
 - (C₃₋₆)cycloalkyl-**X**¹²-, wherein **X**¹² represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-; [especially such group (C₃₋₆)cycloalkyl-**X**¹²- is cyclobutyl-oxy, or cyclopropyl-methoxy]; or
 - **R**^{14a}**R**^{14b}**N**-**X**¹⁴-, wherein **X**¹⁴ represents a direct bond or (C₁₋₃)alkylene; and wherein **R**^{14a} and **R**^{14b} independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R**^{14a} and **R**^{14b} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl (especially methyl), hydroxy, (C₁₋₄)alkoxy (especially methoxy), or dimethylamino;
- [especially such group **R**^{14a}**R**^{14b}**N**-**X**¹⁴- is amino, methylamino-methyl, dimethylamino-methyl, [(2-hydroxyethyl)-methylamino]-methyl, [(2-hydroxyethyl)-ethylamino]-methyl, [(2-methoxy-1-methyl-ethyl)-amino]-methyl, [(2-methoxyethyl)-methylamino]-methyl, [di-(2-hydroxyethyl)-amino]-methyl, (azetidin-1-yl)-methyl, (pyrrolidin-1-yl)-methyl, (piperidin-1-yl)-methyl, morpholin-4-yl, (morpholin-4-yl)-methyl, piperazin-1-ylmethyl, 2-(morpholin-4-yl)-ethyl, 3-(morpholin-4-yl)-propyl, (3-methoxy-azetidin-1-yl)-methyl, 1-(3-methoxy-azetidin-1-yl)-ethyl, (1-methyl-piperazin-4-yl)-methyl, (4-hydroxypiperidin-1-yl)-methyl, (4-

methoxypiperidin-1-yl)-methyl, (3-methoxy-pyrrolidin-1-yl)-methyl, (4-dimethylamino-piperidin-1-yl)-methyl.]; or

- 5- or 6-membered heteroaryl (especially pyrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl); wherein said 5- or 6-membered heteroaryl independently is mono-, di- or tri-substituted (notably mono-, di-, or tri-substituted wherein at least one substituent is attached in *ortho* position with regard to the point of attachment of the rest of the molecule; especially di-substituted in *ortho* position), wherein the substituents are independently selected from
 - (C₁₋₄)alkyl (especially methyl, isopropyl);
 - (C₁₋₄)alkoxy (especially methoxy);
 - (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
 - halogen (especially fluoro, chloro);
 - cyano; or
 - (C₃₋₆)cycloalkyl-**X**¹²-, wherein **X**¹² represents a direct bond, [especially such group (C₃₋₆)cycloalkyl-**X**¹²- is cyclopropyl].

wherein in a sub-embodiment **R**¹ represents phenyl, or 5- or 6-membered heteroaryl (especially pyrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl); wherein said phenyl or 5- or 6-membered heteroaryl are substituted as defined herein before.

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

- -CO-**R**¹¹ wherein **R**¹¹ represents (C₁₋₄)alkyl (especially tert-butyl); or (C₁₋₄)alkoxy (especially methoxy, ethoxy, isopropoxy, n-butoxy, tert-butoxy); [especially such group -CO-**R**¹¹ is tert.-butyl-carbonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, tert.-butoxycarbonyl];
- phenyl which is mono-, or di- or tri-substituted (notably mono- or di-substituted); wherein one substituent is (C₁₋₄)alkyl (especially methyl), (C₁₋₄)alkoxy (especially methoxy), or halogen (especially fluoro) [especially such substituent is methyl, methoxy or fluoro; in particular methyl]; wherein said substituent is attached in *ortho* position with regard to the point of attachment of the rest of the molecule; and, if present, the remaining substituent(s) are independently selected from:
 - (C₁₋₄)alkyl (especially methyl, isopropyl);
 - (C₁₋₄)alkoxy (especially methoxy);
 - (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
 - (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy);
 - halogen (especially fluoro, bromo);
 - cyano;
 - hydroxy-(C₁₋₃)alkyl (especially 1-hydroxyethyl, hydroxymethyl, 1-hydroxy-1-methyl-ethyl);
 - (C₁₋₄)alkoxy-(C₁₋₃)alkyl (especially 1-methoxyethyl);

- (C₁₋₄)alkoxy-(C₂₋₃)alkoxy (especially 2-methoxy-ethoxy);
 - (C₃₋₆)cycloalkyl-**X**¹²-, wherein **X**¹² represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-; [especially such group (C₃₋₆)cycloalkyl-**X**¹²- is , cyclobutyl-oxy or cyclopropyl-methoxy]; or
 - **R**^{14a}**R**^{14b}N-**X**¹⁴-, wherein **X**¹⁴ represents a direct bond or (C₁₋₃)alkylene; and wherein **R**^{14a} and **R**^{14b} independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R**^{14a} and **R**^{14b} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl (especially methyl), hydroxy, (C₁₋₄)alkoxy (especially methoxy), or dimethylamino;
 - [especially such group **R**^{14a}**R**^{14b}N-**X**¹⁴- is amino, methylamino-methyl, dimethylamino-methyl, [(2-hydroxyethyl)-methylamino]-methyl, [(2-hydroxyethyl)-ethylamino]-methyl, [(2-methoxy-1-methyl-ethyl)-amino]-methyl, [(2-methoxyethyl)-methylamino]-methyl, [di-(2-hydroxyethyl)-amino]-methyl, (azetidin-1-yl)-methyl, (pyrrolidin-1-yl)-methyl, (piperidin-1-yl)-methyl, morpholin-4-yl, (morpholin-4-yl)-methyl, piperazin-1-ylmethyl, 2-(morpholin-4-yl)-ethyl, 3-(morpholin-4-yl)-propyl, (3-methoxy-azetidin-1-yl)-methyl, 1-(3-methoxy-azetidin-1-yl)-ethyl, (1-methyl-piperazin-4-yl)-methyl, (4-hydroxypiperidin-1-yl)-methyl, (4-methoxypiperidin-1-yl)-methyl, (3-methoxy-pyrrolidin-1-yl)-methyl, (4-dimethylamino-piperidin-1-yl)-methyl.]; or
 - 5- or 6-membered heteroaryl (especially pyrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl); wherein said 5- or 6-membered heteroaryl independently is mono-, di- or tri-substituted; wherein one substituent is (C₁₋₄)alkyl (especially methyl), (C₁₋₄)alkoxy (especially methoxy), or halogen (especially fluoro); wherein said substituent is attached in *ortho* position with regard to the point of attachment of the rest of the molecule; and, if present, the remaining substituent(s) are independently selected from
 - (C₁₋₄)alkyl (especially methyl, isopropyl);
 - (C₁₋₄)alkoxy (especially methoxy);
 - (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
 - halogen (especially fluoro, chloro);
 - cyano; or
 - (C₃₋₆)cycloalkyl-**X**¹²-, wherein **X**¹² represents a direct bond; [especially such group (C₃₋₆)cycloalkyl-**X**¹²- is cyclopropyl].
- wherein in a sub-embodiment **R**¹ represents phenyl, or 5- or 6-membered heteroaryl selected from pyrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, and pyrimidinyl; wherein said phenyl or 5- or 6-membered heteroaryl are substituted as defined herein before.
- 11) Another embodiment relates to compounds according to any one of embodiments 1) to 7), wherein **R**¹ represents
- -CO-**R**¹¹ wherein **R**¹¹ represents (C₁₋₄)alkoxy (especially isopropoxy, tert-butoxy);

- phenyl which is mono-, or di- or tri-substituted (notably mono- or di-substituted); wherein one substituent is (C₁₋₄)alkyl (especially methyl), (C₁₋₄)alkoxy (especially methoxy), or halogen (especially fluoro) [especially such substituent is methyl, methoxy or fluoro; in particular methyl]; wherein said substituent is attached in *ortho* position with regard to the point of attachment of the rest of the molecule; and, if present, the remaining substituent(s) are independently selected from:
 - (C₁₋₄)alkyl (especially methyl, isopropyl);
 - (C₁₋₄)alkoxy (especially methoxy);
 - (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
 - (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy);
 - halogen (especially fluoro, bromo);
 - cyano;
 - hydroxy-(C₁₋₃)alkyl (especially 1-hydroxyethyl, hydroxymethyl, 1-hydroxy-1-methyl-ethyl);
 - (C₁₋₄)alkoxy-(C₁₋₃)alkyl (especially 1-methoxyethyl);
 - (C₁₋₄)alkoxy-(C₂₋₃)alkoxy (especially 2-methoxy-ethoxy);
 - (C₃₋₆)cycloalkyl-**X**¹²-, wherein **X**¹² represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-; [especially such group (C₃₋₆)cycloalkyl-**X**¹²- is cyclobutyl-oxy, or cyclopropyl-methoxy]; or
 - **R**^{14a}**R**^{14b}**N**-**X**¹⁴-, wherein **X**¹⁴ represents a direct bond or (C₁₋₃)alkylene; and wherein **R**^{14a} represents hydrogen or (C₁₋₄)alkyl, and **R**^{14b} independently represents hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, or (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R**^{14a} and **R**^{14b} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl (especially methyl), hydroxy, (C₁₋₄)alkoxy (especially methoxy), or dimethylamino; [especially such group **R**^{14a}**R**^{14b}**N**-**X**¹⁴- is amino, methylamino-methyl, dimethylamino-methyl, [(2-hydroxyethyl)-methylamino]-methyl, [(2-hydroxyethyl)-ethylamino]-methyl, [(2-methoxy-1-methyl-ethyl)-amino]-methyl, [(2-methoxyethyl)-methylamino]-methyl, [di-(2-hydroxyethyl)-amino]-methyl, (azetidin-1-yl)-methyl, (pyrrolidin-1-yl)-methyl, (piperidin-1-yl)-methyl, morpholin-4-yl, piperazin-1-ylmethyl, (morpholin-4-yl)-methyl, 2-(morpholin-4-yl)-ethyl, 3-(morpholin-4-yl)-propyl, (3-methoxy-azetidin-1-yl)-methyl, 1-(3-methoxy-azetidin-1-yl)-ethyl, (1-methyl-piperazin-4-yl)-methyl, (4-hydroxypiperidin-1-yl)-methyl, (4-methoxypiperidin-1-yl)-methyl, (3-methoxy-pyrrolidin-1-yl)-methyl, (4-dimethylamino-piperidin-1-yl)-methyl.]; or
- 6-membered heteroaryl (especially pyridinyl, pyridazinyl, pyrimidinyl); wherein said 6-membered heteroaryl independently is mono-, di- or tri-substituted (notably mono-, or di-substituted); wherein one substituent is (C₁₋₄)alkyl (especially methyl), (C₁₋₄)alkoxy (especially methoxy), or halogen (especially fluoro); wherein said substituent is attached in *ortho* position with regard to the point of attachment of the rest of the molecule; and, if present, the remaining substituent(s) are independently selected from
 - (C₁₋₄)alkyl (especially methyl, isopropyl);

- (C₁₋₄)alkoxy (especially methoxy);
- (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
- halogen (especially fluoro);
- cyano; or
- 5 ➤ (C₃₋₆)cycloalkyl-**X**¹²-, wherein **X**¹² represents a direct bond [especially such group (C₃₋₆)cycloalkyl-**X**¹²- is cyclopropyl];

wherein in a sub-embodiment **R**¹ represents phenyl, or 6-membered heteroaryl selected from pyridinyl, pyridazinyl, and pyrimidinyl; wherein said phenyl or 6-membered heteroaryl are substituted as defined herein before.

12) Another embodiment relates to compounds according to any one of embodiments 1) to 7), wherein
10 **R**¹ represents phenyl which is mono-, or di- or tri-substituted (notably mono- or di-substituted); wherein

- one substituent is
 - (C₁₋₄)alkyl (especially methyl);
 - (C₁₋₄)alkoxy (especially methoxy); or
 - halogen (especially fluoro);

15 wherein said substituent is attached in *ortho* position with regard to the point of attachment of the rest of the molecule [especially such substituent is methyl, methoxy or fluoro; in particular methyl];

- and, if present, the remaining substituent(s) is/are independently selected from:
 - methyl;
 - methoxy;
 - 20 ➤ halogen (especially fluoro);
 - cyano, or
 - amino.

13) Another embodiment relates to compounds according to any one of embodiments 1) to 12), wherein **R**² represents phenyl, or 6-membered heteroaryl (in particular pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl) [especially
25 **R**² represents phenyl]; wherein said phenyl or 6-membered heteroaryl independently is mono-, or di-substituted (especially mono-substituted, in particular mono-substituted in *ortho* position with regard to the point of attachment of the rest of the molecule), wherein the substituents are independently selected from

- (C₁₋₄)alkyl (especially methyl, isopropyl);
- (C₁₋₄)alkoxy (especially methoxy, isopropoxy);
- 30 ➤ (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
- (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy);
- halogen (especially chloro, fluoro); or
- (C₃₋₆)cycloalkyl-**X**²¹-, wherein **X**²¹ represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen; [especially such group (C₃₋₆)cycloalkyl-**X**²¹- is cyclopropyl, cyclopropyl-oxy, cyclobutyl-oxy, oxetan-3-yl-oxy, cyclopropyl-methoxy].
- 35

14) Another embodiment relates to compounds according to any one of embodiments 1) to 12), wherein **R**² represents phenyl, or 6-membered heteroaryl (in particular pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl) [especially **R**² represents phenyl]; wherein said phenyl or 6-membered heteroaryl is mono-substituted in *ortho* position with regard to the point of attachment of the rest of the molecule, wherein the substituent is independently selected from

- 5 ➤ (C₁₋₄)alkyl (especially methyl, isopropyl);
- (C₁₋₄)alkoxy (especially methoxy, isopropoxy);
- (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
- (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy); or
- 10 ➤ (C₃₋₆)cycloalkyl-**X**²¹-, wherein **X**²¹ represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen; [especially such group (C₃₋₆)cycloalkyl-**X**²¹- is cyclopropyl, cyclopropyl-oxy, cyclobutyl-oxy, oxetan-3-yl-oxy, cyclopropyl-methoxy].

15) Another embodiment relates to compounds according to any one of embodiments 1) to 12), wherein

R² represents phenyl, which is mono-substituted in *ortho* position with regard to the point of attachment of the rest of the molecule, wherein the substituent is independently selected from

- 15 ➤ (C₁₋₄)alkyl (especially isopropyl);
- (C₁₋₄)alkoxy (especially methoxy, isopropoxy);
- (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
- (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy); or
- cyclopropyl-oxy, cyclopropyl-methoxy, cyclobutyl-oxy, oxetan-3-yl-oxy;

20 or **R**² represents 6-membered heteroaryl (in particular pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl); wherein said 6-membered heteroaryl is mono-substituted in *ortho* position with regard to the point of attachment of the rest of the molecule, wherein the substituent is independently selected from

- (C₁₋₄)alkyl (especially isopropyl);
- (C₁₋₄)alkoxy (especially methoxy, isopropoxy);
- 25 ➤ (C₁₋₃)fluoroalkyl (especially trifluoromethyl); or
- (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy).

16) Another embodiment relates to compounds according to any one of embodiments 1) to 15), wherein **R**³ represents hydrogen, or methyl (especially hydrogen). In a sub-embodiment **R**³ represents hydrogen.

17) Another embodiment relates to compounds according to any one of embodiments 1) to 16),

30 **R**⁴ represents

- (C₁₋₄)alkyl (especially methyl);
- hydroxy-(C₁₋₃)alkyl (especially hydroxymethyl);
- -O-**R**⁴¹, wherein **R**⁴¹ represents
 - hydrogen;

- (C₁₋₄)alkyl (especially methyl);
- (C₂₋₄)alkyl which is substituted with one or two hydroxy (especially 2-hydroxyethyl, 2,3-dihydroxypropyl);
- **R**^{41a}**R**^{41b}N-(C₂₋₃)alkylene-, wherein **R**^{41a} and **R**^{41b} independently represent hydrogen or (C₁₋₄)alkyl (especially such group is 2-dimethylamino-ethyl); or
- 5 ➤ (C₄₋₇)heterocyclyl-**X**⁴¹-, wherein **X**⁴¹ represents a direct bond or (C₁₋₃)alkylene, and wherein the (C₄₋₇)heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen and oxygen; wherein the oxygen atom of such group (C₄₋₇)heterocyclyl-**X**⁴¹-O- is separated by at least two (ring and/or chain) carbon atoms from such ring heteroatom; wherein said (C₄₋₇)heterocyclyl independently is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently
10 selected from:
 - (C₁₋₄)alkyl (especially methyl); and/or
 - (C₁₋₄)alkoxy-carbonyl attached to a ring nitrogen atom having a free valency;
 [especially such (C₄₋₇)heterocyclyl-**X**⁴¹- group is oxetan-3-yl, 1-methyl-pyrrolidin-3-yl, 2,2-dimethyl-dioxolan-4-yl-methyl, 2-morpholin-4-yl-ethyl, 1-tert-butoxy-carbonyl-piperidin-4-yl, piperidin-4-yl];
- 15 • -**NR**^{42a}**R**^{42b} wherein **R**^{42a} represents hydrogen or (C₁₋₄)alkyl, and **R**^{42b} independently represents hydrogen, (C₁₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₃)alkyl, hydroxy-(C₂₋₃)alkyl, or **R**^{42a} and **R**^{42b} together with the nitrogen to which they are attached form a 4- to 7-membered saturated ring optionally containing one further ring heteroatom selected from oxygen and nitrogen, wherein said ring is unsubstituted or mono-substituted with (C₁₋₃)alkyl (especially methyl), or (C₁₋₃)alkoxy (especially methoxy) [especially such group -**NR**^{42a}**R**^{42b} is (2-hydroxyethyl)-amino, (2-hydroxyethyl)-methyl-amino, (2-methoxyethyl)-amino, morpholin-4-yl, 3-methoxy-azetidiny, or 4-methyl-
20 piperazin-1-yl]; or
- -CO-**R**⁴³ wherein **R**⁴³ represents (C₁₋₄)alkoxy (especially methoxy); or -**NR**^{43a}**R**^{43b} wherein **R**^{43a} represents hydrogen or (C₁₋₄)alkyl (especially methyl), and **R**^{43b} independently represents hydrogen, (C₁₋₄)alkyl (especially methyl), (C₁₋₃)alkoxy-(C₂₋₃)alkyl (especially 2-methoxy-ethyl), or hydroxy-(C₂₋₃)alkyl (especially 2-hydroxy-ethyl);
25 [especially such group -CO-**R**⁴³ is methoxycarbonyl, carbamoyl, methyl-carbamoyl, dimethylcarbamoyl, hydroxyethylcarbamoyl, methoxyethylcarbamoyl];

wherein in a sub-embodiment **R**⁴ represents -O-**R**⁴¹ as defined herein above; especially **R**⁴ represents (C₁₋₄)alkoxy (in particular methoxy).

18) Another embodiment relates to compounds according to any one of embodiments 1) to 16), wherein

30 **R**⁴ represents

- (C₁₋₄)alkyl (especially methyl);
- hydroxy-(C₁₋₃)alkyl (especially hydroxymethyl);
- -O-**R**⁴¹, wherein **R**⁴¹ represents
 - hydrogen;
 - 35 ➤ (C₁₋₄)alkyl (especially methyl);
 - (C₂₋₄)alkyl which is substituted with one or two hydroxy (especially 2-hydroxyethyl, 2,3-dihydroxypropyl);

- $R^{41a}R^{41b}N-(C_{2-3})$ alkylene-, wherein R^{41a} and R^{41b} independently represent hydrogen or (C_{1-4}) alkyl (especially such group is 2-dimethylamino-ethyl); or
- (C_{4-7}) heterocyclyl- X^{41} -, wherein X^{41} represents a direct bond or $-CH_2-$, and wherein the (C_{4-7}) heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen and oxygen; wherein the oxygen atom of such group (C_{4-7}) heterocyclyl- X^{41} -O- is separated by at least two (ring and/or chain) carbon atoms from such ring heteroatom; wherein said (C_{4-7}) heterocyclyl independently is unsubstituted, or mono-substituted with (C_{1-4}) alkyl (especially methyl) at a ring nitrogen atom having a free valency, or di-substituted with methyl; [especially such (C_{4-7}) heterocyclyl- X^{41} - group is oxetan-3-yl, 1-methyl-pyrrolidin-3-yl, 2,2-dimethyldioxolan-4-yl-methyl, 2-morpholin-4-yl-ethyl];
- $-NR^{42a}R^{42b}$ wherein R^{42a} represents hydrogen or (C_{1-4}) alkyl (especially methyl), and R^{42b} independently represents (C_{1-4}) alkyl, (C_{1-3}) alkoxy- (C_{2-3}) alkyl, hydroxy- (C_{2-3}) alkyl; or R^{42a} and R^{42b} together with the nitrogen to which they are attached form a 4- to 7-membered saturated ring optionally containing one further ring heteroatom selected from oxygen and nitrogen, wherein said ring is unsubstituted, or mono-substituted with (C_{1-3}) alkyl (especially methyl) attached to a ring nitrogen atom having a free valency, or (C_{1-3}) alkoxy (especially methoxy) attached to a ring carbon atom [especially such group $-NR^{42a}R^{42b}$ is (2-hydroxyethyl)-amino, (2-hydroxyethyl)-methyl-amino, (2-methoxyethyl)-amino, morpholin-4-yl, 3-methoxy-azetidiny, or 4-methylpiperazin-1-yl]; or
- $-CO-R^{43}$ wherein R^{43} represents (C_{1-4}) alkoxy (especially methoxy); or $-NR^{43a}R^{43b}$ wherein R^{43a} represents hydrogen or (C_{1-4}) alkyl (especially methyl), and R^{43b} independently represents hydrogen, (C_{1-4}) alkyl (especially methyl), (C_{1-3}) alkoxy- (C_{2-3}) alkyl (especially 2-methoxy-ethyl), or hydroxy- (C_{2-3}) alkyl (especially 2-hydroxy-ethyl); [especially such group $-CO-R^{43}$ is methoxycarbonyl, carbamoyl, methyl-carbamoyl, dimethylcarbamoyl, hydroxyethylcarbamoyl, methoxyethylcarbamoyl];

wherein in a sub-embodiment R^4 represents $-O-R^{41}$ as defined herein above; especially R^4 represents (C_{1-4}) alkoxy (in particular methoxy).

19) Another embodiment relates to compounds according to any one of embodiments 1) to 16), wherein

R^4 represents

- (C_{1-4}) alkyl (especially methyl);
- hydroxy- (C_{1-3}) alkyl (especially hydroxymethyl);
- $-O-R^{41}$, wherein R^{41} represents
 - hydrogen;
 - (C_{1-4}) alkyl (especially methyl);
 - (C_{2-4}) alkyl which is substituted with one or two hydroxy (especially 2-hydroxyethyl, 2,3-dihydroxypropyl);
 - $R^{41a}R^{41b}N-(C_{2-3})$ alkylene-, wherein R^{41a} represent hydrogen or (C_{1-4}) alkyl, and R^{41b} independently represents (C_{1-4}) alkyl (especially such group is 2-dimethylamino-ethyl); or

➤ (C₄₋₇)heterocyclyl-**X**⁴¹-, wherein **X**⁴¹ represents a direct bond, -CH₂-, or -CH₂-CH₂-, and wherein the (C₄₋₇)heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen and oxygen; wherein the oxygen atom of such group (C₄₋₇)heterocyclyl-**X**⁴¹-O- is separated by at least two (ring and/or chain) carbon atoms from such ring heteroatom; wherein said (C₄₋₇)heterocyclyl independently is unsubstituted, or mono-substituted with (C₁₋₄)alkyl (especially methyl) at a ring nitrogen atom having a free valency, or di-substituted with methyl; [especially such (C₄₋₇)heterocyclyl-**X**⁴¹- group is oxetan-3-yl, 1-methyl-pyrrolidin-3-yl, 2,2-dimethyl-dioxolan-4-yl-methyl, 2-morpholin-4-yl-ethyl];

- -NR^{42a}R^{42b} wherein **R**^{42a} represents hydrogen or (C₁₋₄)alkyl (especially methyl), and **R**^{42b} independently represents (C₁₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₃)alkyl, hydroxy-(C₂₋₃)alkyl; or **R**^{42a} and **R**^{42b} together with the nitrogen to which they are attached form a 4- to 7-membered saturated ring optionally containing one further ring heteroatom selected from oxygen and nitrogen, wherein said ring is unsubstituted, or mono-substituted with (C₁₋₃)alkyl (especially methyl) attached to a ring nitrogen atom having a free valency, or mono-substituted with (C₁₋₃)alkoxy (especially methoxy) attached to a ring carbon atom [especially such group -NR^{42a}R^{42b} is (2-hydroxyethyl)-amino, (2-hydroxyethyl)-methyl-amino, (2-methoxyethyl)-amino, morpholin-4-yl, 3-methoxy-azetidiny, or 4-methyl-piperazin-1-yl]; or
- -CO-**R**⁴³ wherein **R**⁴³ represents (C₁₋₄)alkoxy (especially methoxy); or -NR^{43a}R^{43b} wherein **R**^{43a} represents hydrogen or (C₁₋₄)alkyl (especially methyl), and **R**^{43b} independently represents hydrogen, (C₁₋₄)alkyl (especially methyl), (C₁₋₃)alkoxy-(C₂₋₃)alkyl (especially 2-methoxy-ethyl), or hydroxy-(C₂₋₃)alkyl (especially 2-hydroxy-ethyl); [especially such group -CO-**R**⁴³ is methoxycarbonyl, carbamoyl, methyl-carbamoyl, dimethylcarbamoyl, hydroxyethylcarbamoyl, methoxyethylcarbamoyl];

wherein in a sub-embodiment **R**⁴ represents -O-**R**⁴¹ as defined herein above; especially **R**⁴ represents (C₁₋₄)alkoxy (in particular methoxy).

20) Another embodiment relates to compounds according to any one of embodiments 1) to 16), wherein

R⁴ represents

- hydroxy;
- (C₁₋₄)alkoxy (especially methoxy);
- 2-hydroxy-ethoxy, or 2,3-dihydroxy-propoxy;
- (oxetan-3-yl)-oxy-, (2,2-dimethyl-dioxolan-4-yl)-methoxy, or (2-morpholin-4-yl)-ethyl;
- (2-hydroxyethyl)-amino, (2-hydroxyethyl)-methyl-amino, or (2-methoxyethyl)-amino; or
- morpholin-4-yl, or 3-methoxy-azetidiny;

wherein in a sub-embodiment **R**⁴ represents (C₁₋₄)alkoxy (especially methoxy) or 2-hydroxy-ethoxy.

21) Another embodiment relates to compounds according to any one of embodiments 1) to 16), wherein

R⁴ represents

- hydroxy;

- (C₁₋₄)alkoxy (especially methoxy);
- 2-hydroxy-ethoxy;
- 2,3-dihydroxy-propoxy;
- (oxetan-3-yl)-oxy-;
- 5 • (2,2-dimethyl-dioxolan-4-yl)-methoxy;
- (2-hydroxyethyl)-methyl-amino; or
- morpholin-4-yl; or
- 3-methoxy-azetidiny;

wherein in a sub-embodiment **R⁴** represents (C₁₋₄)alkoxy (especially methoxy).

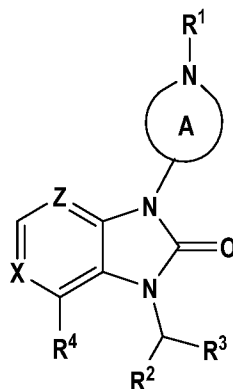
- 10 22) The invention, thus, relates to compounds of the formula (I) as defined in embodiment 1), or to such compounds further limited by the characteristics of any one of embodiments 2) to 21), under consideration of their respective dependencies; to pharmaceutically acceptable salts thereof; and to the use of such compounds as medicaments especially in the treatment of disorders relating to diseases and disorders related to pathogenic events associated with elevated levels of C5a and/or with C5aR activation. For avoidance of any doubt, especially
- 15 the following embodiments relating to the compounds of formula (I) are thus possible and intended and herewith specifically disclosed in individualized form:

- 1, 2+1, 3+1, 5+1, 6+1, 6+2+1, 6+3+1, 7+1, 7+5+1, 8+1, 8+2+1, 8+3+1, 8+6+1, 8+6+2+1, 8+6+3+1, 9+1, 9+2+1, 9+3+1, 9+6+1, 9+6+2+1, 9+6+3+1, 11+1, 11+5+1, 11+7+1, 11+7+5+1, 12+1, 12+5+1, 12+7+1, 12+7+5+1, 13+1, 13+2+1, 13+3+1, 13+6+1, 13+6+2+1, 13+6+3+1, 13+8+1, 13+8+2+1, 13+8+3+1, 13+8+6+1, 13+8+6+2+1,
- 20 13+8+6+3+1, 13+9+1, 13+9+2+1, 13+9+3+1, 13+9+6+1, 13+9+6+2+1, 13+9+6+3+1, 14+1, 14+5+1, 14+7+1, 14+7+5+1, 14+11+1, 14+11+5+1, 14+11+7+1, 14+11+7+5+1, 14+12+1, 14+12+5+1, 14+12+7+1, 14+12+7+5+1, 15+1, 15+5+1, 15+7+1, 15+7+5+1, 15+11+1, 15+11+5+1, 15+11+7+1, 15+11+7+5+1, 15+12+1, 15+12+5+1, 15+12+7+1, 15+12+7+5+1, 16+1, 16+2+1, 16+3+1, 16+5+1, 16+6+1, 16+6+2+1, 16+6+3+1, 16+7+1, 16+7+5+1, 16+8+1, 16+8+2+1, 16+8+3+1, 16+8+6+1, 16+8+6+2+1, 16+8+6+3+1, 16+9+1, 16+9+2+1, 16+9+3+1, 16+9+6+1,
- 25 16+9+6+2+1, 16+9+6+3+1, 16+11+1, 16+11+5+1, 16+11+7+1, 16+11+7+5+1, 16+12+1, 16+12+5+1, 16+12+7+1, 16+12+7+5+1, 16+13+1, 16+13+2+1, 16+13+3+1, 16+13+6+1, 16+13+6+2+1, 16+13+6+3+1, 16+13+8+1, 16+13+8+2+1, 16+13+8+3+1, 16+13+8+6+1, 16+13+8+6+2+1, 16+13+8+6+3+1, 16+13+9+1, 16+13+9+2+1, 16+13+9+3+1, 16+13+9+6+1, 16+13+9+6+2+1, 16+13+9+6+3+1, 16+14+1, 16+14+5+1, 16+14+7+1, 16+14+7+5+1, 16+14+11+1, 16+14+11+5+1, 16+14+11+7+1, 16+14+11+7+5+1, 16+14+12+1, 16+14+12+5+1,
- 30 16+14+12+7+1, 16+14+12+7+5+1, 16+15+1, 16+15+5+1, 16+15+7+1, 16+15+7+5+1, 16+15+11+1, 16+15+11+5+1, 16+15+11+7+1, 16+15+11+7+5+1, 16+15+12+1, 16+15+12+5+1, 16+15+12+7+1, 16+15+12+7+5+1, 17+1, 17+2+1, 17+3+1, 17+6+1, 17+6+2+1, 17+6+3+1, 17+8+1, 17+8+2+1, 17+8+3+1, 17+8+6+1, 17+8+6+2+1, 17+8+6+3+1, 17+9+1, 17+9+2+1, 17+9+3+1, 17+9+6+1, 17+9+6+2+1, 17+9+6+3+1, 17+13+1, 17+13+2+1, 17+13+3+1, 17+13+6+1, 17+13+6+2+1, 17+13+6+3+1, 17+13+8+1, 17+13+8+2+1,
- 35 17+13+8+3+1, 17+13+8+6+1, 17+13+8+6+2+1, 17+13+8+6+3+1, 17+13+9+1, 17+13+9+2+1, 17+13+9+3+1, 17+13+9+6+1, 17+13+9+6+2+1, 17+13+9+6+3+1, 17+16+1, 17+16+2+1, 17+16+3+1, 17+16+5+1, 17+16+6+1,

- 17+16+6+2+1, 17+16+6+3+1, 17+16+7+1, 17+16+7+5+1, 17+16+8+1, 17+16+8+2+1, 17+16+8+3+1,
 17+16+8+6+1, 17+16+8+6+2+1, 17+16+8+6+3+1, 17+16+9+1, 17+16+9+2+1, 17+16+9+3+1, 17+16+9+6+1,
 17+16+9+6+2+1, 17+16+9+6+3+1, 17+16+11+1, 17+16+11+5+1, 17+16+11+7+1, 17+16+11+7+5+1,
 17+16+12+1, 17+16+12+5+1, 17+16+12+7+1, 17+16+12+7+5+1, 17+16+13+1, 17+16+13+2+1, 17+16+13+3+1,
 5 17+16+13+6+1, 17+16+13+6+2+1, 17+16+13+6+3+1, 17+16+13+8+1, 17+16+13+8+2+1, 17+16+13+8+3+1,
 17+16+13+8+6+1, 17+16+13+8+6+2+1, 17+16+13+8+6+3+1, 17+16+13+9+1, 17+16+13+9+2+1,
 17+16+13+9+3+1, 17+16+13+9+6+1, 17+16+13+9+6+2+1, 17+16+13+9+6+3+1, 17+16+14+1, 17+16+14+5+1,
 17+16+14+7+1, 17+16+14+7+5+1, 17+16+14+11+1, 17+16+14+11+5+1, 17+16+14+11+7+1,
 17+16+14+11+7+5+1, 17+16+14+12+1, 17+16+14+12+5+1, 17+16+14+12+7+1, 17+16+14+12+7+5+1,
 10 17+16+15+1, 17+16+15+5+1, 17+16+15+7+1, 17+16+15+7+5+1, 17+16+15+11+1, 17+16+15+11+5+1,
 17+16+15+11+7+1, 17+16+15+11+7+5+1, 17+16+15+12+1, 17+16+15+12+5+1, 17+16+15+12+7+1,
 17+16+15+12+7+5+1, 19+1, 19+5+1, 19+7+1, 19+7+5+1, 19+11+1, 19+11+5+1, 19+11+7+1, 19+11+7+5+1,
 19+12+1, 19+12+5+1, 19+12+7+1, 19+12+7+5+1, 19+14+1, 19+14+5+1, 19+14+7+1, 19+14+7+5+1,
 19+14+11+1, 19+14+11+5+1, 19+14+11+7+1, 19+14+11+7+5+1, 19+14+12+1, 19+14+12+5+1, 19+14+12+7+1,
 15 19+14+12+7+5+1, 19+15+1, 19+15+5+1, 19+15+7+1, 19+15+7+5+1, 19+15+11+1, 19+15+11+5+1,
 19+15+11+7+1, 19+15+11+7+5+1, 19+15+12+1, 19+15+12+5+1, 19+15+12+7+1, 19+15+12+7+5+1, 19+16+1,
 19+16+2+1, 19+16+3+1, 19+16+5+1, 19+16+6+1, 19+16+6+2+1, 19+16+6+3+1, 19+16+7+1, 19+16+7+5+1,
 19+16+8+1, 19+16+8+2+1, 19+16+8+3+1, 19+16+8+6+1, 19+16+8+6+2+1, 19+16+8+6+3+1, 19+16+9+1,
 19+16+9+2+1, 19+16+9+3+1, 19+16+9+6+1, 19+16+9+6+2+1, 19+16+9+6+3+1, 19+16+11+1, 19+16+11+5+1,
 20 19+16+11+7+1, 19+16+11+7+5+1, 19+16+12+1, 19+16+12+5+1, 19+16+12+7+1, 19+16+12+7+5+1,
 19+16+13+1, 19+16+13+2+1, 19+16+13+3+1, 19+16+13+6+1, 19+16+13+6+2+1, 19+16+13+6+3+1,
 19+16+13+8+1, 19+16+13+8+2+1, 19+16+13+8+3+1, 19+16+13+8+6+1, 19+16+13+8+6+2+1,
 19+16+13+8+6+3+1, 19+16+13+9+1, 19+16+13+9+2+1, 19+16+13+9+3+1, 19+16+13+9+6+1,
 19+16+13+9+6+2+1, 19+16+13+9+6+3+1, 19+16+14+1, 19+16+14+5+1, 19+16+14+7+1, 19+16+14+7+5+1,
 25 19+16+14+11+1, 19+16+14+11+5+1, 19+16+14+11+7+1, 19+16+14+11+7+5+1, 19+16+14+12+1,
 19+16+14+12+5+1, 19+16+14+12+7+1, 19+16+14+12+7+5+1, 19+16+15+1, 19+16+15+5+1, 19+16+15+7+1,
 19+16+15+7+5+1, 19+16+15+11+1, 19+16+15+11+5+1, 19+16+15+11+7+1, 19+16+15+11+7+5+1,
 19+16+15+12+1, 19+16+15+12+5+1, 19+16+15+12+7+1, 19+16+15+12+7+5+1, 20+1, 20+5+1, 20+7+1,
 20+7+5+1, 20+11+1, 20+11+5+1, 20+11+7+1, 20+11+7+5+1, 20+12+1, 20+12+5+1, 20+12+7+1, 20+12+7+5+1,
 30 20+14+1, 20+14+5+1, 20+14+7+1, 20+14+7+5+1, 20+14+11+1, 20+14+11+5+1, 20+14+11+7+1,
 20+14+11+7+5+1, 20+14+12+1, 20+14+12+5+1, 20+14+12+7+1, 20+14+12+7+5+1, 20+15+1, 20+15+5+1,
 20+15+7+1, 20+15+7+5+1, 20+15+11+1, 20+15+11+5+1, 20+15+11+7+1, 20+15+11+7+5+1, 20+15+12+1,
 20+15+12+5+1, 20+15+12+7+1, 20+15+12+7+5+1, 20+16+1, 20+16+2+1, 20+16+3+1, 20+16+5+1, 20+16+6+1,
 20+16+6+2+1, 20+16+6+3+1, 20+16+7+1, 20+16+7+5+1, 20+16+8+1, 20+16+8+2+1, 20+16+8+3+1,
 35 20+16+8+6+1, 20+16+8+6+2+1, 20+16+8+6+3+1, 20+16+9+1, 20+16+9+2+1, 20+16+9+3+1, 20+16+9+6+1,
 20+16+9+6+2+1, 20+16+9+6+3+1, 20+16+11+1, 20+16+11+5+1, 20+16+11+7+1, 20+16+11+7+5+1,
 20+16+12+1, 20+16+12+5+1, 20+16+12+7+1, 20+16+12+7+5+1, 20+16+13+1, 20+16+13+2+1, 20+16+13+3+1,

- 20+16+13+6+1, 20+16+13+6+2+1, 20+16+13+6+3+1, 20+16+13+8+1, 20+16+13+8+2+1, 20+16+13+8+3+1,
 20+16+13+8+6+1, 20+16+13+8+6+2+1, 20+16+13+8+6+3+1, 20+16+13+9+1, 20+16+13+9+2+1,
 20+16+13+9+3+1, 20+16+13+9+6+1, 20+16+13+9+6+2+1, 20+16+13+9+6+3+1, 20+16+14+1, 20+16+14+5+1,
 20+16+14+7+1, 20+16+14+7+5+1, 20+16+14+11+1, 20+16+14+11+5+1, 20+16+14+11+7+1,
 5 20+16+14+11+7+5+1, 20+16+14+12+1, 20+16+14+12+5+1, 20+16+14+12+7+1, 20+16+14+12+7+5+1,
 20+16+15+1, 20+16+15+5+1, 20+16+15+7+1, 20+16+15+7+5+1, 20+16+15+11+1, 20+16+15+11+5+1,
 20+16+15+11+7+1, 20+16+15+11+7+5+1, 20+16+15+12+1, 20+16+15+12+5+1, 20+16+15+12+7+1,
 20+16+15+12+7+5+1, 21+1, 21+5+1, 21+7+1, 21+7+5+1, 21+11+1, 21+11+5+1, 21+11+7+1, 21+11+7+5+1,
 21+12+1, 21+12+5+1, 21+12+7+1, 21+12+7+5+1, 21+14+1, 21+14+5+1, 21+14+7+1, 21+14+7+5+1,
 10 21+14+11+1, 21+14+11+5+1, 21+14+11+7+1, 21+14+11+7+5+1, 21+14+12+1, 21+14+12+5+1, 21+14+12+7+1,
 21+14+12+7+5+1, 21+15+1, 21+15+5+1, 21+15+7+1, 21+15+7+5+1, 21+15+11+1, 21+15+11+5+1,
 21+15+11+7+1, 21+15+11+7+5+1, 21+15+12+1, 21+15+12+5+1, 21+15+12+7+1, 21+15+12+7+5+1, 21+16+1,
 21+16+2+1, 21+16+3+1, 21+16+5+1, 21+16+6+1, 21+16+6+2+1, 21+16+6+3+1, 21+16+7+1, 21+16+7+5+1,
 21+16+8+1, 21+16+8+2+1, 21+16+8+3+1, 21+16+8+6+1, 21+16+8+6+2+1, 21+16+8+6+3+1, 21+16+9+1,
 15 21+16+9+2+1, 21+16+9+3+1, 21+16+9+6+1, 21+16+9+6+2+1, 21+16+9+6+3+1, 21+16+11+1, 21+16+11+5+1,
 21+16+11+7+1, 21+16+11+7+5+1, 21+16+12+1, 21+16+12+5+1, 21+16+12+7+1, 21+16+12+7+5+1,
 21+16+13+1, 21+16+13+2+1, 21+16+13+3+1, 21+16+13+6+1, 21+16+13+6+2+1, 21+16+13+6+3+1,
 21+16+13+8+1, 21+16+13+8+2+1, 21+16+13+8+3+1, 21+16+13+8+6+1, 21+16+13+8+6+2+1,
 21+16+13+8+6+3+1, 21+16+13+9+1, 21+16+13+9+2+1, 21+16+13+9+3+1, 21+16+13+9+6+1,
 20 21+16+13+9+6+2+1, 21+16+13+9+6+3+1, 21+16+14+1, 21+16+14+5+1, 21+16+14+7+1, 21+16+14+7+5+1,
 21+16+14+11+1, 21+16+14+11+5+1, 21+16+14+11+7+1, 21+16+14+11+7+5+1, 21+16+14+12+1,
 21+16+14+12+5+1, 21+16+14+12+7+1, 21+16+14+12+7+5+1, 21+16+15+1, 21+16+15+5+1, 21+16+15+7+1,
 21+16+15+7+5+1, 21+16+15+11+1, 21+16+15+11+5+1, 21+16+15+11+7+1, 21+16+15+11+7+5+1,
 21+16+15+12+1, 21+16+15+12+5+1, 21+16+15+12+7+1, 21+16+15+12+7+5+1.
- 25 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, "20+15+12+1" for example refers to embodiment 20) depending on
 embodiment 15), depending on embodiment 12), depending on embodiment 1), i.e. embodiment "20+15+12+1"
 corresponds to the compounds of formula (I) according to embodiment 1) further limited by all the features of the
 30 embodiments 12), 15), and 20).

23) A second aspect of the invention relates to compounds of the formula (I) according to embodiment 1) which are also compounds of the formula (II)



Formula (II)

5 wherein X is CH and Z is CH, X is N and Z is CH, or X is CH and Z is N;

- ring **A** represents a saturated 4- to 7-membered mono-cyclic carbocyclic ring containing the ring nitrogen atom to which **R**¹ is attached, wherein said ring independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from (C₁₋₃)alkyl (especially methyl), fluoro, or (C₁₋₄)alkoxy-carbonyl (especially ethoxy-carbonyl) [especially such ring **A** is azetidin-1,3-diyl, pyrrolidin-1,3-diyl, 4-methyl-pyrrolidin-1,3-diyl, piperidin-1,3-diyl, piperidin-1,4-diyl, 3-fluoro-piperidin-1,4-diyl, 2-methyl-piperidin-1,4-diyl, 3-methyl-piperidin-1,4-diyl, 3-(ethoxycarbonyl)-piperidin-1,4-diyl, 3,3-dimethyl-piperidin-1,4-diyl, azepan-1,4-diyl]; or
- ring **A** represents a saturated 7- or 8-membered bridged bi-cyclic carbocyclic ring containing the ring nitrogen atom to which **R**¹ is attached, wherein said ring is unsubstituted [especially such ring is 2-aza-bicyclo[2.2.1]heptane-2,5-diyl, 3-aza-bicyclo[3.1.1]heptane-3,6-diyl];

15 **R**¹ represents

- (C₁₋₄)alkyl (especially methyl, isopropyl);
 - -CO-**R**¹¹ wherein **R**¹¹ represents (C₁₋₄)alkyl; (C₁₋₄)alkoxy; phenyl, phenoxy; (C₃₋₆)cycloalkyl; or (C₃₋₆)cycloalkoxy optionally containing one ring oxygen and optionally mono-substituted with methyl or trifluoromethyl [especially such group -CO-**R**¹¹ is tert.-butyl-carbonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, tert.-butoxycarbonyl, oxetan-3-yl-oxy-carbonyl, (3-methyl-oxetan-3-yl)-oxy-carbonyl, (3-trifluoromethyl-oxetan-3-yl)-oxy-carbonyl, phenylcarbonyl, phenoxy-carbonyl, cyclopropylcarbonyl];
 - benzyl wherein the phenyl ring of said benzyl is optionally mono- or di-substituted with halogen [especially 2,4-dichlorobenzyl]; or
 - phenyl, or 5- or 6-membered heteroaryl (especially pyrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl);
- 20 wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from
- 25 ➤ (C₁₋₄)alkyl (especially methyl, isopropyl);

- (C₁₋₄)alkoxy (especially methoxy, n-butyloxy);
- (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
- (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy);
- halogen (especially fluoro, chloro, bromo);
- 5 ➤ cyano;
- nitro;
- hydroxy;
- hydroxy-(C₁₋₃)alkyl (especially 1-hydroxyethyl, hydroxymethyl, 1-hydroxy-1-methyl-ethyl);
- (C₁₋₄)alkoxy-(C₁₋₃)alkyl (especially 1-methoxyethyl);
- 10 ➤ hydroxy-(C₂₋₃)alkoxy (especially 2-hydroxy-ethoxy);
- (C₁₋₄)alkoxy-(C₂₋₃)alkoxy (especially 2-methoxy-ethoxy);
- (C₃₋₆)cycloalkyl-**X**¹²-, wherein **X**¹² represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen [especially such group (C₃₋₆)cycloalkyl-**X**¹²- is cyclopropyl, cyclopropyl-oxy, cyclobutyl-oxy, oxetan-3-yl-oxy, cyclopropyl-methoxy, or tetrahydropyran-4-yl-oxy];
- 15 ➤ **R**¹³-CO-**X**¹³-, wherein **X**¹³ represents a direct bond or (C₁₋₃)alkylene, and **R**¹³ represents hydrogen or (C₁₋₄)alkyl (especially such group **R**¹³-CO-**X**¹³ is formyl, acetyl, 2-oxo-ethyl);
- 3-(morpholin-4-yl)-prop-1-ynyl;
- **R**^{14a}**R**^{14b}N-**X**¹⁴-, wherein **X**¹⁴ represents a direct bond or (C₁₋₃)alkylene; and wherein **R**^{14a} and **R**^{14b} independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R**^{14a} and **R**^{14b} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl (especially methyl), hydroxy, (C₁₋₄)alkoxy (especially methoxy), or dimethylamino,
- 20 [especially such group **R**^{14a}**R**^{14b}N-**X**¹⁴- is amino, methylamino-methyl, dimethylamino-methyl, [(2-hydroxyethyl)-methylamino]-methyl, [(2-hydroxyethyl)-ethylamino]-methyl, [(2-methoxy-1-methyl-ethyl)-amino]-methyl, [(2-methoxyethyl)-methylamino]-methyl, [di-(2-hydroxyethyl)-amino]-methyl, (azetidin-1-yl)-methyl, (pyrrolidin-1-yl)-methyl, (piperidin-1-yl)-methyl, morpholin-4-yl, piperazin-1-ylmethyl, (morpholin-4-yl)-methyl, 2-(morpholin-4-yl)-ethyl, 3-(morpholin-4-yl)-propyl, (3-methoxy-azetidin-1-yl)-methyl, 1-(3-methoxy-azetidin-1-yl)-ethyl, (1-methyl-piperazin-4-yl)-methyl, (4-hydroxypiperidin-1-yl)-methyl, (4-methoxypiperidin-1-yl)-methyl, (3-methoxy-pyrrolidin-1-yl)-methyl, (4-dimethylamino-piperidin-1-yl)-methyl];
- 30 or
- benzyloxy, wherein the phenylring of benzyloxy is optionally mono- or di-substituted with halogen or methyl);
- 35 wherein in a sub-embodiment **R**¹ represents phenyl, or 5- or 6-membered heteroaryl (especially pyrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl); wherein said phenyl or 5- or 6-membered heteroaryl are substituted as defined herein before;

R² represents phenyl, or 5- or 6-membered heteroaryl (notably 6-membered heteroaryl; in particular thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl); wherein said phenyl or 5- or 6-membered heteroaryl independently is mono-, di- or tri-substituted (especially mono-substituted, in particular in *ortho* position with regard to the point of attachment of the rest of the molecule), wherein the substituents are independently selected from

- 5 ➤ (C₁₋₄)alkyl (especially methyl, isopropyl);
- (C₁₋₄)alkoxy (especially methoxy, isopropoxy);
- (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
- (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy);
- halogen (especially chloro, fluoro); or
- 10 ➤ (C₃₋₆)cycloalkyl-**X²¹**-, wherein **X²¹** represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen [especially such group (C₃₋₆)cycloalkyl-**X²¹**- is cyclopropyl, cyclopropyl-oxy, cyclobutyl-oxy, oxetan-3-yl-oxy, cyclopropyl-methoxy];

R³ represents hydrogen, or (C₁₋₃)alkyl (especially methyl); and

R⁴ represents

- 15 • (C₁₋₄)alkyl (especially methyl);
- hydroxy-(C₁₋₃)alkyl (especially hydroxymethyl);
- -O-**R⁴¹**, wherein **R⁴¹** represents
 - hydrogen;
 - (C₁₋₄)alkyl (especially methyl);
 - 20 ➤ (C₂₋₄)alkyl which is substituted with one or two hydroxy (especially 2-hydroxyethyl, 2,3-dihydroxypropyl);
 - **R^{41a}R^{41b}N**-(C₂₋₃)alkylene-, wherein **R^{41a}** and **R^{41b}** independently represent hydrogen or (C₁₋₄)alkyl (especially such group is 2-dimethylamino-ethyl); or
 - (C₄₋₇)heterocyclyl-**X⁴¹**-, wherein **X⁴¹** represents a direct bond or (C₁₋₃)alkylene, and wherein the (C₄₋₇)heterocyclyl independently contains one or two ring heteroatoms independently selected from
 - 25 nitrogen and oxygen; wherein said (C₄₋₇)heterocyclyl independently is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from:
 - (C₁₋₄)alkyl (especially methyl); and/or
 - (C₁₋₄)alkoxy-carbonyl attached to a ring nitrogen atom having a free valency;
- [especially such (C₄₋₇)heterocyclyl-**X⁴¹**- group is oxetan-3-yl, 1-methyl-pyrrolidin-3-yl, 2,2-dimethyl-dioxolan-4-yl-methyl, 2-morpholin-4-yl-ethyl, 1-tert-butoxy-carbonyl-piperidin-4-yl, piperidin-4-yl];
- 30 • -**NR^{42a}R^{42b}** wherein **R^{42a}** and **R^{42b}** independently represent hydrogen, (C₁₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₃)alkyl, hydroxy-(C₂₋₃)alkyl, or **R^{42a}** and **R^{42b}** together with the nitrogen to which they are attached form a 4- to 7-membered saturated ring optionally containing one further ring heteroatom selected from oxygen and nitrogen, wherein said ring is unsubstituted or mono-substituted with (C₁₋₃)alkyl (especially methyl), or (C₁₋₃)alkoxy (especially methoxy) [especially such group -**NR^{42a}R^{42b}** is (2-hydroxyethyl)-amino, (2-hydroxyethyl)-methyl-amino, (2-methoxyethyl)-amino, morpholin-4-yl, 3-methoxy-azetidiny, or 4-methyl-piperazin-1-yl]; or
- 35

- -CO-R⁴³ wherein R⁴³ represents (C₁₋₄)alkoxy (especially methoxy); or -NR^{43a}R^{43b} wherein R^{43a} and R^{43b} independently represent hydrogen, (C₁₋₄)alkyl (especially methyl), (C₁₋₃)alkoxy-(C₂₋₃)alkyl (especially 2-methoxy-ethyl), or hydroxy-(C₂₋₃)alkyl (especially 2-hydroxy-ethyl); [especially such group -CO-R⁴³ is methoxycarbonyl, carbamoyl, methyl-carbamoyl, dimethylcarbamoyl, hydroxyethylcarbamoyl, methoxyethylcarbamoyl].

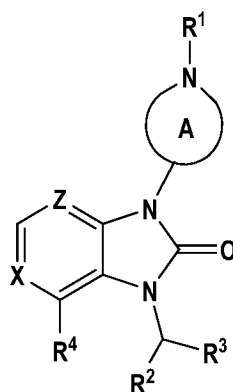
wherein the characteristics disclosed in embodiments 2) to 22) are intended to apply *mutatis mutandis* also to the compounds formula (II) according to embodiment 23); wherein especially the following embodiments are thus possible and intended and herewith specifically disclosed in individualized form:

- 23+2, 23+3, 23+5, 23+8+2, 23+8+3, 23+8+6, 8, 23+9+2, 23+9+3, 23+9+6, 9, 23+11+5, 23+11, 23+12+5, 23+12, 23+13+2, 23+13+3, 23+13+8+2, 23+13+8+3, 23+13+8+6, 13+8, 23+13+9+2, 23+13+9+3, 23+13+9+6, 13+9, 23+13, 23+14+5, 23+14+11+5, 23+14+11, 23+14+12+5, 23+14+12, 23+14, 23+15+5, 23+15+11+5, 23+15+11, 23+15+12+5, 23+15+12, 23+15, 23+16+2, 23+16+3, 23+16+5, 23+16+8+2, 23+16+8+3, 23+16+8+6, 16+8, 23+16+9+2, 23+16+9+3, 23+16+9+6, 16+9, 23+16+11+5, 23+16+11, 23+16+12+5, 23+16+12, 23+16+13+2, 23+16+13+3, 23+16+13+8+2, 23+16+13+8+3, 23+16+13+8+6, 16+13+8, 23+16+13+9+2, 23+16+13+9+3, 23+16+13+9+6, 16+13+9, 23+16+13, 23+16+14+5, 23+16+14+11+5, 23+16+14+11, 23+16+14+12+5, 23+16+14+12, 23+16+14, 23+16+15+5, 23+16+15+11+5, 23+16+15+11, 23+16+15+12+5, 23+16+15+12, 23+16+15, 23+16, 23+17+2, 23+17+3, 23+17+8+2, 23+17+8+3, 23+17+8+6, 17+8, 23+17+9+2, 23+17+9+3, 23+17+9+6, 17+9, 23+17+13+2, 23+17+13+3, 23+17+13+8+2, 23+17+13+8+3, 23+17+13+8+6, 17+13+8, 23+17+13+9+2, 23+17+13+9+3, 23+17+13+9+6, 17+13+9, 23+17+13, 23+17+16+2, 23+17+16+3, 23+17+16+5, 23+17+16+8+2, 23+17+16+8+3, 23+17+16+8+6, 17+16+8, 23+17+16+9+2, 23+17+16+9+3, 23+17+16+9+6, 17+16+9, 23+17+16+11+5, 23+17+16+11, 23+17+16+12+5, 23+17+16+12, 23+17+16+13+2, 23+17+16+13+3, 23+17+16+13+8+2, 23+17+16+13+8+3, 23+17+16+13+8+6, 17+16+13+8, 23+17+16+13+9+2, 23+17+16+13+9+3, 23+17+16+13+9+6, 17+16+13+9, 23+17+16+13, 23+17+16+14+5, 23+17+16+14+11+5, 23+17+16+14+11, 23+17+16+14+12+5, 23+17+16+14+12, 23+17+16+14, 23+17+16+15+5, 23+17+16+15+11+5, 23+17+16+15+11, 23+17+16+15+12+5, 23+17+16+15+12, 23+17+16+15, 23+17+16, 23+17, 23+19+5, 23+19+11+5, 23+19+11, 23+19+12+5, 23+19+12, 23+19+14+5, 23+19+14+11+5, 23+19+14+11, 23+19+14+12+5, 23+19+14+12, 23+19+14, 23+19+15+5, 23+19+15+11+5, 23+19+15+11, 23+19+15+12+5, 23+19+15+12, 23+19+15, 23+19+16+2, 23+19+16+3, 23+19+16+5, 23+19+16+8+2, 23+19+16+8+3, 23+19+16+8+6, 19+16+8, 23+19+16+9+2, 23+19+16+9+3, 23+19+16+9+6, 19+16+9, 23+19+16+11+5, 23+19+16+11, 23+19+16+12+5, 23+19+16+12, 23+19+16+13+2, 23+19+16+13+3, 23+19+16+13+8+2, 23+19+16+13+8+3, 23+19+16+13+8+6, 19+16+13+8, 23+19+16+13+9+2, 23+19+16+13+9+3, 23+19+16+13+9+6, 19+16+13+9, 23+19+16+13, 23+19+16+14+5, 23+19+16+14+11+5, 23+19+16+14+11, 23+19+16+14+12+5, 23+19+16+14+12, 23+19+16+14, 23+19+16+15+5, 23+19+16+15+11+5, 23+19+16+15+11, 23+19+16+15+12+5, 23+19+16+15+12, 23+19+16+15, 23+19+16, 23+19, 23+20+5, 23+20+11+5, 23+20+11, 23+20+12+5, 23+20+12, 23+20+14+5, 23+20+14+11+5, 23+20+14+11, 23+20+14+12+5, 23+20+14+12, 23+20+14, 23+20+15+5, 23+20+15+11+5, 23+20+15+11, 23+20+15+12+5, 23+20+15+12, 23+20+15, 23+20+16+2, 23+20+16+3, 23+20+16+5, 23+20+16+8+2, 23+20+16+8+3, 23+20+16+8+6, 20+16+8, 23+20+16+9+2, 23+20+16+9+3, 23+20+16+9+6, 20+16+9, 23+20+16+11+5, 23+20+16+11, 23+20+16+12+5, 23+20+16+12, 23+20+16+13+2, 23+20+16+13+3, 23+20+16+13+8+2, 23+20+16+13+8+3, 23+20+16+13+8+6, 20+16+13+8, 23+20+16+13+9+2, 23+20+16+13+9+3, 23+20+16+13+9+6, 20+16+13+9, 23+20+16+13, 23+20+16+14+5, 23+20+16+14+11+5, 23+20+16+14+11, 23+20+16+14+12+5, 23+20+16+14+12, 23+20+16+14, 23+20+16+15+5, 23+20+16+15+11+5, 23+20+16+15+11, 23+20+16+15+12+5, 23+20+16+15+12, 23+20+16+15, 23+20+16, 23+20, 23+21+5, 23+21+11+5, 23+21+11,

23+21+12+5, 23+21+12, 23+21+14+5, 23+21+14+11+5, 23+21+14+11, 23+21+14+12+5, 23+21+14+12, 23+21+14, 23+21+15+5, 23+21+15+11+5, 23+21+15+11, 23+21+15+12+5, 23+21+15+12, 23+21+15, 23+21+16+2, 23+21+16+3, 23+21+16+5, 23+21+16+8+2, 23+21+16+8+3, 23+21+16+8+6, 21+16+8, 23+21+16+9+2, 23+21+16+9+3, 23+21+16+9+6, 21+16+9, 23+21+16+11+5, 23+21+16+11, 23+21+16+12+5, 23+21+16+12, 23+21+16+13+2, 23+21+16+13+3, 23+21+16+13+8+2, 23+21+16+13+8+3, 23+21+16+13+8+6, 21+16+13+8, 23+21+16+13+9+2, 23+21+16+13+9+3, 23+21+16+13+9+6, 21+16+13+9, 23+21+16+13, 23+21+16+14+5, 23+21+16+14+11+5, 23+21+16+14+11, 23+21+16+14+12+5, 23+21+16+14+12, 23+21+16+14, 23+21+16+15+5, 23+21+16+15+11+5, 23+21+16+15+11, 23+21+16+15+12+5, 23+21+16+15+12, 23+21+16+15, 23+21+16, 23+21.

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

24) A third aspect of the invention relates to compounds of the formula (I) according to embodiment 1) which are also compounds of the formula (III)



Formula (III)

wherein X is CH and Z is CH, X is N and Z is CH, or X is CH and Z is N;

- ring **A** represents a saturated 4- to 7-membered mono-cyclic carbocyclic ring containing the ring nitrogen atom to which **R**¹ is attached, wherein said ring independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from (C₁₋₃)alkyl (especially methyl), fluoro, or (C₁₋₄)alkoxy-carbonyl (especially ethoxy-carbonyl) [especially such ring **A** is azetidin-1,3-diyl, pyrrolidin-1,3-diyl, 4-methyl-pyrrolidin-1,3-diyl, piperidin-1,3-diyl, piperidin-1,4-diyl, 3-fluoro-piperidin-1,4-diyl, 2-methyl-piperidin-1,4-diyl, 3-methyl-piperidin-1,4-diyl, 3-(ethoxycarbonyl)-piperidin-1,4-diyl, 3,3-dimethyl-piperidin-1,4-diyl, azepan-1,4-diyl]; or
- ring **A** represents a saturated 7- or 8-membered bridged bi-cyclic carbocyclic ring containing the ring nitrogen atom to which **R**¹ is attached, wherein said ring is unsubstituted [especially such ring is 2-aza-bicyclo[2.2.1]heptane-2,5-diyl, 3-aza-bicyclo[3.1.1]heptane-3,6-diyl];

R¹ represents

- (C₁₋₄)alkyl (especially methyl, isopropyl);
- -CO-R¹¹ wherein R¹¹ represents (C₁₋₄)alkyl; (C₁₋₄)alkoxy; phenyl, phenoxy; (C₃₋₆)cycloalkyl; or (C₃₋₆)cycloalkoxy optionally containing one ring oxygen and optionally mono-substituted with methyl or trifluoromethyl [especially such group -CO-R¹¹ is tert.-butyl-carbonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, tert.-butoxycarbonyl, oxetan-3-yl-oxy-carbonyl, (3-methyl-oxetan-3-yl)-oxy-carbonyl, (3-trifluoromethyl-oxetan-3-yl)-oxy-carbonyl, phenylcarbonyl, phenoxycarbonyl, cyclopropylcarbonyl];
- benzyl wherein the phenyl ring of said benzyl is optionally mono- or di-substituted with halogen [especially 2,4-dichlorobenzyl]; or
- phenyl, or 5- or 6-membered heteroaryl (especially pyrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl); wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from
 - (C₁₋₄)alkyl (especially methyl, isopropyl);
 - (C₁₋₄)alkoxy (especially methoxy, n-butyloxy);
 - (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
 - (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy);
 - halogen (especially fluoro, chloro, bromo);
 - cyano;
 - nitro;
 - hydroxy;
 - hydroxy-(C₁₋₃)alkyl (especially 1-hydroxyethyl, hydroxymethyl, 1-hydroxy-1-methyl-ethyl);
 - (C₁₋₄)alkoxy-(C₁₋₃)alkyl (especially 1-methoxyethyl);
 - hydroxy-(C₂₋₃)alkoxy (especially 2-hydroxy-ethoxy);
 - (C₁₋₄)alkoxy-(C₂₋₃)alkoxy (especially 2-methoxy-ethoxy);
 - (C₃₋₆)cycloalkyl-X¹²-, wherein X¹² represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen [especially such group (C₃₋₆)cycloalkyl-X¹²- is cyclopropyl, cyclopropyl-oxy, cyclobutyl-oxy, oxetan-3-yl-oxy, cyclopropyl-methoxy, or tetrahydropyran-4-yl-oxy];
 - R¹³-CO-X¹³-, wherein X¹³ represents a direct bond or (C₁₋₃)alkylene, and R¹³ represents hydrogen or (C₁₋₄)alkyl (especially such group R¹³-CO-X¹³ is formyl, acetyl, 2-oxo-ethyl);
 - 3-(morpholin-4-yl)-prop-1-ynyl;
 - R^{14a}R^{14b}N-X¹⁴-, wherein X¹⁴ represents a direct bond or (C₁₋₃)alkylene; and wherein R^{14a} and R^{14b} independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or R^{14a} and R^{14b} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl (especially methyl), hydroxy, (C₁₋₄)alkoxy (especially methoxy), or dimethylamino,

[especially such group $R^{14a}R^{14b}N-X^{14-}$ is amino, methylamino-methyl, dimethylamino-methyl, [(2-hydroxyethyl)-methylamino]-methyl, [(2-hydroxyethyl)-ethylamino]-methyl, [(2-methoxy-1-methyl-ethyl)-amino]-methyl, [(2-methoxyethyl)-methylamino]-methyl, [di-(2-hydroxyethyl)-amino]-methyl, (azetidin-1-yl)-methyl, (pyrrolidin-1-yl)-methyl, (piperidin-1-yl)-methyl, morpholin-4-yl, piperazin-1-ylmethyl, (morpholin-4-yl)-methyl, 2-(morpholin-4-yl)-ethyl, 3-(morpholin-4-yl)-propyl, (3-methoxy-azetidin-1-yl)-methyl, 1-(3-methoxy-azetidin-1-yl)-ethyl, (1-methyl-piperazin-4-yl)-methyl, (4-hydroxypiperidin-1-yl)-methyl, (4-methoxypiperidin-1-yl)-methyl, (3-methoxy-pyrrolidin-1-yl)-methyl, (4-dimethylamino-piperidin-1-yl)-methyl];

or

- benzyloxy, wherein the phenylring of benzyloxy is optionally mono- or di-substituted with halogen or methyl);

wherein in a sub-embodiment R^1 represents phenyl, or 5- or 6-membered heteroaryl (especially pyrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl); wherein said phenyl or 5- or 6-membered heteroaryl are substituted as defined herein before;

R^2 represents phenyl, or 6-membered heteroaryl (especially pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl); wherein said phenyl or 6-membered heteroaryl independently is mono-substituted in *ortho* position with regard to the point of attachment of the rest of the molecule, wherein the substituents is independently selected from

- (C₁₋₄)alkyl (especially methyl, isopropyl);
- (C₁₋₄)alkoxy (especially methoxy, isopropoxy);
- (C₁₋₃)fluoroalkyl (especially trifluoromethyl);
- (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy);
- (C₃₋₆)cycloalkyl- X^{21-} , wherein X^{21} represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen [especially such group (C₃₋₆)cycloalkyl- X^{21-} is cyclopropyl, cyclopropyl-oxy, cyclobutyl-oxy, oxetan-3-yl-oxy, cyclopropyl-methoxy];

R^3 represents hydrogen, or (C₁₋₃)alkyl (especially methyl) [R^3 represents hydrogen]; and

R^4 represents

- -O- R^{41} , wherein R^{41} represents
 - hydrogen;
 - (C₁₋₄)alkyl (especially methyl);
 - (C₂₋₄)alkyl which is substituted with one or two hydroxy (especially 2-hydroxyethyl, 2,3-dihydroxypropyl);
 - oxetan-3-yl;
 - 2,2-dimethyl-dioxolan-4-yl-methyl; or
- (2-hydroxyethyl)-methyl-amino, morpholin-4-yl, or 3-methoxy-azetidiny;

wherein in a sub-embodiment R^4 represents -O- R^{41} as defined herein above; especially R^4 represents (C₁₋₄)alkoxy (in particular methoxy).

wherein the characteristics disclosed in embodiments 2) to 22) are intended to apply *mutatis mutandis* also to the compounds formula (III) according to embodiment 24); wherein especially the following embodiments are thus possible and intended and herewith specifically disclosed in individualized form:

24, 24+2, 24+3, 24+5, 24+8+2, 24+8+3, 24+8, 24+9+2, 24+9+3, 24+9, 24+11+5, 24+11, 24+12+5, 24+12,
 5 24+15+5, 24+15+11+5, 24+15+11, 24+15+12+5, 24+15+12, 24+15, 24+16+2, 24+16+3, 24+16+5, 24+16+8+2,
 24+16+8+3, 24+16+8, 24+16+9+2, 24+16+9+3, 24+16+9, 24+16+11+5, 24+16+11, 24+16+12+5, 24+16+12,
 24+16+15+5, 24+16+15+11+5, 24+16+15+11, 24+16+15+12+5, 24+16+15+12, 24+16+15, 24+16, 24+21+5,
 24+21+11+5, 24+21+11, 24+21+12+5, 24+21+12, 24+21+15+5, 24+21+15+11+5, 24+21+15+11, 24+21+15+12+5,
 24+21+15+12, 24+21+15, 24+21+16+2, 24+21+16+3, 24+21+16+5, 24+21+16+8+2, 24+21+16+8+3, 24+21+16+8,
 10 24+21+16+9+2, 24+21+16+9+3, 24+21+16+9, 24+21+16+11+5, 24+21+16+11, 24+21+16+12+5, 24+21+16+12,
 24+21+16+15+5, 24+21+16+15+11+5, 24+21+16+15+11, 24+21+16+15+12+5, 24+21+16+15+12, 24+21+16+15,
 24+21+16, 24+21.

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

15 25) Another embodiment relates to compounds according to embodiment 1) which are selected from the following compounds:
 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester;
 1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
 20 1-[1-(2,6-dimethylphenyl)piperidin-4-yl]-4-methoxy-3-(2-(trifluoromethyl)benzyl)-1,3-dihydro-benzoimidazol-2-one-7-d;
 4-Methoxy-1-(1-phenyl-piperidin-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
 1-[1-(2,4-Dichloro-benzyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
 (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid
 25 tert-butyl ester;
 1-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
 30 1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
 1-[1-(2,6-Dimethoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
 1-[1-(2-Fluoro-6-methoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
 35 4-Methoxy-1-[1-(2-methoxy-6-methyl-phenyl)-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;

- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 3-Cyclopropyl-5-{4-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-piperidin-1-yl}-1-methyl-1H-pyrazole-4-carbaldehyde;
- 5 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-Methoxy-1-[(R)-1-(2-methoxy-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2,6-Dimethoxy-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 10 4-Methoxy-1-[(R)-1-(2-methoxy-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methoxy-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 15 (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethoxy-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 1-[1-(5-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethoxy-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 20 2-one;
- 1-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethoxy-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(4-Chloro-5-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 25 1-[1-(5-Cyclopropyl-2,4-dimethyl-2H-pyrazol-3-yl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid methyl ester;
- 1-[(R)-1-Benzoyl-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 30 1-[1-(2,2-Dimethyl-propionyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid methyl ester;
- 1-(1-Benzoyl-piperidin-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 35 4-Methoxy-1-[(R)-1-methyl-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-Isopropyl-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

- 4-Methoxy-1-[(R)-1-(2-methoxy-4-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(3,5-Difluoro-pyridin-4-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 5 1-(1-Isopropyl-piperidin-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(3,5-Dimethyl-pyridin-4-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-4-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 10 1-[(R)-1-(3,5-Dimethoxy-pyridin-4-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-imidazo[4,5-c]pyridin-1-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-hydroxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 15 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 20 (R)-3-[7-Methoxy-2-oxo-1-(2-trifluoromethyl-benzyl)-1,2-dihydro-imidazo[4,5-b]pyridin-3-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-hydroxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 3-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-7-methoxy-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one;
- 25 3-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-7-methoxy-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one;
- 4-Methoxy-1-[(R)-1-(2-methoxy-4-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 30 1-[(R)-1-(2-Fluoro-4-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methoxy-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 35 4-Methoxy-1-[(R)-1-(2-methoxy-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;

- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-(2-hydroxy-ethoxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-[4-Methoxy-2-oxo-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester;
- 5 1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methoxy-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione;
- 10 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione;
- 1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 15 1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid ethyl ester;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid isopropyl ester;
- 20 (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid butyl ester;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid phenyl ester;
- 25 4-[4-Methoxy-2-oxo-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester;
- (R)-3-[4-Methoxy-3-(2-methoxy-benzyl)-2-oxo-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 1-[(R)-1-(2,4-Dimethyl-pyridin-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 30 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(5-Isopropyl-[1,3,4]oxadiazol-2-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 35 (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid 3-methyl-oxetan-3-yl ester;

- 5-[(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-1,3-dimethyl-1H-pyrazole-4-carbaldehyde;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid oxetan-3-yl ester;
- 5 1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-4-ylmethyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-4-ylmethyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-
- 10 benzoimidazol-2-one;
- 1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 15 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2,5-Dimethyl-2H-pyrazol-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(4-Chloro-2,5-dimethyl-2H-pyrazol-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-
- 20 benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-methoxy-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione;
- 3-Fluoro-2-[(R)-3-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile;
- 25 3-Fluoro-2-[(R)-3-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzaldehyde;
- 4-Methoxy-3-(2-trifluoromethyl-benzyl)-1-[(R)-1-(5-trifluoromethyl-[1,3,4]oxadiazol-2-yl)-pyrrolidin-3-yl]-1,3-dihydro-benzoimidazol-2-one;
- 4-Methoxy-3-(2-trifluoromethyl-benzyl)-1-[(R)-1-(2,4,5-trimethyl-2H-pyrazol-3-yl)-pyrrolidin-3-yl]-1,3-dihydro-
- 30 benzoimidazol-2-one;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid 3-trifluoromethyl-oxetan-3-yl ester;
- 5-[(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-1,3-dimethyl-1H-pyrazole-4-carbonitrile;
- 35 1-[(R)-1-(2-Fluoro-6-hydroxymethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;

- 1-[(R)-1-[2-Fluoro-6-(1-hydroxy-ethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Acetyl-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 5 1-[(R)-1-[2-Fluoro-6-(1-hydroxy-1-methyl-ethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 3-(6-Chloro-4-methoxy-pyridazin-3-ylmethyl)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione;
- 10 1-[(R)-1-(2-Methoxy-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-methoxy-pyridazin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 15 3-Fluoro-2-{4-[4-methoxy-2-oxo-3-(3-trifluoromethyl-pyrazin-2-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-piperidin-1-yl}-benzonitrile;
- 3-Fluoro-2-{4-[4-methoxy-3-(3-methoxy-pyrazin-2-ylmethyl)-2-oxo-2,3-dihydro-benzimidazol-1-yl]-piperidin-1-yl}-benzonitrile;
- 1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid methyl ester;
- 20 1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid methylamide;
- 1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid amide;
- 25 1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid dimethylamide;
- 3-Fluoro-2-{(R)-3-[4-hydroxymethyl-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidin-1-yl}-benzonitrile;
- 1-[(R)-1-(2-Fluoro-6-methylaminomethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 30 3-Fluoro-2-{(R)-3-[6-methoxy-8-oxo-7-(2-trifluoromethyl-benzyl)-7,8-dihydro-purin-9-yl]-pyrrolidin-1-yl}-benzonitrile;
- 3-Fluoro-2-{(R)-3-[6-methoxy-7-(2-methoxy-benzyl)-8-oxo-7,8-dihydro-purin-9-yl]-pyrrolidin-1-yl}-benzonitrile;
- 1-[(R)-1-(2-Dimethylaminomethyl-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 35 1-[(R)-1-(2-Fluoro-6-[[2-hydroxy-ethyl]-methyl-amino]-methyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

- 1-[(R)-1-(2-Azetidin-1-ylmethyl-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 3-Fluoro-2-[(R)-3-[4-methoxy-3-(2-methoxy-benzyl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile;
- 5 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 3-Fluoro-2-[(R)-3-[4-methoxy-2-oxo-3-(3-trifluoromethyl-pyrazin-2-ylmethyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile;
- 3-Fluoro-2-[(R)-3-[4-methoxy-3-(3-methoxy-pyrazin-2-ylmethyl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile;
- 10 3-Fluoro-2-[4-[4-methoxy-3-(4-methoxy-pyrimidin-5-ylmethyl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-piperidin-1-yl]-benzonitrile;
- 3-Fluoro-2-[(R)-3-[4-methoxy-3-(4-methoxy-pyrimidin-5-ylmethyl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile;
- 15 1-[(R)-1-(2-Fluoro-6-morpholin-4-ylmethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-pyrrolidin-1-ylmethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 3-Fluoro-2-[4-[4-methoxy-2-oxo-3-(4-trifluoromethyl-pyrimidin-5-ylmethyl)-2,3-dihydro-benzoimidazol-1-yl]-piperidin-1-yl]-benzonitrile;
- 20 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-(2-hydroxy-ethylamino)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-(2-hydroxy-ethoxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 25 4-(2-Dimethylamino-ethoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(2-morpholin-4-yl-ethoxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 4-[1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-imidazo[4,5-c]pyridin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;
- 30 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-[(2-hydroxy-ethyl)-methyl-amino]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(piperidin-4-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 35 4-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;

- (3-Fluoro-2-((R)-3-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl)-phenyl)-acetaldehyde;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(oxetan-3-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 5 4-(2,3-Dihydroxy-propoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-morpholin-4-yl-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(1-methyl-pyrrolidin-3-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 10 1-[(R)-1-[2-Fluoro-6-(2-morpholin-4-yl-ethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-[2-Fluoro-6-(4-methyl-piperazin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 15 1-[(R)-1-(2-Fluoro-6-piperidin-1-ylmethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-[2-Fluoro-6-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-piperazin-1-ylmethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 20 1-[(R)-1-[2-(4-Dimethylamino-piperidin-1-ylmethyl)-6-fluoro-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-[2-Fluoro-6-(4-methoxy-piperidin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 25 1-[(R)-1-[2-Fluoro-6-(3-methoxy-pyrrolidin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-[[2-methoxy-ethyl]-methyl-amino]-methyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-[[Ethyl-(2-hydroxy-ethyl)-amino]-methyl]-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 30 1-[(R)-1-(2-[[Bis-(2-hydroxy-ethyl)-amino]-methyl]-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-[2-Fluoro-6-[(2-methoxy-1-methyl-ethylamino)-methyl]-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 35 1-[(R)-1-[2-Fluoro-6-(3-methoxy-azetidin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;

- 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-2-methyl-piperidine-1-carboxylic acid tert-butyl ester;
- 3-Fluoro-2-{4-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-2-methyl-piperidin-1-yl}-benzaldehyde;
- 5 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-3-methyl-piperidine-1-carboxylic acid tert-butyl ester;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-3-methyl-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-[2-Fluoro-6-(1-methoxy-ethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 10 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(oxetan-3-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(2-hydroxy-ethoxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 15 4-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 4-(2,3-Dihydroxy-propoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 3-Fluoro-2-[(R)-3-[4-methoxy-2-oxo-3-(4-trifluoromethyl-pyrimidin-5-ylmethyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile;
- 20 1-[(R)-1-(2-Fluoro-6-nitro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Amino-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 25 1-[(R)-1-(2-Bromo-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(4,5-Dichloro-pyridazin-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(3,5-Dichloro-pyridazin-4-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 30 1-[(R)-1-[2-Fluoro-6-(3-morpholin-4-yl-prop-1-ynyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-morpholin-4-yl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 35 1-[(R)-1-[2-Fluoro-6-(3-morpholin-4-yl-propyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;

- 1-((R)-1-(2-Fluoro-6-[1-(3-methoxy-azetidin-1-yl)-ethyl]-phenyl)-pyrrolidin-3-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester;
- 5 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-isopropoxy-benzyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(2-isopropoxy-benzyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(3-trifluoromethyl-pyrazin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 10 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyrazin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(3-methoxy-pyrazin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 15 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-methoxy-pyrazin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 3-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-7-methoxy-5-methyl-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one;
- 3-(6-Chloro-4-isopropoxy-pyridazin-3-ylmethyl)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 20 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(4-isopropoxy-pyridazin-3-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-methyl-pyridazin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 25 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-methoxy-pyrimidin-5-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-trifluoromethyl-pyrimidin-5-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(3-isopropoxy-pyrazin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 30 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(3-isopropoxy-pyrazin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-azepane-1-carboxylic acid tert-butyl ester;
- 35 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(4-isopropyl-pyridin-3-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;

- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(4-isopropyl-pyridin-3-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(3-isopropoxy-pyridin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 5 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(3-isopropoxy-pyridin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-azepan-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2,6-Dimethyl-phenyl)-azepan-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 10 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(4-isopropyl-pyrimidin-5-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(3-isopropyl-pyrazin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 5-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester;
- 15 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(3-isopropyl-pyrazin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[2-(2-Fluoro-6-methyl-phenyl)-2-aza-bicyclo[2.2.1]hept-5-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 20 6-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-3-aza-bicyclo[3.1.1]heptane-3-carboxylic acid tert-butyl ester;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(4-isopropyl-pyrimidin-5-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-
- 25 benzoimidazole-4-carboxylic acid (2-hydroxy-ethyl)-amide;
- 1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzoimidazole-4-carboxylic acid (2-methoxy-ethyl)-amide;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 30 (3R*,4S*)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 1-[3-(2-Fluoro-6-methyl-phenyl)-3-aza-bicyclo[3.1.1]hept-6-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(3R*,4S*)-1-(2-Fluoro-6-methyl-phenyl)-4-methyl-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-
- 35 dihydro-benzimidazol-2-one;
- (3R*,4R*)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester;

- 1-[(3R*,4R*)-1-(2-Fluoro-6-methyl-phenyl)-4-methyl-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
4-Methoxy-1-[(R)-1-(2-trifluoromethoxy-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 5 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
4-Methoxy-1-[(R)-1-[2-(2-methoxy-ethoxy)-phenyl]-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-
- 10 benzimidazol-2-one;
1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(3-methoxy-azetidin-1-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(4-methyl-piperazin-1-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 15 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(2-methoxy-ethylamino)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
3-(2-Cyclopropoxy-benzyl)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
3-(2-Cyclopropoxy-benzyl)-1-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-
- 20 one;
3-Fluoro-4-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester;
1-[3-Fluoro-1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 25 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-azetidine-1-carboxylic acid tert-butyl ester;
3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid tert-
- 30 butyl ester;
1-[1-(2-Fluoro-6-methyl-phenyl)-azetidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 35 1-[1-(2,6-Dimethyl-phenyl)-piperidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-thiazol-4-ylmethyl)-1,3-dihydro-benzimidazol-2-one;

- 1-[1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-[(S)-1-(2-trifluoromethyl-phenyl)-ethyl]-1,3-dihydro-benzimidazol-2-one;
- 3-(2,4-Difluoro-6-isopropoxy-benzyl)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 5 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methyl-4-trifluoromethyl-thiazol-5-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-(1-Cyclopropanecarbonyl-piperidin-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 3-(2-Cyclopropyl-benzyl)-1-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 10 3-(2-Cyclopropylmethoxy-benzyl)-1-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-[2-(oxetan-3-yloxy)-benzyl]-1,3-dihydro-benzimidazol-2-one;
- 3-(2-Cyclobutoxy-benzyl)-1-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 15 1-[1-(2-Fluoro-6-methyl-phenyl)-3,3-dimethyl-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-3,3-dimethyl-piperidine-1-carboxylic acid tert-butyl ester;
- 20 3-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methoxy-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[1-(2-Hydroxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2-Benzyloxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-Methoxy-1-(3'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 25 4-Methoxy-1-(3'-methoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-Methoxy-1-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 30 1-(2'-Fluoro-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-(3'-Fluoro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-(2',4'-Dimethyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 35 1-[1-[2-(2-Hydroxy-ethoxy)-phenyl]-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

4-Methoxy-1-[1-[2-(tetrahydro-pyran-4-yloxy)-phenyl]-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

1-[1-(2-Cyclopropylmethoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

5 1-[1-(2-Cyclobutoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

4-Methoxy-1-[1-[2-(oxetan-3-yloxy)-phenyl]-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

1-[1-(2-Butoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

10 1-(4'-Fluoro-2'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methyl-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

15 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-2'-carbonitrile;

4-Methoxy-1-(4'-methoxy-2'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

1-(2',4'-Dimethoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

20 4-Methoxy-1-[1-(4-methoxy-6-methyl-pyrimidin-5-yl)-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one; or

1-[1-(4,6-Dimethoxy-pyrimidin-5-yl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one ;

or a pharmaceutically acceptable salt thereof.

25 The compounds of formula (I), (II) and (III) according to embodiments 1) to 25) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral (such especially oral) or parenteral administration (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, 30 "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds of formula (I), (II) or (III), or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

The present invention also relates to a method for the prevention or treatment of a disease or disorder mentioned 35 herein comprising administering to a subject a pharmaceutically active amount of a compound of formula (I), (II) or (III) as defined in any one of embodiments 1) to 25).

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

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

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

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

The compounds of formula (I), (II) and (III) as defined in any one of embodiments 1) to 25) are useful for the prevention / prophylaxis or treatment of diseases and disorders related to pathogenic events associated with elevated levels of C5a and/or with C5aR activation.

Such diseases and disorders related to pathogenic events associated with elevated levels of C5a and/or with C5aR
20 activation are especially:

- vasculitic diseases or disorders,
- inflammatory diseases or disorders involving intravascular microvesicle release,
- immune complex (IC) diseases or disorders,
- neurodegenerative diseases or disorders,
- 25 • complement related inflammatory diseases or disorders,
- bullous diseases or disorders,
- diseases or disorders related to ischemia and/or ischemic reperfusion injury,
- inflammatory bowel diseases or disorders,
- autoimmune diseases or disorders, or, in addition to the above listed;
- 30 • cancer.

In addition to the above-listed diseases and disorders, further diseases and disorders related to pathogenic events associated with elevated levels of C5a and/or with C5aR activation are:

- further inflammatory diseases or disorders associated with elevated levels of C5a and/or with C5aR activation such as especially neutropenia, sepsis, septic shock, stroke, inflammation associated with

severe burns, osteoarthritis, acute (adult) respiratory distress syndrome (ARDS), chronic pulmonary obstructive disorder (COPD), asthma (especially bronchial asthma), systemic inflammatory response syndrome (SIRS), tissue graft rejection, hyperacute rejection of transplanted organs, multiple organ dysfunction syndrome (MODS), diabetic retinopathy, neuromyelitis optica, and glomerulonephritis including Heyman nephritis / membranous glomerulonephritis, Berger's disease (IgA nephropathy), and other forms of glomerulonephritis including C3 glomerulopathy;

as well as

- hemotological diseases which are associated with activation of coagulation and fibrinolytic systems, disseminated intravascular coagulation (DIC), pernicious anemia, warm and cold autoimmune hemolytic anemia (AIHA), anti-phospholipid syndrome and its associated complications, arterial or venous thrombosis, pregnancy complications such as recurrent miscarriage and fetal death, preeclampsia, placental insufficiency, fetal growth restriction, cervical remodeling and preterm birth, idiopathic thrombocytopenic purpura (ITP), atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), allergic transfusion reactions, acute antibody-mediated kidney allograft rejection, cold agglutinin disease and glaucoma.

The present compounds may in addition be useful for

- the prevention or treatment of deleterious consequences of contact sensitivity and inflammation caused by contact with artificial surfaces;
- the prevention or treatment of increased leukocyte and platelet activation (and infiltration to tissues thereof);
- the prevention or treatment of pathologic sequelae (such as especially prevention or treatment of the development of tissue injury, especially of pulmonary tissue injury) associated to an intoxication or an injury such as a trauma, an hemorrhage, a shock, or surgery including transplantation, including multiple organ failure (MOF), septic shock, shock due to intoxication (such as shock due to snake venom), or acute lung inflammatory injury;
- the prevention or treatment of pathologic sequelae associated with insulin-dependent diabetes mellitus;
- the prevention of / the reduction of the risk of myocardial infarction or thrombosis; prevention or treatment of edema or increased capillary permeability;
- the prevention of / the reduction of coronary endothelial dysfunction induced by cardiopulmonary bypass and/or cardioplegia.

Vasculitic diseases or disorders include especially vasculitis, ANCA associated vasculitis and glomerulonephritis (GN, especially rapidly progressive GN) associated with ANCA associated vasculitis, leukoclastic vasculitis, granulomatosis with polyangiitis (GPA, also referred to as Wegener's granulomatosis), microscopic polyangiitis, Churg-Strauss syndrome, Henoch-Schönlein purpura, polyarteritis nodosa, cryoglobulinaemia, giant cell arteritis (GCA), Behcet's disease, and Takayasu's arteritis (TAK).

Inflammatory diseases or disorders involving intravascular microvesicle release include especially thrombotic microangiopathy, and sickle cell disease.

- Immune complex (IC) diseases or disorders include especially cryoglobulinemia, Sjögren's syndrome (and associated immunological profiles), Goodpasture syndrome (antiglomerular basement antibody disease) and
 5 glomerulonephritis (GN, especially rapidly progressive GN) or pulmonary hemorrhage associated with Goodpasture syndrome, and hypersensitivity;

Neurodegenerative diseases and disorders include especially amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, Guillain-Barre syndrome, neuropathy, , and cognitive function decline associated with cardiopulmonary bypass surgery and related procedures.

- 10 Complement related inflammatory diseases or disorders include especially coronary thrombosis, vascular occlusion, post-surgical vascular reocclusion, atherosclerosis, traumatic central nervous system injury, arrhythmogenic cardiomyopathy, bronchoconstriction, acute respiratory distress syndrome (ARDS), Chronic Obstructive Pulmonary Disorder (COPD), complement mediated thrombotic microangiopathies including atypical haemolytic uremic syndrome, and Gaucher disease.

- 15 Bullous diseases or disorders include especially bullous pemphigoid, bullous acquisita, pemphigus foliaceus, pemphigus vulgaris, and sub-epidermal blisters.

Diseases or disorders related to ischemia and/or ischemic reperfusion injury include especially ischemic reperfusion injury (including myocardial ischemia-reperfusion injury, and ischemic / reperfusion injury resulting from transplantation, including solid organ transplant), ischemic colitis, and cardiac ischemia.

- 20 Inflammatory bowel diseases or disorders include especially irritable bowel syndrome, ulcerative colitis, Crohn's disease, and inflammatory bowel disease (IBD).

- Autoimmune diseases or disorders include especially rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus (SLE) and glomerulonephritis (GN, especially rapidly progressive GN) associated with lupus erythematosus (lupus nephritis), central nervous system (CNS) lupus, dermatomyositis, pemphigus, systemic
 25 sclerosis (scleroderma), autoimmune hemolytic and thrombocytopenic states, immunovascularitis, mixed cryoglobulinemia, atopic dermatitis, chronic urticaria, psoriasis, myasthenia gravis, and anti-phospholipid syndrome.

- Further inflammatory diseases or disorders associated with elevated levels of C5a and/or with C5aR activation include especially neutropenia, sepsis, septic shock, stroke, inflammation associated with severe burns,
 30 osteoarthritis, acute (adult) respiratory distress syndrome (ARDS), chronic pulmonary obstructive disorder (COPD), asthma, especially bronchial asthma, systemic inflammatory response syndrome (SIRS), tissue graft rejection, hyperacute rejection of transplanted organs, multiple organ dysfunction syndrome (MODS), diabetic retinopathy, neuromyelitis optica, and glomerulonephritis including Heyman nephritis / membranous glomerulonephritis, Berger's disease (IgA nephropathy), and other forms of glomerulonephritis including C3 glomerulopathy.

The term "cancer" notably refers to 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; or virally induced tumors.

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

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

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

When used in combination with the present compounds, 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;
- 5 e) Immune Checkpoint inhibitors (for example: anti-PD1 antibodies such as Pembrolizumab (Lambrolizumab, MK-3475), Nivolumab, Pidilizumab (CT-011), AMP-514/MED10680, PDR001, SHR-1210; REGN2810, BGBA317; fusion proteins targeting PD-1 such as AMP-224; small molecule anti-PD1 agents such as for example compounds disclosed in WO2015/033299, WO2015/044900 and WO2015/034820; anti-PD1L antibodies, such as BMS-936559, atezolizumab (MPDL3280A, RG7446), MEDI4736, avelumab (MSB0010718C), durvalumab (MEDI4736); anti-PDL2 antibodies, such as AMP224; anti-CTLA-4 antibodies, such as ipilimumab, tremilumab; anti-Lymphocyte-activation gene 3 (LAG-3) antibodies, such as BMS-986016, IMP701, MK-4280, ImmuFact IMP321; anti T cell immunoglobulin mucin-3 (TIM-3) antibodies, such as MBG453; anti-CD137/4-1BB antibodies, such as BMS-663513 / urelumab, PF-05082566; anti T cell immunoreceptor with Ig and ITIM domains (TIGIT) antibodies, such as RG6058 (anti-TIGIT, MTIG7192A);
- 10 (anti-TIGIT, MTIG7192A);
- f) Vaccination approaches (for example dendritic cell vaccination, peptide or protein vaccination (for example with gp100 peptide or MAGE-A3 peptide);
- g) Re-introduction of patient derived or allogenic (non-self) cancer cells genetically modified to secrete immunomodulatory factors such as granulocyte monocyte colony stimulating factor (GM-CSF) gene-transfected tumor cell vaccine (GVAX) or Fms-related tyrosine kinase 3 (Flt-3) ligand gene-transfected tumor cell vaccine (FVAX), or Toll like receptor enhanced GM-CSF tumor based vaccine (TEGVAX);
- 20 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);
- 25 j) Toll-like receptor (TLR) agonists (for example resiquimod, imiquimod, glucopyranosyl lipid A, CpG oligodeoxynucleotides);
- k) Thalidomide analogues (for example Lenalidomide, Pomalidomide);
- l) Indoleamin-2,3-Dioxygenase (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);
- 30 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);
- 35

- 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);
- 5 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);
- 10 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 present compounds, immune checkpoint inhibitors, and especially those targeting the PD-1 receptor or its ligand PD-L1, are preferred.

The invention further relates to a method of modulating (especially downregulating) the consequences of the complement activation (especially by activating innate cells) in a subject in need thereof [especially in a subject
15 having a disease or disorder related to pathogenic events associated with elevated levels of C5a and/or with C5aR activation; in particular in a subject having a vasculitic disease or disorder, an inflammatory disease or disorder involving intravascular microvesicle release, an immune complex (IC) disease or disorder, a neurodegenerative disease or disorder, a complement related inflammatory disease or disorder, a bullous disease or disorder, a
20 disease or disorder related to ischemia and/or ischemic reperfusion injury, an inflammatory bowel disease or disorder, or an autoimmune disease or disorder; or in a subject having a contact sensitivity or an inflammation caused by contact with artificial surfaces; an increased leukocyte and platelet activation (and infiltration to tissues thereof); a pathologic sequelae associated to an intoxication or an injury such as a trauma, an hemorrhage, a shock, or surgery including transplantation, including multiple organ failure (MOF), septic shock, shock due to
25 intoxication (such as shock due to snake venom), or acute lung inflammatory injury; a pathologic sequelae associated with insulin-dependent diabetes mellitus; a myocardial infarction or thrombosis; an edema or an increased capillary permeability; or a reduction of coronary endothelial dysfunction induced by cardiopulmonary bypass and/or cardioplegia], comprising administering to said subject a pharmaceutically active amount of a compound of formula (I), (II) and (III) as defined in any one of embodiments 1) to 25). For avoidance of doubt, the
30 term "modulating the complement activation" is to be understood as downregulating / reducing the amplification of the immune response and downregulating / reducing the activation of the cell-killing membrane attack complex, especially by activating innate cells.

Preparation of compounds of formula (I):

35 The compounds of formula (I), (II) and (III) can be prepared 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 the schemes below, the generic groups Ring A, R¹, R^{1a}, R^{14a}, R^{14b}, X¹⁴, R², R^{2a}, X²¹, R³, R⁴, R⁴¹, R^{41a}, R^{41b}, X⁴¹, R^{42a}, R^{42b}, R^{43a}, R^{43b} are as defined for the compounds of formula (I), (II) and (III). In some instances, the generic groups Ring A, R¹, R^{1a}, R^{14a}, R^{14b}, X¹⁴, R², R^{2a}, X²¹, R³, R⁴, R⁴¹, R^{41a}, R^{41b}, X⁴¹, R^{42a}, R^{42b}, R^{43a}, R^{43b} may be incompatible with the assembly illustrated in the schemes, or 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, and hydrolysis 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 structure **1a** can be prepared according to the synthetic route given in scheme A below.

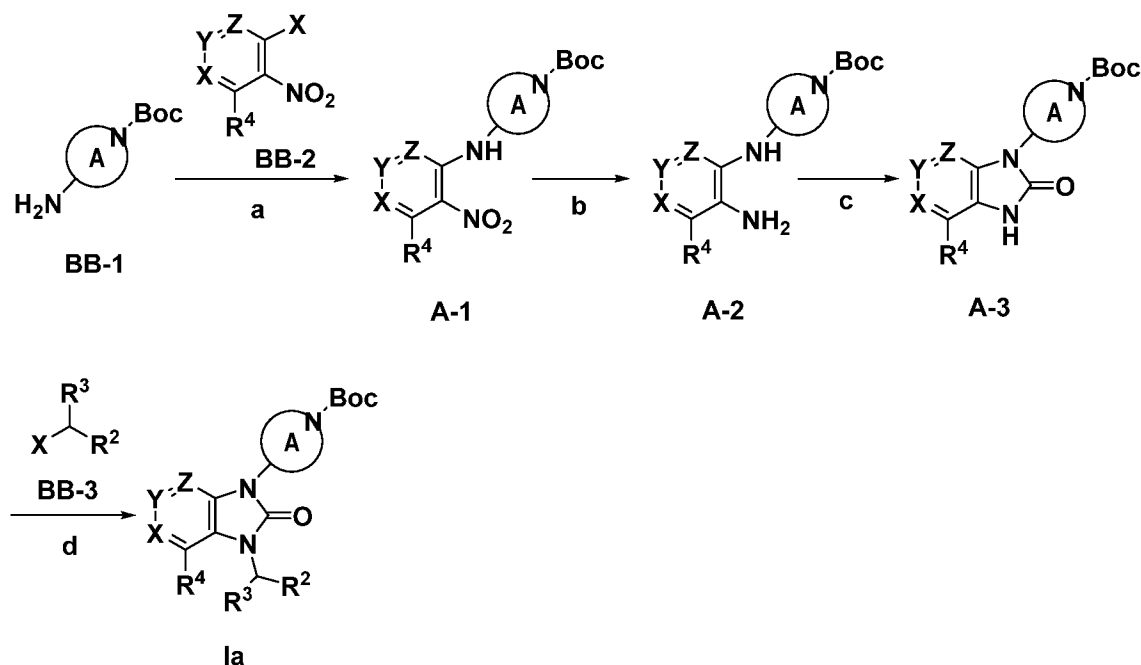
Compounds of structure **A-1** can be prepared by aromatic nucleophilic substitution of amine of structure **BB-1** on halides of structure **BB-2** wherein **X** represents fluorine or chlorine in the presence of a suitable base such as DIPEA and heating in a suitable solvent such as DMSO at temperatures between 80°C and 100°C (Scheme A, step a).

Diamino compounds of structure **A-2** can be prepared by reduction of the nitro group in compounds of structure **A-1** using standard conditions such as catalytic hydrogenation with a suitable catalyst such as Pd/C and in the presence of a suitable solvent such as EtOAc and under a hydrogen atmosphere. Alternatively, reduction of the nitro group in compounds of structure **A-1** may be performed by treatment with zinc dust and ammonium formate in solvents such as MeOH at temperatures around 0°C (Scheme A, step b).

Cyclic ureas of structure **A-3** can be prepared by cyclisation of diamines of structure **A-2** by treatment with a suitable carbonyl transfer agent such as CDI in the presence of a suitable non protic solvent such as MeCN at temperatures between RT and 45°C (Scheme A, step c).

Alkylation of the nitrogen atom having a free valency in compounds of structure **A-3** with a suitable halide of structure **BB-3** wherein **X** represents chlorine or bromine, in the presence of a suitable base such as NaH or K₂CO₃ and in solvents such as THF, DMF or a mixture of both at temperatures between 0°C and 50°C may afford compounds of structure **1a** (Scheme A, step d).

Scheme A



Alternatively, compounds of structure **Ia** can be prepared according to the synthetic route given in scheme B below.

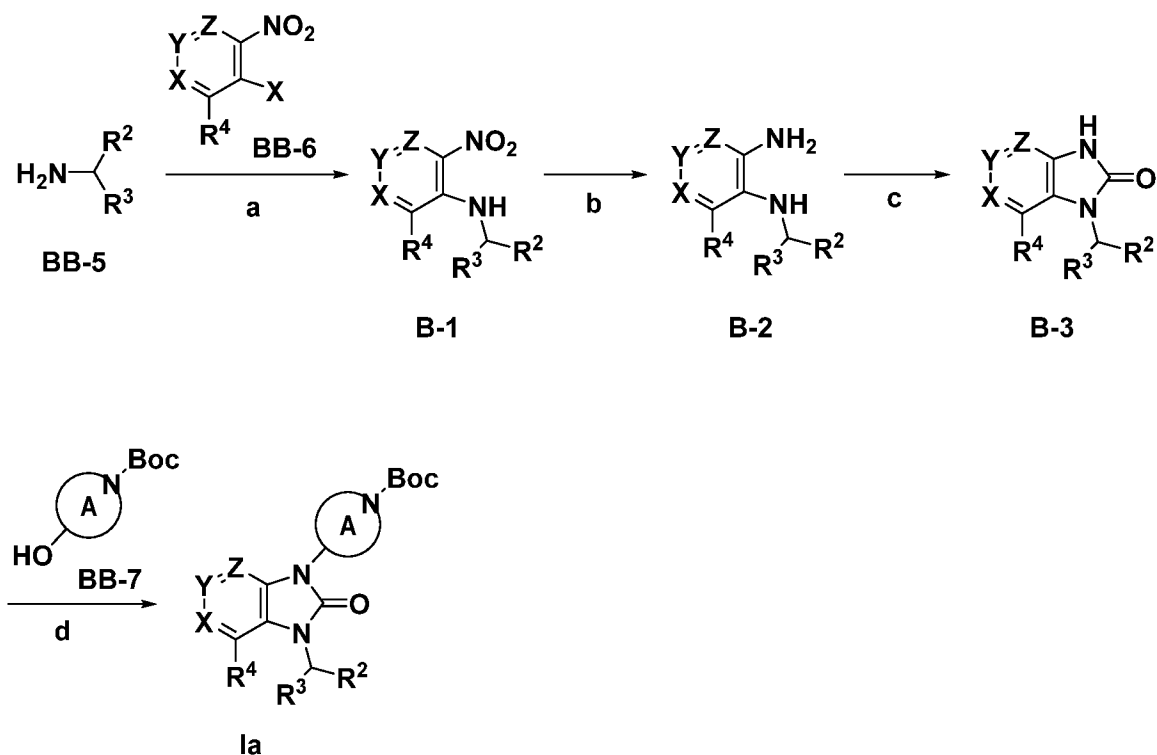
Compounds of structure **B-1** can be prepared by aromatic nucleophilic substitution of amine of structure **BB-5** on
 5 halides of structure **BB-6** wherein **X** represents fluorine or chlorine in the presence of a suitable base such as DIPEA and heating at temperatures between 150°C and 180°C (Scheme B, step a).

Reduction of the nitro group in compounds of structure **B-1** using standard conditions such as treatment by zinc
 dust and ammonium formate in solvents such as MeOH at temperatures around 0°C may afford diamines of
 structure **B-2**. Alternatively, reduction of the nitro group in compounds of structure **B-1** may be performed by
 10 catalytic hydrogenation with a suitable catalyst such as Pd/C in the presence of a suitable solvent such as EtOAc
 and under a hydrogen atmosphere (Scheme B, step b).

Cyclisation of diamines of structure **B-2** to form cyclic urea of structure **B-3** (Scheme B, step c) can be performed
 following conditions as those previously described for the synthesis of compounds of structure **A-3** (Scheme A,
 step c).

15 Alkylation of the nitrogen atom having a free valency in compounds of structure **B-3** can be achieved using
 Mitsunobu conditions by treatment with a suitable alcohol of structure **BB-7** and for instance a
 (cyanomethylene)trialkylphosphorane reagent in the presence of a suitable solvent such as toluene at
 temperatures around 110°C (Scheme B, step d).

Scheme B



Compounds of structure **1b**, **1c**, **1g**, **1h**, **1i**, **1q** and **1ag** can be prepared according to the synthetic route given in scheme C below.

Cleavage of the Boc protecting group in compounds of formula **1a** can be performed using a suitable acid such as HCl or TFA in the presence of a suitable solvent such as dioxane, MeOH or DCM at temperatures around RT (Scheme C, step a).

Compounds of structure **1b** wherein **R¹** represents an unsubstituted, mono-, di- or tri-substituted phenyl or 5- or 6-membered heteroaryl can be prepared by Buchwald-Hartwig cross coupling of halides of structure **R¹-X** wherein **X** represents iodine, bromine or chloride and **R¹** represents an unsubstituted, mono-, di- or tri-substituted phenyl or 5- or 6-membered heteroaryl with an amine of structure **C-1** in the presence of a suitable palladium catalyst such as Pd₂(dba)₃ and a ligand such as BINAP, in the presence of a suitable base such as sodium tert-butoxide and heating in a suitable solvent such as toluene at temperatures between 100°C and 110°C (Scheme C, step b).

Compounds of structure **1b** wherein **R¹** represents an unsubstituted, mono- or di-substituted benzyl can be prepared by reductive amination of benzaldehyde of structure **R^{1a}-CHO** wherein **R^{1a}** represents a mono- or di-substituted phenyl with an amine of structure **C-1** using standard conditions such as treatment with NaBH(OAc)₃ in the presence of AcOH and a suitable solvent such as DCM or THF at temperatures around RT (Scheme C, step b).

Compounds of structure **1c** wherein **R¹** represents an unsubstituted, mono-, di- or tri-substituted phenyl or 5- or 6-membered heteroaryl can be prepared by aromatic nucleophilic substitution of amines of structure **C-1** on activated

halides of structure **R¹-X** wherein **X** represents fluorine or chlorine and **R¹** represents a suitable unsubstituted, mono-, di- or tri-substituted phenyl or 5- or 6- membered heteroaryl in the presence of a suitable base such as CsF or K₂CO₃ and heating in a suitable solvent such as DMSO at temperatures between 60°C and 110°C (Scheme C, step b).

5 Alternatively, compounds of structure **1c** wherein **R¹** represents a 5- or 6- membered heteroaryl can be prepared by aromatic nucleophilic substitution of amines of structure **C-1** on alcohol of structure **R¹-X** wherein **X** represents hydroxy and **R¹** represents a suitable 5- or 6- membered heteroaryl by activation of the corresponding alcohol with PyBOP in the presence of a suitable base such as DIPEA in solvents such as DMF at temperatures around RT (Scheme C, step b).

10 Compounds of structure **1g** wherein **R¹** represents a (C₁₋₄)alkoxy-carbonyl, phenoxy-carbonyl or (C₃₋₆)cycloalkoxy-carbonyl can be prepared by treatment of amines of structure **C-1** with chloroformate (or pentafluorophenylcarbonate, respectively) of structure **R¹-X** wherein **R¹** represents (C₁₋₄)alkoxy-carbonyl, phenoxy-carbonyl or (C₃₋₆)cycloalkoxy-carbonyl and **X** represents chlorine (or **X** represents pentafluorophenoxy, respectively) in the presence of a suitable base such as TEA and in a suitable solvent such as DCM or DMF at
15 temperatures between RT and 110°C (Scheme C, step b).

Compounds of structure **1h** wherein **R¹** represents a (C₁₋₄)alkyl-carbonyl, phenyl-carbonyl or (C₃₋₆)cycloalkyl-carbonyl optionally containing one ring oxygen and optionally mono-substituted with methyl or trifluoromethyl can be prepared by treatment of amines of structure **C-1** with acid chlorides of structure **R¹-X** wherein **R¹** represents (C₁₋₄)alkyl-carbonyl, phenyl-carbonyl or (C₃₋₆)cycloalkyl-carbonyl optionally containing one ring oxygen and
20 optionally mono-substituted with methyl or trifluoromethyl and **X** represents chlorine in the presence of a suitable base such as TEA and in a suitable solvent such as DCM at temperatures between 0°C and RT (Scheme C, step b).

Compounds of structure **1i** wherein **R¹** represents (C₁₋₄)alkyl can be prepared by reductive amination of a suitable aldehyde of structure **R^{1a}-CHO** wherein **R^{1a}** represents hydrogen or (C₁₋₃)alkyl, acetone or butanone with amines of
25 structure **C-1** using standard conditions such as treatment with NaBH(OAc)₃ in the presence of AcOH and a suitable solvent such as DCM, MeOH, THF or mixture thereof at temperatures around RT (Scheme C, step b). Alternatively, triethylsilane in solvents such as MeOH in the presence of catalytic amount of indium chloride (III) at temperatures around RT can be used as reductive conditions. Alternatively, alkylation of amines of structure **C-1** with halides of structure **R¹-X** wherein **X** represents chlorine, bromine or iodine in the presence of a suitable base
30 such as K₂CO₃ and a suitable solvent such as MeCN at temperatures between RT and 65°C may afford compounds of structure **1i** (Scheme C, step b).

Compounds of structure **C-2** can be prepared by alkylation of carbamates of structure **BB-10** by treatment with an appropriate halide of formula **BB-3** wherein **X** represents chlorine or bromine in the presence of a suitable base such as K₂CO₃ and carrying out the rxn in a suitable solvent such as MeCN at temperatures around 80°C (Scheme
35 C, step c).

Compounds of formula **lag** can be prepared by Buchwald-Hartwig cross coupling of halides of formula **C-2** with amines of formula **BB-4** by treatment with a suitable palladium catalyst such as BrettPhos precatalyst and a suitable ligand such as BrettPhos, in the presence of a suitable base such as sodium tert-butoxide and heating in a suitable solvent such as dioxane at temperatures around 80°C. Using those conditions, the consecutive cyclisation to form the cyclic urea occurred and afforded the compounds of formula **lag** (Scheme C, step d).

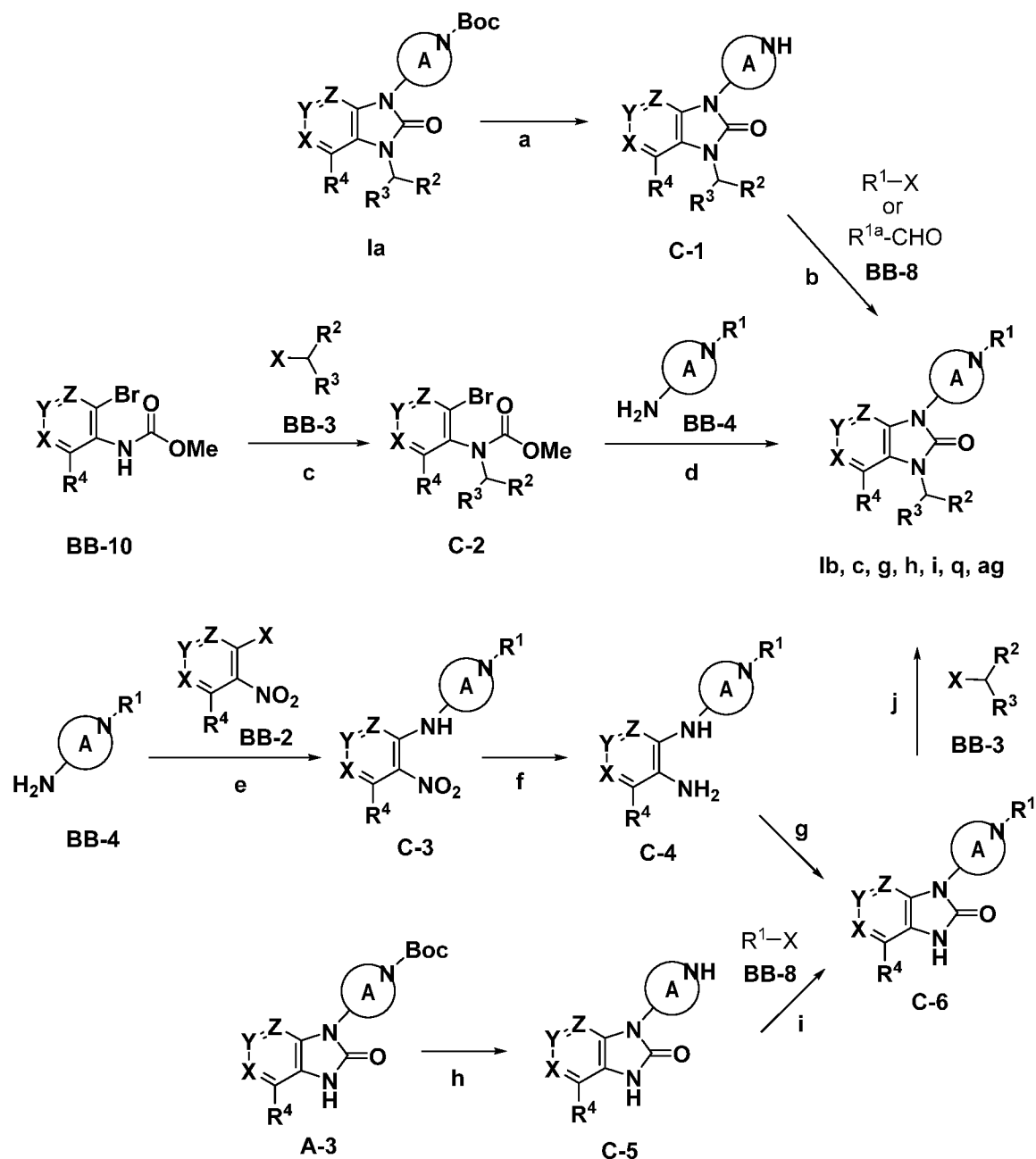
Compounds of structure **C-3** can be prepared by aromatic nucleophilic substitution of amine of structure **BB-4** on halides of structure **BB-2** wherein **X** represents fluorine or chlorine in the presence of a suitable base such as DIPEA and heating in a suitable solvent such as DMSO at temperatures between 50°C and 105°C (Scheme C, step e).

10 Diamino compounds of structure **C-4** can be prepared by reduction of the nitro group in compounds of structure **C-3** using standard conditions such as catalytic hydrogenation with a suitable catalyst such as Pd/C and in the presence of a suitable solvent such as EtOAc and under a hydrogen atmosphere. Alternatively, the reduction of the nitro group can be performed by treatment with ammonium formate and zinc dust in the presence of a suitable solvent such as MeOH at temperatures around RT (Scheme C, step f).

15 Cyclic urea of structure **C-6** can be prepared by cyclisation of diamines of structure **C-4** by treatment with a suitable carbonyl transfer agent such as CDI in the presence of a suitable non protic solvent such as MeCN at temperatures between RT and 45°C (Scheme C, step g).

Alternatively, compounds of structure **C-6** can be prepared by aromatic nucleophilic substitution of amines of structure **C-5** on halides of structure **BB-8** wherein **X** represents fluorine or chlorine in the presence of a suitable base such as K₂CO₃ and heating in a suitable solvent such as DMSO at temperatures around 100°C (Scheme C, step i). Compounds of structure **C-5** can be prepared by cleavage of the Boc protecting group in compounds of formula **A-3** using a suitable acid such as HCl or TFA in the presence of a suitable solvent such as dioxane, MeOH or DCM at temperatures around RT (Scheme C, step h).

Scheme C



Compounds of structure **ld** to **lf**, **lj** to **lp**, **lu** to **lz** and **lae** can be prepared according to the synthetic route given in scheme D below.

- 5 Alkylation of the nitrogen atom having a free valency in compounds of structure **C-6** with a suitable halide of structure **BB-3** wherein **X** represents chlorine or bromine, in the presence of a suitable base such as NaH or K₂CO₃ and in solvents such as THF, DMF or a mixture of both at temperatures between 0°C and 50°C may afford compounds of structure **lq** (Scheme C, step j). Alternatively, alkylation of the nitrogen atom having a free valency in compounds of structure **C-6** can be achieved using Mitsunobu conditions by treatment with a suitable alcohol of

structure **BB-3** wherein **X** represents hydroxy and for instance a (cyanomethylene)trialkylphosphorane reagent in the presence of a suitable solvent such as toluene at temperatures around 110°C (Scheme C, step j).

Compounds of structure **Id** wherein **R¹** represents a 5- or 6- membered heteroaryl with at least one unsubstituted position can be prepared by decarbonylation of compounds of formula **Ib** or **Ic** wherein **R¹** represents a 5- or 6- membered heteroaryl which is substituted by a formyl group by treatment with a suitable acid such as toluene-4-sulfonic acid and in the presence of a suitable solvent such as MeOH under microwave conditions at temperatures around 120°C (Scheme D, step a).

Compounds of structure **If** wherein **R¹** represents a 5- or 6- membered heteroaryl with at least one methyl substituent can be prepared by Wolff-Kishner type reduction of compounds of formula **Ib** or **Ic** wherein **R¹** represents a 5- or 6- membered heteroaryl which is substituted by one formyl group. The treatment with 4-toluene-sulfonyl hydrazide in the presence of toluene-4-sulfonic acid monohydrate with a suitable solvent such as a mixture of DMF and tetramethylene sulfone at temperatures around 100°C affords the hydrazone intermediate which is consecutively reduced by treatment with sodium cyanoborohydride at temperatures around 100°C (Scheme D, step a).

Compounds of structure **Ij** wherein **R⁴** represents hydroxy can be prepared by treatment of suitable compounds of formula **Ib** and **Ic** wherein **R⁴** represents methoxy with a suitable Lewis acid such as boron tribromide in the presence of a suitable solvent such as DCM at temperatures between -10°C and RT (Scheme D, step a).

Compounds of structure **Im** wherein **R¹** represents a hydroxymethyl substituted phenyl or 5- or 6- membered heteroaryl can be prepared by treatment of compounds of formula **Ib** and **Ic** wherein **R¹** represents a formyl substituted phenyl or 5- or 6- membered heteroaryl by treatment with a suitable reducing reagent such as NaBH₄ in the presence of a suitable solvent such as MeOH or THF at temperatures between 0°C and RT (Scheme D, step a).

Compounds of structure **In** wherein **R¹** represents a 1-hydroxy-(C₂-C₃)-alkyl substituted phenyl or 5- or 6- membered heteroaryl can be prepared by treatment of compounds of formula **Ib** and **Ic** wherein **R¹** represents a formyl substituted phenyl or 5- or 6- membered heteroaryl by treatment with a suitable Grignard reagent in the presence of a suitable solvent such as THF at temperatures between 0°C and RT (Scheme D, step a).

Compounds of structure **Iu** wherein **R¹** represents a **R^{14a}R^{14b}N-X¹⁴**- substituted phenyl, 5- or 6-membered heterocycle wherein **X¹⁴** represents a methylene and **R^{14a}** and **R^{14b}** independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R^{14a}** and **R^{14b}** together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl can be prepared by reductive amination of compounds of formula **Ib** or **Ic** wherein **R¹** represents a formyl substituted phenyl or 5- or 6- membered heteroaryl using standard conditions such as treatment with NaBH(OAc)₃ in the optional presence of AcOH and a suitable solvent such as DCM or THF at temperatures around RT (Scheme D, step a).

Compounds of structure **le** wherein **R¹** represents a chlorine substituted 5- or 6- membered heteroaryl can be prepared by chlorination of compounds of formula **ld** wherein **R¹** represents a 5- or 6- membered heteroaryl with one unsubstituted position by treatment with a chlorinating reagent such as NCS in the presence of a suitable solvent such as THF at temperatures around RT (Scheme D, step b).

5 Compounds of structure **lk** wherein **X** and **Z** represents CH and **R⁴** represents $-O-R^{41}$ wherein **R⁴¹** represents (C₁₋₄)alkyl, (C₂₋₄)alkyl which is substituted with one or two hydroxyl, **R^{41a}R^{41b}N**-(C₂₋₃)alkylene-, wherein **R^{41a}** and **R^{41b}** independently represent hydrogen or (C₁₋₄)alkyl; or (C₄₋₇)heterocyclyl-**X⁴¹**-, wherein **X⁴¹** represents a direct bond or (C₁₋₃)alkylene, and wherein the (C₄₋₇)heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen and oxygen; wherein said (C₄₋₇)heterocyclyl independently is unsubstituted,
10 or mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl or (C₁₋₄)alkoxy-carbonyl attached to a ring nitrogen atom having a free valency can be prepared by alkylation of compounds of formula **lj** wherein **X** and **Z** represents CH and **R⁴** represents hydroxyl by treatment with an appropriate halide such as **R⁴¹-W** wherein **W** represents chlorine or bromine in the presence of a suitable base such as K₂CO₃ and carrying out the rxn in a suitable solvent such as DMSO at temperatures between 50 and 105°C (Scheme D, step b).

15 Compounds of structure **lo** wherein **R¹** represents a 1-oxo-(C₂-C₅)-alkyl substituted phenyl or 5- or 6- membered heteroaryl can be prepared by oxidation of compounds of formula **ln** wherein **R¹** represents a (C₁-C₄)-alkyl-hydroxymethyl substituted phenyl or 5- or 6- membered heteroaryl by treatment with an oxidizing reagent such as DMP in the presence of a suitable solvent such as DCM at temperatures around RT (Scheme D, step b).

Compounds of structure **ll** can be prepared by Suzuki cross coupling of chlorides of structure **le** wherein **R¹**
20 represents a chlorine substituted 5- or 6-membered heteroaryl with a (C₁-C₄)-alkyl boronic acid or boroxine in the presence of a suitable palladium catalyst such as PEPPSI-IPr, in the presence of a suitable base such as K₂CO₃ and heating in a suitable solvent such as dioxane at temperatures between 115°C (Scheme D, step c).

Compounds of structure **lp** wherein **R¹** represents a 1-hydroxy-1-methyl-ethyl substituted phenyl or 5- or 6-membered heteroaryl can be prepared by treatment of compounds of formula **lo** wherein **R¹** represents an acetyl
25 substituted phenyl or 5- or 6- membered heteroaryl by treatment with a suitable Grignard reagent in the presence of a suitable solvent such as THF at temperatures between 0°C and RT (Scheme D, step c).

Compounds of structure **lx** wherein **X** and **Z** represents CH and **R⁴** represents a diol containing substituent (respectively a substituent containing a nitrogen atom having a free valency) can be prepared by acidic deprotection of compounds of structure **lk** wherein **R⁴** represents a substituent which contains a ketal protected diol
30 (respectively a substituent containing a Boc protected nitrogen) in the presence of a suitable acid such as aqueous HCl (respectively TFA) and a suitable solvent such as THF (respectively DCM) at temperatures between 0°C and RT (Scheme D, step c).

Alkylation of the free hydroxyl group in compounds of structure **lm** wherein **R¹** represents a hydroxymethyl substituted phenyl or 5- or 6- membered heteroaryl or in compounds of structure **ln** wherein **R¹** represents a 1-
35 hydroxy-(C₂-C₃)-alkyl substituted phenyl or 5- or 6- membered heteroaryl with a suitable (C₁-C₄)-alkyl halide, in the

presence of a suitable base such as NaH and in solvents such as THF, DMF or a mixture of both at temperatures between 0°C and 50°C may afford compounds of structure **Iz** (Scheme D, step d).

Compounds of structure **Iae** wherein **R¹** represents a **R^{14a}R^{14b}N-CH(Me)-**, **R^{14a}R^{14b}N-CH(Et)-**, or **R^{14a}R^{14b}N-C(Me)₂-** substituted phenyl or 5- or 6- membered heteroaryl wherein **R^{14a}** and **R^{14b}** independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R^{14a}** and **R^{14b}** together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl (especially methyl), hydroxy, (C₁₋₄)alkoxy (especially methoxy), or dimethylamino can be prepared following a two-step procedure: (i) chlorination by treatment of compounds of formula **In** wherein **R¹** represents a 1-hydroxy-(C₂₋₃)-alkyl substituted phenyl or 5- or 6- membered heteroaryl with a chlorinating reagent such as SOCl₂ in the presence of a suitable solvent such as DCM at temperatures around RT and (ii) consecutive nucleophilic substitution with amines of formula **R^{14a}R^{14b}NH** wherein **R^{14a}** and **R^{14b}** independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R^{14a}** and **R^{14b}** together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl (especially methyl), hydroxy, (C₁₋₄)alkoxy (especially methoxy), or dimethylamino in the presence of a base such as TEA and a suitable solvent such as DCM at temperatures between 0°C and RT (Scheme D, step e).

Compounds of structure **D-1** can be prepared by chlorination of compounds of structure **Ij** wherein **R⁴** represents hydroxyl, **Y** represents **CR⁵** wherein **R⁵** represents hydrogen or (C₁₋₃)alkyl and one of **X** and **Z** or both represents N and the possible other one represents **CR⁵** wherein **R⁵** represents hydrogen or (C₁₋₃)alkyl, using a neat chlorinating reagent such as POCl₃ and heating at temperatures around 85°C (Scheme D, step f).

Compounds of structure **Iv** wherein **R⁵** represents hydrogen or (C₁₋₃)alkyl, one of **X** and **Z** or both represents N and the possible other one represents **CR⁵** wherein **R⁵** represents hydrogen or (C₁₋₃)alkyl and **R⁴** represents –**NR^{42a}R^{42b}** wherein **R^{42a}** and **R^{42b}** independently represent hydrogen, (C₁₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₃)alkyl, hydroxy-(C₂₋₃)alkyl, or **R^{42a}** and **R^{42b}** together with the nitrogen to which they are attached form a 4- to 7-membered saturated ring optionally containing one further ring heteroatom selected from oxygen and nitrogen, wherein said ring is unsubstituted or mono-substituted with (C₁₋₃)alkyl (especially methyl), or (C₁₋₃)alkoxy (especially methoxy) can be prepared by aromatic nucleophilic substitution of neat amines of structure **HNR^{42a}R^{42b}** wherein **R^{42a}** and **R^{42b}** are defined above on compounds of structure **D-1** at temperatures between 100 and 140°C. Alternatively, Buchwald-Hartwig cross coupling conditions can be used by treatment with a suitable palladium catalyst such as RuPhos precatalyst and a suitable ligand such as RuPhos, in the presence of a suitable base such as Cs₂CO₃ and heating in a suitable solvent such as *t*-BuOH at temperatures around 110°C (Scheme D, step g).

Compounds of structure **Iv** wherein **R⁵** represents hydrogen or (C₁₋₃)alkyl, one of **X** and **Z** or both represents N and the possible other one represents **CR⁵** wherein **R⁵** represents hydrogen or (C₁₋₃)alkyl and **R⁴** represents –**O-R⁴¹** wherein **R⁴¹** represents (C₁₋₄)alkyl (especially methyl); (C₂₋₄)alkyl which is substituted with one or two hydroxy (especially 2-hydroxyethyl, 2,3-dihydroxypropyl); **R^{41a}R^{41b}N-(C₂₋₃)alkylene-**, wherein **R^{41a}** and **R^{41b}** independently

represent hydrogen or (C₁₋₄)alkyl (especially such group is 2-dimethylamino-ethyl); or (C₄₋₇)heterocyclyl-**X**⁴¹-, wherein **X**⁴¹ represents a direct bond or (C₁₋₃)alkylene, and wherein the (C₄₋₇)heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen and oxygen; wherein said (C₄₋₇)heterocyclyl independently is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl); and/or (C₁₋₄)alkoxy-carbonyl attached to a ring nitrogen atom having a free valency can be prepared by aromatic nucleophilic substitution of alcohol of structure HOR⁴¹ wherein **R**⁴¹ is defined above on compounds of structure **D-1** in the presence of a suitable base such as KOH and heating in a suitable solvent such as DMSO at temperatures around 50 (Scheme D, step g).

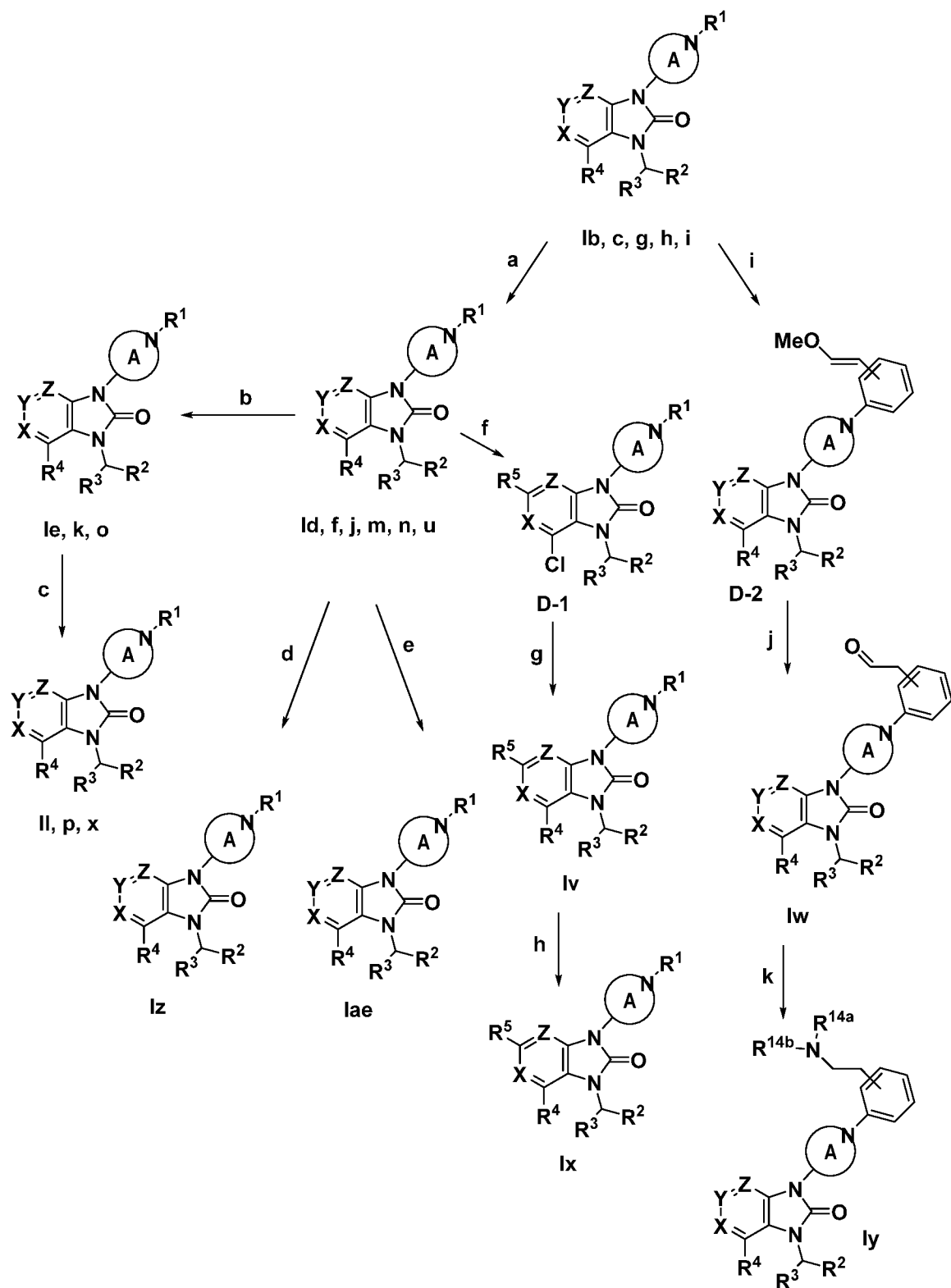
Compounds of structure **Ix** wherein **R**⁵ represents hydrogen or (C₁₋₃)alkyl, one of **X** and **Z** or both represents N and the possible other one represents CR⁵ wherein **R**⁵ represents hydrogen or (C₁₋₃)alkyl and **R**⁴ represents a diol containing substituent (respectively a substituent containing a nitrogen atom having a free valency) can be prepared by acidic deprotection of compounds of structure **Iv** wherein **R**⁴ represents a substituent which contains a ketal protected diol (respectively a substituent containing a Boc protected nitrogen) in the presence of a suitable acid such as aqueous HCl (respectively TFA) and a suitable solvent such as THF (respectively DCM) at temperatures between 0°C and RT (Scheme D, step h).

Compounds of structure **D-2** can be prepared by Wittig type rxn between compounds of formula **Ic** wherein **R**¹ represents a formyl substituted phenyl and (methoxymethyl)triphenylphosphonium chloride by treatment with a strong base such as n-butyllithium in the presence of a suitable solvent such as THF at temperatures around -78°C (Scheme D, step i).

Compounds of structure **Iw** can be prepared by acidic hydrolysis of enol ether of structure **D-2** in the presence of a suitable acid such as aqueous HCl and heating in a suitable solvent such as THF at temperatures around 70°C (Scheme D, step j).

Compounds of structure **Iy** wherein **R**¹ represents a **R**^{14a}**R**^{14b}N-**X**¹⁴- substituted phenyl, wherein **X**¹⁴ represents a ethylene; and wherein **R**^{14a} and **R**^{14b} independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R**^{14a} and **R**^{14b} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl (especially methyl), hydroxy, (C₁₋₄)alkoxy (especially methoxy), or dimethylamino can be prepared by reductive amination of compounds of structure **Iw** with amines of structure **R**^{14a}**R**^{14b}NH wherein **R**^{14a} and **R**^{14b} are defined above using standard conditions such as treatment with NaBH(OAc)₃ in the presence of AcOH and a suitable solvent such as DCM or THF at temperatures around RT (Scheme D, step k).

Scheme D



Compounds of structure Ia to Ii and Iaf can be prepared according to the synthetic route given in scheme E below.

The chlorine or bromine atom on either **R**¹ or **R**² which represent a phenyl or 5- or 6-membered heteroaryl or when **X**, **Y** or **Z** represents C-Cl or C-Br in compounds of structure **1q** can be replaced by one hydrogen atom (respectively by one deuterium atom) by catalytic hydrogenation (respectively deuteration) using a suitable catalyst such as Pd/C in the presence of a suitable solvent such as EtOAc, MeOH or a mixture of both and under a hydrogen (respectively a deuterium) atmosphere at temperatures around RT. That transformation provides compounds of structure **1r**. Catalytic transfer hydrogenation conditions using for instance ammonium formate can be an alternative procedure (Scheme E, step a).

Compounds of structure **1q** wherein **R**⁴ represents methoxycarbonyl can be transformed to compounds of formula **E-1** by hydrolysis with a suitable base such as LiOH, NaOH or KOH in the presence of water and a suitable organic solvent such as THF, MeOH or EtOH or a mixture of them at temperatures between RT and 50°C (Scheme E, step b).

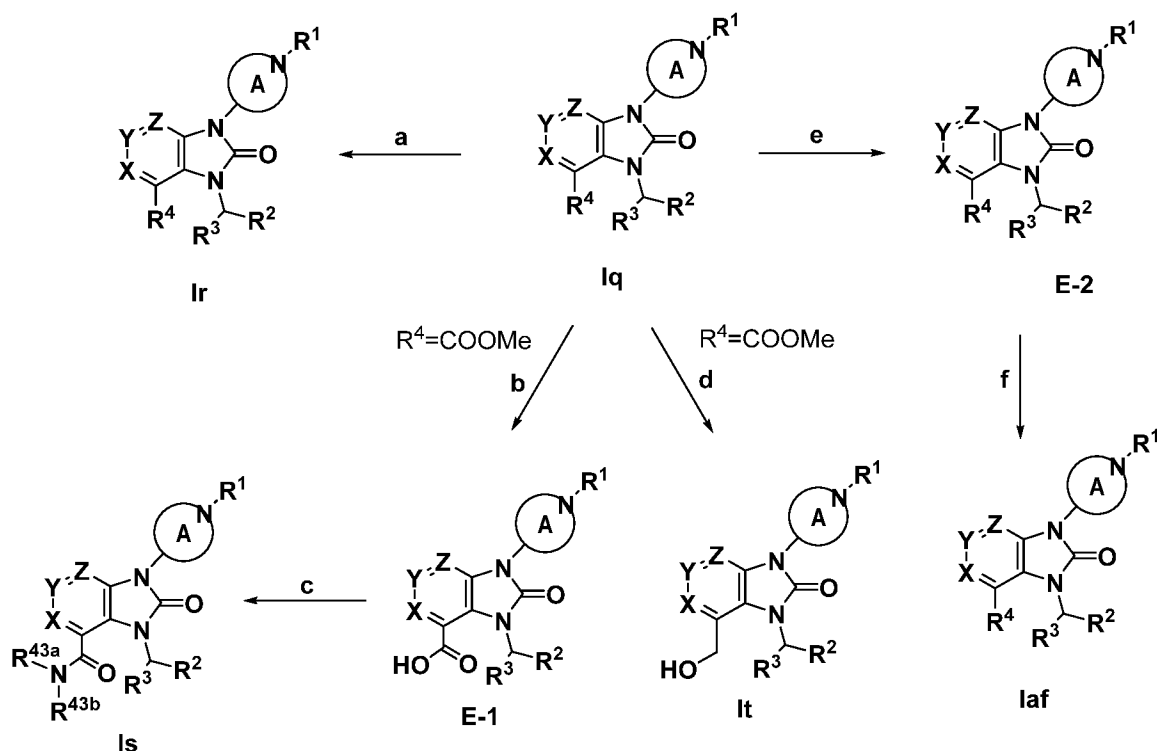
Compounds of structure **1s** can be prepared by amide coupling of carboxylic acids of structure **E-1** with amines of structure **R**^{43a}**R**^{43b}NH wherein **R**^{43a} and **R**^{43b} independently represents hydrogen, (C₁₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₃)alkyl, or hydroxy-(C₂₋₃)alkyl using standard amide coupling reagent such as EDC.HCl/HOBt, HATU or PyBOP in the presence of a suitable base such as DIPEA or Et₃N and in a suitable solvent such as DCM or DMF at temperatures around RT (Scheme E, step c).

Compounds of structure **1t** can be prepared by reduction of compounds of structure **1q** wherein **R**⁴ represents methoxycarbonyl by treatment with a suitable reducing reagent such as CaBH₄ (formed in situ from NaBH₄ and CaCl₂) in the presence of a suitable solvent such as EtOH at temperatures between 0°C and RT (Scheme E, step d).

Compounds of structure **1q** wherein **R**² represents an acetoxy substituted phenyl or 5- or 6-membered heteroaryl can be transformed to compounds of formula **E-2** wherein **R**² represents an hydroxy substituted phenyl or 5- or 6-membered heteroaryl by hydrolysis with a suitable base such as LiOH, NaOH or KOH in the presence of water and a suitable organic solvent such as THF, MeOH or EtOH or a mixture of them at temperatures around RT (Scheme E, step e).

Compounds of structure **1af** wherein **R**² represents a (C₁₋₄)alkoxy or (C₃₋₆)cycloalkyl-**X**²¹- substituted phenyl, wherein **X**²¹ represents a -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen can be prepared by O-alkylation of compounds of structure **E-2** wherein **R**² represents an hydroxy substituted phenyl with halogenide of formula **R**^{2a}-**X** wherein **X** represents chlorine or bromine and **R**^{2a} represents (C₁₋₄)alkyl, (C₃₋₆)cycloalkyl or (C₃₋₆)cycloalkyl-(C₁₋₃)alkylene-, in the presence of a suitable base such as NaH or K₂CO₃ and in solvents such as THF, DMF or a mixture of both at temperatures between 0°C and 100°C (Scheme E, step f).

Scheme E



Compounds of structure **laa**, **lab**, **lac**, **lad**, **lah**, **lai** and **laj** can be prepared according to the synthetic route given in scheme F below.

Compounds of structure **lah** wherein R^1 represents a hydroxy substituted phenyl or 5- or 6-membered heteroaryl can be prepared by hydrolysis of the acetyl protecting group (respectively by cleavage of the benzyl protecting group) on compounds of formula **lc** wherein R^1 represents a suitable acetoxy (respectively benzyloxy) substituted phenyl or 5- or 6-membered heteroaryl with a suitable base such as LiOH, NaOH or KOH in the presence of water and a suitable organic solvent such as THF, MeOH or EtOH or a mixture of them (respectively by catalytic hydrogenation using a suitable catalyst such as palladium hydroxide on carbon under a hydrogen atmosphere in the presence of a suitable solvent such as EtOAc) at temperatures around RT (Scheme F, step a).

Alkylation of the free hydroxyl group in compounds of structure **lah** wherein R^1 represents a hydroxy substituted phenyl or 5- or 6-membered heteroaryl with a suitable halide of structure $R^{15}-X$ wherein X represents bromine or chlorine and R^{15} represents (C_1-C_4) -alkyl, hydroxy- (C_{2-3}) -alkyl, (C_{1-4}) -alkoxy- (C_{2-3}) -alkyl, (C_{3-6}) -cycloalkyl, or (C_{3-6}) -cycloalkyl- (C_{1-3}) -alkyl in the presence of a suitable base such as NaH or K_2CO_3 and in solvents such as THF, DMF or a mixture of both at temperatures between $0^\circ C$ and $80^\circ C$ may afford compounds of structure **lai** wherein R^1 represents a (C_{1-4}) -alkoxy, hydroxy- (C_{2-3}) -alkoxy, or (C_{3-6}) -cycloalkyl- X^{12} -substituted phenyl or 5- or 6-membered heteroaryl, wherein X^{12} represents a $-O-$, or $-(C_{1-3})$ -alkylene- $O-$, and wherein the (C_{3-6}) -cycloalkyl independently contains one optional ring oxygen (Scheme F, step b). Alternatively, alkylation of the free hydroxyl group in compounds of structure **lah** wherein R^1 represents a hydroxy substituted phenyl or 5- or 6-membered heteroaryl

can be achieved using Mitsunobu conditions by treatment with a suitable alcohol of structure **R¹⁵-OH** wherein **R¹⁵** represents (C₁₋₄)-alkyl, hydroxy-(C₂₋₃)-alkyl, (C₁₋₄)-alkoxy-(C₂₋₃)-alkyl, (C₃₋₆)-cycloalkyl, or (C₃₋₆)-cycloalkyl-(C₁₋₃)-alkyl and for instance a (cyanomethylene)trialkyl phosphorane reagent in the presence of a suitable solvent such as toluene at temperatures around 110°C (Scheme F, step b). A possible protective group on the substituent **R¹⁵** can be consecutively cleaved by standard deprotection conditions to provide compounds of structure **1aj**. Treatment for instance by TBAF in THF at temperatures around RT can lead to deprotection of TBDMS protected alcohol.

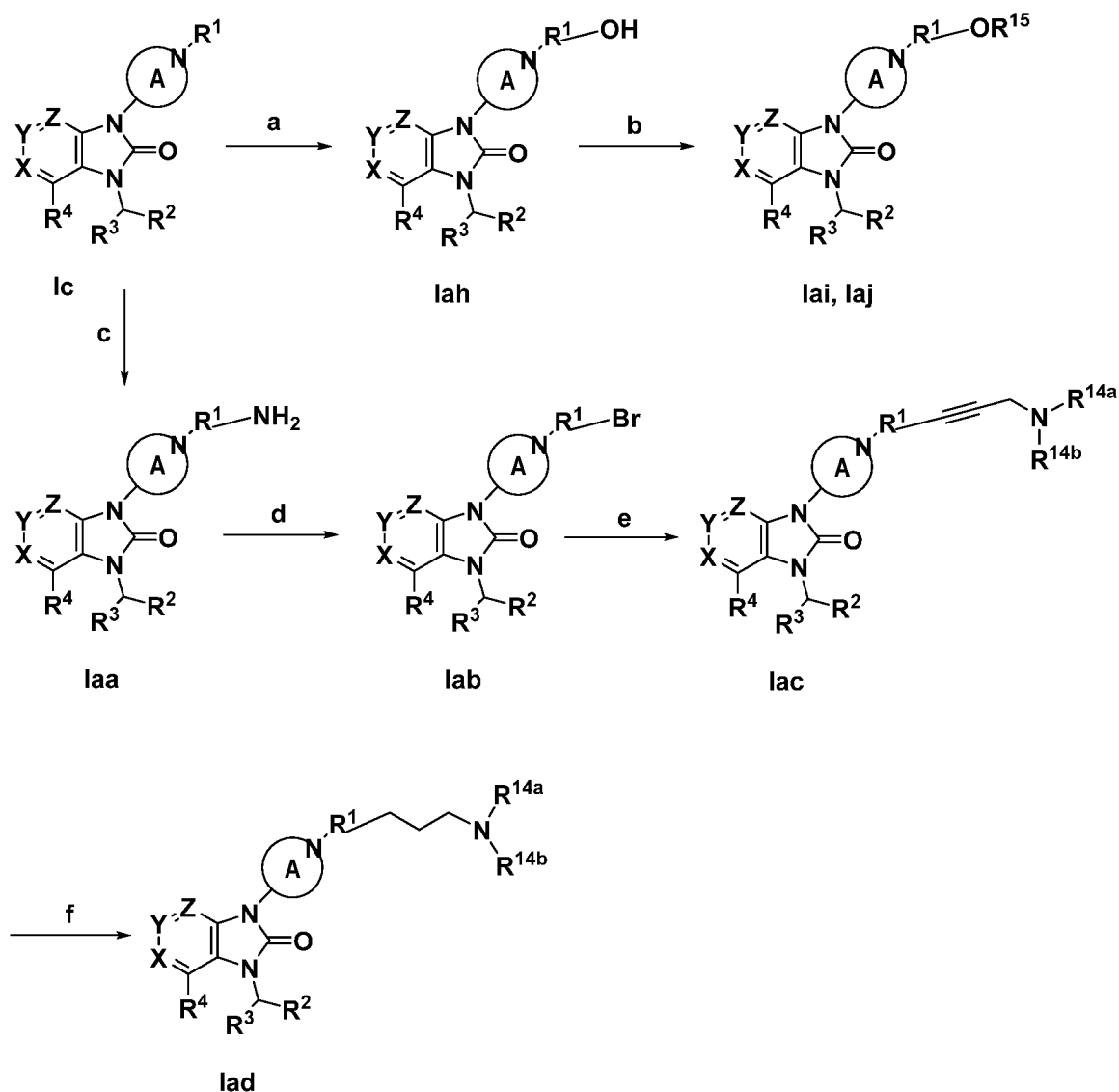
Compounds of structure **1aa** wherein **R¹** represents an amino substituted phenyl can be prepared by reduction of compounds of formula **1c** wherein **R¹** represents a nitro substituted phenyl by catalytic hydrogenation for instance using a suitable catalyst such as Pd/C under a hydrogen atmosphere in the presence of a suitable solvent such as EtOAc at temperatures around RT (Scheme F, step c).

Compounds of structure **1ab** wherein **R¹** represents a bromine substituted phenyl can be prepared by a Sandmeyer type rxn of compounds of formula **1aa** wherein **R¹** represents an amino substituted phenyl using standard conditions such as treatment with NaNO₂ in aq. HBr at temperatures around -20°C and consecutive treatment with CuBr at temperatures around 60°C (Scheme F, step d).

Compounds of structure **1ac** wherein **R¹** represents a **R^{14a}R^{14b}N-X¹⁴**-substituted phenyl wherein **X¹⁴** represents 1,3-prop-1-ynylene; and wherein **R^{14a}** and **R^{14b}** independently represent (C₁₋₄)-alkyl, (C₁₋₃)-alkoxy-(C₂₋₄)-alkyl; or **R^{14a}** and **R^{14b}** together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)-alkyl (especially methyl), (C₁₋₄)-alkoxy (especially methoxy), or dimethylamino can be prepared by Sonogashira type cross-coupling of bromides of formula **1ab** wherein **R¹** represents a bromine substituted phenyl with **R^{14a}R^{14b}N-CH₂-C≡CH** wherein **R^{14a}** and **R^{14b}** are defined above, in the presence of a suitable palladium catalyst such as bis(tri-tert-butylphosphine)palladium(0), in the presence of a suitable copper catalyst such as copper iodide, in the presence of a suitable base such as DBU and heating in a suitable solvent such as THF at temperatures around 70°C (Scheme F, step e).

Compounds of structure **1ad** wherein **R¹** represents a **R^{14a}R^{14b}N-X¹⁴**-substituted phenyl wherein **X¹⁴** represents 1,3-propylene; and wherein **R^{14a}** and **R^{14b}** independently represent (C₁₋₄)-alkyl, (C₁₋₃)-alkoxy-(C₂₋₄)-alkyl; or **R^{14a}** and **R^{14b}** together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)-alkyl (especially methyl), (C₁₋₄)-alkoxy (especially methoxy), or dimethylamino can be prepared by reduction of the acetylenic group in compounds of formula **1ac** wherein **R¹** represents a **R^{14a}R^{14b}N-X¹⁴**-substituted phenyl wherein **X¹⁴** represents 1,3-prop-1-ynylene; and wherein **R^{14a}** and **R^{14b}** are defined above using standard conditions such as catalytic hydrogenation with a suitable catalyst such as Pd/C and in the presence of a suitable solvent such as EtOAc and under a hydrogen atmosphere (Scheme F, step f).

Scheme F



If not commercially available, amines of structure **BB-4** can be prepared according to the synthetic route given in scheme G below.

- 5 Compounds of structure **G-2** wherein R^1 represents an unsubstituted, mono-, di- or tri-substituted phenyl or 5- or 6-membered heteroaryl can be prepared by Buchwald-Hartwig cross coupling of halides of structure **R¹-X** wherein **X** represents iodine, bromine or chloride and R^1 represents an unsubstituted, mono-, di- or tri-substituted phenyl or 5- or 6-membered heteroaryl with an amine of structure **G-1** in the presence of a suitable palladium catalyst such as $Pd_2(dba)_3$ and a ligand such as BINAP, in the presence of a suitable base such as sodium tert-butoxide and heating in a suitable solvent such as toluene at temperatures between 100°C and 110°C (Scheme G, step a).
- 10

Alternatively, compounds of structure **G-2** wherein R^1 represents an unsubstituted, mono-, di- or tri-substituted phenyl or 5- or 6-membered heteroaryl can be prepared by aromatic nucleophilic substitution of amines of structure **G-1** on activated halides of structure **R¹-X** wherein **X** represents fluorine or chlorine and R^1 represents a suitable

mono-, di- or tri-substituted phenyl or 5- or 6- membered heteroaryl in the presence of a suitable base such as K_2CO_3 and heating in a suitable solvent such as DMSO at temperatures between 60°C and 110°C (Scheme G, step a).

5 Cleavage of the ketal protecting group in compounds of structure **G-2** by acidic hydrolysis in the presence of a suitable acid such as aq. HCl and heating in a suitable solvent such as THF at temperatures around 70°C may afford ketones of structure **G-3** (Scheme G, step b).

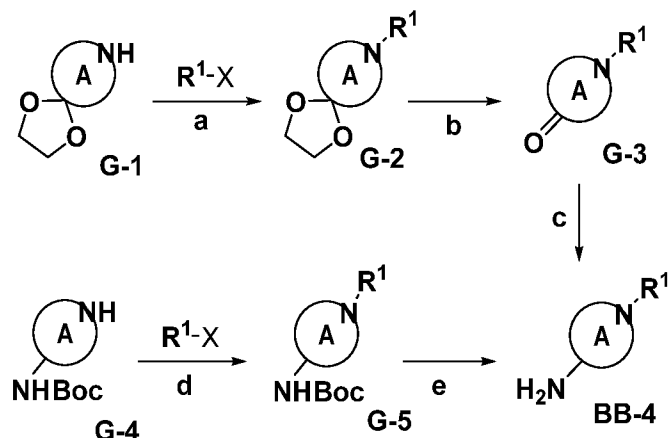
Transformation of ketones of structure **G-3** to amines of structure **BB-4** can be achieved by reductive amination with for instance aq. ammonia under catalytic hydrogenation conditions using a suitable catalyst such as Pd/C in the presence of a suitable solvent such as dioxane under a hydrogen atmosphere at temperatures around RT
10 (Scheme G, step c).

Compounds of structure **G-5** wherein **R¹** represents an unsubstituted, mono-, di- or tri-substituted phenyl or 5- or 6- membered heteroaryl can be prepared by aromatic nucleophilic substitution of amines of structure **G-4** on activated halides of structure **R¹-X** wherein **X** represents fluorine or chlorine and **R¹** represents a suitable mono-, di- or tri-substituted phenyl or 5- or 6- membered heteroaryl in the presence of a suitable base such as K_2CO_3 and heating
15 in a suitable solvent such as DMSO at temperatures between 60°C and 110°C (Scheme G, step d).

Compounds of structure **G-5** wherein **R¹** represents a mono-, di- or tri-substituted phenyl which is substituted by one methyl group can be prepared following a four-step procedure: (i) aromatic nucleophilic substitution of amines of structure **G-4** on halides of structure **R¹-X** wherein **X** represents fluorine or chlorine and **R¹** represents a suitable mono-, di- or tri-substituted phenyl which is substituted by one formyl group in the presence of a suitable base such as K_2CO_3 and heating in a suitable solvent such as DMSO at temperatures between 60°C and 110°C and (ii)
20 consecutive reduction of the benzaldehyde derivative by treatment with a suitable reducing reagent such as $NaBH_4$ in the presence of a suitable solvent such as MeOH at temperatures between 0°C and RT and (iii) consecutive acetylation of the resulting benzyl alcohol by treatment with acetyl chloride in the presence of a suitable base such as TEA and in a suitable solvent such as DCM at temperatures between 0°C and RT and (iv) final catalytic
25 hydrogenation of the resulting benzyl ester with a suitable catalyst such as Pd/C in the presence of a suitable solvent such as EtOAc, MeOH or mixture thereof and under a hydrogen atmosphere at temperatures around RT (Scheme G, step d).

Cleavage of the Boc protecting group in compounds of structure **G-5** can be performed using a suitable acid such as HCl or TFA in the presence of a suitable solvent such as dioxane, MeOH or DCM at temperatures around RT to
30 afford amines of structure **BB-4** (Scheme G, step e).

Scheme G



Experimental Part

5 Chemistry

All temperatures are stated in °C. Commercially available starting materials were used as received without further purification. If not explicitly indicated as having a specific absolute configuration, example compounds or intermediates that are chiral are in general prepared as a racemic mixture of two enantiomers, even if the corresponding example compound's name or precursor's name is not preceded with the mention rac. Relative configuration is indicated for example as (R^*, R^*) meaning that the two respective absolute configurations are either (R, R) or (S, S); likewise, (R^*, S^*) indicates a relative configuration of either (R, S) or (S, R).

Characterization of compounds

Compounds described in the invention are characterized by LC-MS data (retention time t_R is given in min) and/or NMR using the conditions described below.

15 Analytical LC-MS:

Dionex Ultimate 3000 system with Dionex HPG-3200RS binary pump, Thermo MSQ Plus MS detector and Dionex DAD-3000RS PDA detector.

Eluents (acidic conditions): A: H_2O + 0.04% TFA; B: MeCN; gradient: 5% B $\rightarrow$ 95% B; runtime: 1.5 min ; flow: 4.5 mL/min ; detection: UV/Vis + MS

20 Column Agilent Zorbax SB-aq, 4.6 x 50 mm, 3.5 μm

NMR spectroscopy:

Bruker Avance HD spectrometer equipped with a 500MHz Ultrashield™ Magnet and a 5 mm DCH cryoprobe or Bruker Avance II spectrometer equipped with a 400 MHz Ultrashield™ Magnet and a BBO 5mm probehead.

Chemical shifts (δ) are reported in parts per million (ppm) relative to proton resonances resulting from incomplete deuteration of the NMR solvent, e.g. for dimethylsulfoxide $\delta(H)$ 2.49 ppm, for chloroform $\delta(H)$ 7.24 ppm. The

abbreviations *s*, *d*, *t*, *q* and *m* refer to singlet, doublet, triplet, quartet, multiplet, respectively and *br* to broad. Coupling constants *J* are reported in Hz.

Purification of compounds

The compounds were purified by either column chromatography on silica-gel and/or prep. LC-MS using the conditions described below.

Column chromatography

Column chromatography (CC) was performed using prepacked cartridges (SNAP Ultra™, SNAP KP-SIL™, SNAP KP-NH™, Isolute™ Silica II or Isolute™ NH₂) from Biotage.

Preparative LC-MS:

10 Gilson 333/334 Prep-Scale HPLC pump equipped with Gilson LH215 autosampler, Dionex SRD-3200 degasser, Dionex ISO-3100A make-up pump, Dionex DAD-3000 DAD detector and Thermo MSQ Plus Single Quadrupole MS detector. Flow: 75 mL/min. Detection: UV/Vis and/or MS.

Additional informations for the purification are summarized in the table below using following explanations:

XBridge: column Waters XBridge C18, 10μm, 30x75 mm

15 Acidic: eluant: A = H₂O with 0.5% HCOOH, B = MeCN

Basic: eluant: A = H₂O with 0.125% NH₄OH, B = MeCN

Very lipophilic gradient: 50% B → 95% B over 4 min then 95%B over 2 min

Lipophilic gradient: 30% B → 95% B over 4 min then 95%B over 2 min

Normal gradient: 20% B → 95% B over 4 min then 95%B over 2 min

20 Polar gradient: 10% B → 95% B over 4 min then 95%B over 2 min

Very polar gradient: 5% B → 50% B over 3 min then 50% B → 95% B over 1 min and finally 95%B over 2 min

	XBridge	
	acidic	basic
Very lipophilic gradient	Method 1	Method 5
Lipophilic gradient	Method 2	Method 6
Normal gradient	Method 3	
Polar gradient	Method 4	

Abbreviations (as used hereinbefore or hereinafter):

Ac acetyl
 25 AcOH acetic acid
 AIBN azobisisobutyronitrile

	anh.	anhydrous
	aq.	aqueous
	BINAP	racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
	Boc	<i>tert.</i> -butyloxycarbonyl
5	BrettPhos	2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
	BrettPhos precatalyst	chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2'-4'-6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II)
	CC	column chromatography
	CDI	carbonyl diimidazole
10	CPhos	2-dicyclohexylphosphino-2',6'-bis(N,N-dimethylamino)biphenyl
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
	DCM	dichloromethane
	dioxane	1,4-dioxane
	DIPEA	diisopropyl-ethylamine, Hünig's base, ethyl-diisopropylamine
15	DMA	dimethylacetamide
	DMF	dimethylformamide
	DMP	Dess Martin periodinane
	DMSO	dimethylsulfoxide
	eq	equivalent(s)
20	EtOAc	ethyl acetate
	EtOH	ethanol
	Et ₂ O	diethylether
	g	gram(s)
	h	hour(s)
25	HATU	2-(7-aza-1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
	Hept	heptane
	HPLC	high performance liquid chromatography
	LC-MS	liquid chromatography – mass spectrometry
	MeCN	acetonitrile
30	Mel	methyl iodide
	MeOH	methanol
	mg	milligram(s)
	mL	milliliter(s)
	min	minute(s)
35	mmol	millimole(s)
	MS	mass spectroscopy

	NaBH(OAc) ₃	sodium triacetoxyborohydride
	NaOMe	sodium methoxide
	NBS	N-bromosuccinimide
	<i>n</i> -BuOH	<i>n</i> -butanol
5	NCS	N-chlorosuccinimide
	NMR	nuclear magnetic resonance spectroscopy
	OAc	acetate
	org.	organic
	ON	overnight
10	PBS	phosphate buffer saline
	PEPPSI-IPr	[1,3-bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
	prep.	preparative
	rac	racemic
15	RT	room temperature
	RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
	RuPhos precatalyst	chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)
	rxn	reaction
20	sat.	saturated
	SEM	[2-(trimethylsilyl)ethoxy]methyl
	soln.	solution
	TBAF	tetrabutylammonium fluoride
	TBDMS	<i>tert</i> -butyldimethylsilyl
25	<i>t</i> -BuOH	<i>tert</i> -butanol
	TEA	triethylamine
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	<i>t</i> _R	retention time

30

Synthesis of building blocks BB-2**Synthesis of 4-chloro-2-methoxy-3-nitropyridine (BB-2-1)**

To a suspension of 4-chloro-3-nitro-2-pyridone (1.0 g, 5.7 mmol) and silver carbonate (1.9 g, 6.9 mmol) in hexane (17 mL) was added MeI (0.72 mL, 11.5 mmol). The rxn mixture was heated to 80°C for 1h and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc to give the title compound as white solid.

35

LC-MS: *t*_R=0.82 min

¹H NMR (400 MHz, DMSO-d₆) δ: 8.41 (d, *J* = 5.6 Hz, 1 H), 7.50 (d, *J* = 5.6 Hz, 1 H), 4.02 (s, 3 H)

Synthesis of 4-chloro-1-methyl-3-nitro-1H-pyridin-2-one (BB-2-2)

To a suspension of 4-chloro-3-nitro-2-pyridone (1.0 g, 5.7 mmol) and K₂CO₃ (1.6 g, 11.5 mmol) in DMA (5 mL) was added MeI (0.72 mL, 11.5 mmol). The rxn mixture was heated to 45°C and stirred for 1h. It was quenched with H₂O, acidified to pH 5 with a 25% aq. soln. of HCl and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo.

LC-MS: *t_R*=0.60 min ; [M+H]⁺: 189.15

¹H NMR (400 MHz, DMSO-d₆) δ: 8.10 (d, *J* = 7.4 Hz, 1 H), 6.70 (d, *J* = 7.4 Hz, 1 H), 3.55 (s, 3 H)

Synthesis of 4-chloro-6-methoxy-5-nitro-pyrimidine (BB-2-3)

A suspension of 4,6-dichloro-5-nitropyrimidine (2.0 g, 10.2 mmol) in anh. MeOH (37 mL) was cooled to 0°C and NaOMe (579 mg, 10.2 mmol) was portionwise added over 10 min. The rxn mixture was stirred for 30 min and filtered. The filtrate was concentrated in vacuo and the crude was purified by CC using Hept/EtOAc.

LC-MS: *t_R*=0.75 min

¹H NMR (400 MHz, DMSO-d₆) δ: 8.93 (s, 1 H), 4.14 (s, 3 H)

15 Synthesis of building blocks BB-3

Synthesis of 3-bromomethyl-2-trifluoromethyl-pyridine (BB-3-1) and 2-bromomethyl-3-trifluoromethyl-pyrazine (BB-3-5)

A suspension of methyl-heteroarene (1 eq) in chlorobenzene (4 mL/mmol) was heated to 50°C and NBS (1.3 eq) was dropwise added at 50°C. The flask was purged with argon and AIBN (0.1 eq) was added in one portion. The rxn mixture was heated to 80°C and stirred for 5h (see Table 1). After cooling to RT, the mixture was diluted with Et₂O and washed with a 1M aq. soln. of HCl (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 1

BB-3	Name	Methyl-heteroarene	<i>t_R</i> [min]	¹ H NMR (400 MHz, DMSO-d ₆) δ:
BB-3-1	3-Bromomethyl-2-trifluoromethyl-pyridine	3-Methyl-2-(trifluoromethyl) pyridine	0.80	8.72 (d, <i>J</i> = 4.6 Hz, 1 H), 8.23 (d, <i>J</i> = 7.8 Hz, 1 H), 7.79 (dd, <i>J</i> ₁ = 4.6 Hz, <i>J</i> ₂ = 7.9 Hz, 1 H), 4.84 (d, <i>J</i> = 0.7 Hz, 2 H)
BB-3-5	2-Bromomethyl-3-trifluoromethyl-pyrazine	2-Methyl-3-(trifluoromethyl) pyrazine	0.76	9.03 (d, <i>J</i> = 2.2 Hz, 1 H), 8.84 (d, <i>J</i> = 2.3 Hz, 1 H), 4.84 (d, <i>J</i> = 0.9 Hz, 2 H)

Synthesis of 3-chloromethyl-4-trifluoromethyl-pyridine (BB-3-2)

To a soln. of 4-trifluoromethyl-pyridin-3-yl-methanol (419 mg, 2.3 mmol) in DCM (7 mL) was added SOCl₂ (0.84 mL, 11.6 mmol). The rxn mixture was stirred for 1h at RT, quenched with a 10% aq. soln. of Na₂CO₃ and extracted with DCM (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

LC-MS: t_R=0.79 min, [M+MeCN+H]⁺: 237.05

¹H NMR (400 MHz, DMSO-d₆) δ: 9.00 (s, 1 H), 8.86 (dd, J₁ = 0.5 Hz, J₂ = 5.1 Hz, 1 H), 7.81 (d, J = 5.1 Hz, 1 H), 4.95 (s, 2 H)

Synthesis of 4-bromomethyl-3-trifluoromethyl-pyridine (BB-3-3) and 2-bromomethyl-3-trifluoromethyl-pyridine (BB-3-4)

The appropriate methylpyridine (1 eq) was dissolved in a 1M soln. of bromine in acetic acid (1 mL/mmol) and the solution was stirred ON at RT and for 6h at 80°C (see Table 2). The mixture was basified with a 1M aq. soln. of NaOH and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude dibromo product was dissolved in THF (4 mL/mmol) and DIPEA (1.05 eq) and diethyl phosphite (1.05 eq) were sequentially added at 0°C. The mixture was stirred for 10 min at 0°C and ON at RT. It was quenched with water and extracted with EtOAc (3x). The combined org. phases were washed with a sat. aq. soln. of NH₄Cl and brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 2

BB-3	Name	Methyl-pyridine	t _R [min]	¹ H NMR (400 MHz, DMSO-d ₆) δ:
BB-3-3	4-Bromomethyl-3-trifluoromethyl-pyridine	4-Methyl-3-(trifluoromethyl)pyridine	0.80	8.96 (s, 1 H), 8.91 (d, J = 5.1 Hz, 1 H), 7.78 (d, J = 5.1 Hz, 1 H), 4.77 (s, 2 H)
BB-3-4	2-Bromomethyl-3-trifluoromethyl-pyridine	2-Methyl-3-(trifluoromethyl)pyridine	0.79	8.88 (d, J = 4.7 Hz, 1 H), 8.24 (d, J = 8.0 Hz, 1 H), 7.63 (m, 1 H), 4.76 (s, 2 H)

Synthesis of (4-methoxy-pyrimidin-5-yl)-methanol (BB-3-6) and (4-trifluoromethyl-pyrimidin-5-yl)-methanol (BB-3-8)

To a suspension of carboxylic acid (1 eq) in anh. THF (5 mL/mmol) was added at -10°C 4-methylmorpholine (1.8 eq) and ethyl chloroformate (1.5 eq). The mixture was stirred for 30 min at -10°C and NaBH₄ (3 eq) was added in one portion. It was warmed to 0°C and MeOH (3 mL/mmol) was added dropwise (see Table 3). The rxn mixture was stirred for 1h at 0°C and for 1h at RT. It was quenched with water, acidified with a 1M aq. soln. of HCl until pH

4 and extracted with *n*-BuOH (3x). The combined org. phases were dried and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc/MeOH.

Table 3

BB-3	Name	Carboxylic acid	t _R [min]	MS-data m/z [M+H] ⁺
BB-3-6	(4-Methoxy-pyrimidin-5-yl)-methanol	4-Methoxypyrimidine-5-carboxylic acid	0.29	141.19
BB-3-8	(4-Trifluoromethyl-pyrimidin-5-yl)-methanol	4-(Trifluoromethyl)pyrimidine-5-carboxylic acid	0.47	220.08 [M+MeCN+H ⁺]

5 **Synthesis of 5-(chloromethyl)-4-methoxypyrimidine (BB-3-7) and 5-(chloromethyl)-4-(trifluoromethyl)pyrimidine (BB-3-9)**

To a soln. of alcohol (1 eq) in DCM (5 mL/mmol) was added SOCl₂ (1.5 to 2.5 eq) at 0°C. The rxn mixture was stirred for 2h at RT (see Table 4) and partitioned between EtOAc and a sat. aq. soln. of NaHCO₃. The org. phase was washed with a sat. aq. soln. of NaHCO₃ (1x) and brine (1x), dried over MgSO₄ and concentrated in vacuo.

10 **Table 4**

BB-3	Name	Alcohol	t _R [min]	MS-data m/z [M+H] ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ:
BB-3-7	5-(Chloromethyl)-4-methoxypyrimidine	(4-Methoxy-pyrimidin-5-yl)-methanol	0.61	159.25	
BB-3-9	5-(Chloromethyl)-4-(trifluoromethyl)pyrimidine	(4-Trifluoromethyl-pyrimidin-5-yl)-methanol	0.72		9.46 (s, 1 H), 9.33 (s, 1 H), 4.99 (d, J = 0.9 Hz, 2 H)

Synthesis of 6-chloro-3-chloromethyl-4-methoxy-pyridazine (BB-3-10)

Step A: 6-Chloro-4-methoxy-pyridazine-3-carboxylic acid methyl ester

To a soln. of methyl 4,6-dichloropyridazine-3-carboxylate (550 mg, 2.66 mmol) in anh. THF (13 mL) was added dropwise at 0°C a 25% soln. of NaOMe in MeOH (0.638 mL, 2.79 mmol). The rxn mixture was stirred ON at RT and poured onto a 1M aq. soln. of HCl. The soln. was neutralized with a sat. aq. soln. of NaHCO₃ and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

LC-MS: t_R=0.54 min, [M+H]⁺: 203.14

Step B: (6-Chloro-4-methoxy-pyridazin-3-yl)-methanol

To a soln. of 6-chloro-4-methoxy-pyridazine-3-carboxylic acid methyl ester (120 mg, 0.592 mmol) in anh. EtOH (4.7 mL) was added CaCl_2 (20 mg, 0.178 mmol) and the rxn mixture was cooled to -10°C . NaBH_4 (56 mg, 1.48 mmol) was added portionwise and the mixture was stirred for 1.5 h at -10°C and for 30 min at RT. It was quenched at 0°C with water and EtOH was evaporated off. The residue was partitioned between EtOAc and water and the aq. phase was further extracted with EtOAc (2x). The combined org. phases were washed with brine (1x), dried over MgSO_4 and concentrated in vacuo.

LC-MS: $t_R=0.40$ min, $[\text{M}+\text{H}]^+$: 175.20

Step C: 6-Chloro-3-chloromethyl-4-methoxy-pyridazine (BB-3-10)

To a soln. of (6-Chloro-4-methoxy-pyridazin-3-yl)-methanol (73 mg, 0.393 mmol) in DCM (1.97 mL) was added SOCl_2 (0.043 mL, 0.59 mmol) at 0°C . The rxn mixture was stirred for 2h at RT and partitioned between EtOAc and a sat. aq. soln. of NaHCO_3 . The org. phase was washed with a sat. aq. soln. of NaHCO_3 (1x) and brine (1x), dried over MgSO_4 and concentrated in vacuo.

LC-MS: $t_R=0.63$ min, $[\text{M}+\text{H}]^+$: 193.13

Synthesis of (6-chloro-4-isopropoxy-pyridazin-3-yl)-methanol (BB-3-11)*Step A: 6-Chloro-4-isopropoxy-pyridazine-3-carboxylic acid isopropyl ester*

To a soln. of 4,6-dichloropyridazine-3-carboxylic acid methyl ester (500 mg, 2.42 mmol) in anh. THF (12 mL) was added dropwise at 0°C a 2M soln. of lithium isopropoxide in THF (1.27 mL, 2.54 mmol). The rxn mixture was stirred for 30 min at 0°C and poured into a 1M aq. soln. of HCl. The aq. soln. was neutralized with a sat. aq. soln. of NaHCO_3 and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO_4 and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

LC-MS: $t_R=0.82$ min, $[\text{M}+\text{H}]^+$: 259.12

Step B: (6-Chloro-4-isopropoxy-pyridazin-3-yl)-methanol (BB-3-11)

To a soln. of 6-chloro-4-isopropoxy-pyridazine-3-carboxylic acid isopropyl ester (80 mg, 0.309 mmol) in anh. EtOH (4.6 mL) was added CaCl_2 (10 mg, 0.093 mmol) and the rxn mixture was cooled to -10°C . NaBH_4 (29 mg, 0.773 mmol) was added portionwise and the mixture was stirred for 30 min at -10°C and for 1h min at RT. It was quenched at 0°C with water and EtOH was evaporated off. The residue was partitioned between EtOAc and water and the aq. phase was further extracted with EtOAc (2x). The combined org. phases were washed with brine (1x), dried over MgSO_4 and concentrated in vacuo.

LC-MS: $t_R=0.55$ min, $[\text{M}+\text{H}]^+$: 203.14

Synthesis of (BB-3-12), (BB-3-13), (BB-3-14), (BB-3-15), (BB-3-16), (BB-3-17)*Step A: Esterification*

To a soln. of carboxylic acid (1 eq) in anh. MeOH (4 mL/mmol) was added AcCl (3 eq) and the rxn mixture was stirred for 2.5 h at 80°C (see Table 5). MeOH was evaporated off and the residue was partitioned between a sat.

aq. soln. of NaHCO₃ and EtOAc. The org. phase was washed with a 10% aq. soln. of Na₂CO₃ (1x) and with brine (1x), dried over MgSO₄ and concentrated in vacuo.

Table 5

BB-3A	Name	Carboxylic acid reactant	t _R [min]	MS-data m/z [M+H] ⁺
BB-3-12A	4-Methylpyridazine-3-carboxylic acid methyl ester	4-methylpyridazine-3-carboxylic acid	0.47	153.43
BB-3-13A	3-Isopropoxy-pyrazine-2-carboxylic acid methyl ester	3-Isopropoxy-pyrazine-2-carboxylic acid	0.70	197.17
BB-3-15A	3-Isopropoxy-pyridine-2-carboxylic acid methyl ester	3-Isopropoxy-pyridine-2-carboxylic acid	0.64	196.21

5 *Step A (Negishi): synthesis of 3-isopropyl-pyrazine-2-carboxylic acid ethyl ester (BB-3-17A)*

An oven dried flask was charged with 3-chloropyrazine-2-carboxylic acid ethyl ester (500 mg, 2.63 mmol), PEPPSI-IPr (18 mg, 0.026 mmol) and CPhos (12 mg, 0.026 mmol). The flask was evacuated and refilled with argon (3x) and toluene (5 mL) was added. The rxn mixture was cooled to 0°C and a 0.5M soln. of 2-propyl zinc bromide in THF (6.83 mL, 3.41 mmol) was added dropwise. The rxn mixture was stirred for 72h at RT and partitioned between half sat. brine and DCM. The org. phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

LC-MS: t_R=0.74 min, [M+H]⁺: 195.18

Step A (O-alkylation): synthesis of 2,4-difluoro-6-isopropoxybenzoic acid methyl ester (BB-3-19A)

To a soln. of methyl 2,4-difluoro-6-hydroxybenzoic acid methyl ester (200 mg, 1.01 mmol) and 2-propanol (0.116 mL, 1.51 mmol) in toluene (1.5 mL) was added a 1M soln. of (tributylphosphoranylidene)acetonitrile in toluene (2.02 mL, 2.02 mmol) under argon. The rxn mixture was heated to 110°C and stirred for 2h. It was quenched with water and extracted with DCM (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

LC-MS: t_R=0.89 min, [M+H]⁺: 231.10

20 *Step B: Methyl/ethyl ester reduction using CaCl₂/NaBH₄ (method A)*

To a soln. of methyl ester (BB-3A) (1 eq) in anh. EtOH (15 mL/mmol) was added CaCl₂ (0.3 eq) and the rxn mixture was cooled to -10°C. NaBH₄ (2.5 eq) was added portionwise and the mixture was stirred for 30 min at -10°C and for a given time at a given temperature (see Table 6). It was quenched at 0°C with water and EtOH was evaporated off. The residue was partitioned between EtOAc and water and the aq. phase was further extracted with EtOAc (2x). The combined org. phases were washed with brine (1x), dried over MgSO₄ and concentrated in vacuo.

Step B: Methyl/ethyl ester reduction using LiAlH₄ (method B)

To a soln. of methyl or ethyl ester (1 eq) in anh. THF (4.5 to 7 mL/mmol) was added dropwise at 0°C a 2.4 M soln. of LiAlH₄ in THF (1 eq). The rxn mixture was stirred for 1.5 h at 0°C (see Table 6), quenched with a sat. aq. soln. of NH₄Cl and extracted with EtOAc (3x). The combined org. phases were dried over MgSO₄ and concentrated in vacuo. When necessary the crude was purified by CC using EtOAc.

Table 6

BB-3	Name	Methyl/ethyl ester reactant	Method T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ:
BB-3-12	(4-Methyl-pyridazin-3-yl)-methanol	BB-3-12A	A RT 0.5	0.18	125.44	
BB-3-13	(3-Isopropoxy-pyrazin-2-yl)-methanol	BB-3-13A	A RT 0.5	0.58	169.11	
BB-3-14	(4-Isopropylpyridin-3-yl)methanol	4-Isopropyl pyridine-3-carboxylic acid ethyl ester	A RT 48	0.34	152.45	
BB-3-15	(3-Isopropoxy-pyridin-2-yl)-methanol	BB-3-15A	A RT 24	0.40	168.47	
BB-3-16	(4-Isopropyl-pyrimidin-5-yl)-methanol	4-Isopropyl pyrimidine-5-carboxylic acid ethyl ester	A 70 1	0.46	153.47	
BB-3-17	(3-Isopropyl-pyrazin-2-yl)-methanol	BB-3-17A	A 0 2.5	0.48	153.45	

BB-3-18	Mixture of (5-(trifluoromethyl)thiazol-4-yl)methanol and (2-(trifluoromethyl)thiazol-4-yl)methanol	Mixture of 5-(trifluoromethyl)thiazole-4-carboxylic acid ethyl ester and 2-(trifluoromethyl)thiazole-4-carboxylic acid ethyl ester	B 0 1.5	0.52	184.05	
BB-3-19	(2,4-Difluoro-6-isopropoxy-phenyl)-methanol	BB-3-19A	B 0 1.5	0.78	no ionisation	6.41-6.47 (m, 2 H), 4.70 (d, J = 1.5 Hz, 2 H), 4.58 (m, 1 H), 1.40-1.45 (m, 6 H)

Synthesis of building blocks BB-4 (via G-5)

Step A: Aromatic nucleophilic substitution

To a solution of the appropriate amine (1 eq) and the appropriate fluoroarene (1.1 eq) in DMSO (0.9 mL/mmol) was added K_2CO_3 (2 eq) and the mixture was heated to 105°C and stirred for 18h (see Table 7). It was quenched with water and extracted with DCM. The org. phase was washed with water (5x) and brine (1x), dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using DCM/MeOH.

Table 7

BB-4A	Name	Reactant amine	Reactant fluoroarene	t_R [min]	MS-data m/z [M+H] ⁺
BB-4-1A	[(R)-1-(2-Fluoro-6-formyl-phenyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester	(R)-(+)-3-(Boc-amino)pyrrolidine	2,3-Difluoro benzaldehyde	0.90	309.10
BB-4-2A	[1-(2-Fluoro-6-formyl-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester	4-(N-Boc-amino) piperidine	2,3-Difluoro benzaldehyde	0.93	323.20
BB-4-3A	[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester	(R)-(+)-3-(Boc-amino)pyrrolidine	2,3-Difluoro benzonitrile	0.91	306.03

Step B: Reduction

A suspension of intermediate BB-4A (1 eq) in anh. MeOH (2 mL/mmol) was cooled to 0°C and NaBH₄ (1.3- to 1.5 eq) was added portionwise at 0°C (see Table 8). The rxn mixture was stirred for 1h at 0°C to reach completion. It was carefully quenched by dropwise addition of water at 0°C and extracted with EtOAc. The org. phase was washed with water and brine, dried over MgSO₄ and concentrated in vacuo.

Table 8

BB-4B	Name	Reactant BB-4A	t _R [min]	MS-data m/z [M+H] ⁺
BB-4-1B	[(R)-1-(2-Fluoro-6-hydroxymethyl-phenyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester	BB-4-1A	0.77	311.11
BB-4-2B	[1-(2-Fluoro-6-hydroxymethyl-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester	BB-4-2A	0.82	325.24

Step C: Acetylation

A solution of intermediate BB-4B (1 eq) and TEA (1.5 eq) in DCM (0.5 mL/mmol) was cooled to 0°C and AcCl (1.5 eq) was added dropwise at 0°C (see Table 9). The rxn mixture was stirred for 1h at 0°C to reach completion. It was diluted with DCM and washed with a 10% solution of citric acid (2x), with a sat. solution of NaHCO₃ (2x) and with brine (1x). The org. phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 9

BB-4C	Name	Reactant BB-4B	t _R [min]	MS-data m/z [M+H] ⁺
BB-4-1C	Acetic acid 2-((R)-3-tert-butoxycarbonylamino-pyrrolidin-1-yl)-3-fluoro-benzyl ester	BB-4-1B	0.94	353.13
BB-4-2C	Acetic acid 2-(4-tert-butoxycarbonylamino-piperidin-1-yl)-3-fluoro-benzyl ester	BB-4-2B	0.97	367.25

Step D: Hydrogenation

Intermediate BB-4C (1 eq) was dissolved in a mixture of MeOH (6 mL/mmol) and EtOAc (2 mL/mmol) and the flask was evacuated three times and refilled with nitrogen. Wet Pd/C (0.08 eq) was added and the flask was evacuated and refilled three times with hydrogen. The suspension was stirred under a hydrogen atmosphere for 3h (see Table 10) and filtered over a pad of Celite. The cake was washed with EtOAc and MeOH and the filtrate was concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 10

BB-4D (G-5)	Name	Reactant BB-4C	t _R [min]	MS-data m/z [M+H] ⁺
BB-4-1D	[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester	BB-4-1C	0.91	295.14
BB-4-2D	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester	BB-4-2C	1.00	309.16

Final step: Boc cleavage

To a solution of intermediate BB-4D or BB-4A (1 eq) in DCM (4 mL/mmol) was added dropwise TFA (1 mL/mmol) and the rxn mixture was stirred for 1h to 18h at RT (see Table 11). It was basified with a 1M solution of NaOH until pH 12-13 and extracted with DCM (3x). The combined org. phases were dried over MgSO₄ and concentrated in vacuo.

Table 11

BB-4	Name	Reactant BB-4D (G-5) or BB-4A	t _R [min]	MS-data m/z [M+H] ⁺
BB-4-1	(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-ylamine	BB-4-1D	0.57	195.29
BB-4-2	1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-ylamine	BB-4-2D	0.60	209.28
BB-4-3	2-((R)-3-Amino-pyrrolidin-1-yl)-3-fluoro-benzonitrile	BB-4-3A	0.49	205.89

Synthesis of building blocks BB-4 (via G-2 and G-3)10 *Step A: Buchwald Hartwig*

To a mixture of the appropriate amine G-1 (1 eq), the appropriate halide (1.2 eq) and sodium tert-butoxide (2 eq) in toluene (3 mL/mmol) under N₂, was added BINAP (0.2 eq) and Pd₂(dba)₃ (0.1 eq) (see Table 12). The rxn mixture was flushed with N₂, heated to 100°C in a sealed vial and stirred for 24h. It was partitioned between water and EtOAc and the org. phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

15

Table 12

G-2	Name	Reactant amine (G-1)	Reactant halide	t _R [min]	MS-data m/z [M+H] ⁺
G-2-1	8-(2,6-Dimethyl-phenyl)-1,4-dioxo- 8-aza-spiro[4.5]decane	1,4-Dioxo-8- azaspiro[4.5] decane	2-Bromo-1,3- dimethylbenzene	0.92	248.24

Step B: Ketal cleavage

To a soln. of ketal intermediate G-2 (1 eq) in anh. THF (3 mL/mmol) was added a 1M aq. soln. of HCl (2 mL/mmol) at RT (see Table 13). The rxn mixture was heated to 70°C and stirred for 24h. It was quenched with a sat. aq. soln. of NaHCO₃ and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 13

G-3	Name	Reactant G-2	t _R [min]	MS-data m/z [M+H] ⁺
G-3-1	1-(2,6-Dimethyl-phenyl)- piperidin-4-one	G-2-1	0.88	204.22

Final step: Reductive amination

To a soln. of ketone intermediate G-3 (1 eq) in dioxane (9.1 mL/mmol) was added a 25% aq. soln. of NH₄OH (38 eq) and H₂O (0.35 mL/mmol). The flask was evacuated three times and refilled with nitrogen. Wet Pd/C (0.06 eq) was added and the flask was evacuated and refilled three times with hydrogen. The suspension was stirred under a hydrogen atmosphere for 24h (see Table 14) and filtered over a pad of Celite. The cake was washed with dioxane and MeOH and the filtrate was concentrated in vacuo. The crude was purified by CC using DCM/MeOH.

Table 14

BB-4	Name	Reactant G-3	t _R [min]	MS-data m/z [M+H] ⁺
BB-4-4	1-(2,6-Dimethyl-phenyl)- piperidin-4-ylamine	G-3-1	0.63	205.33

Synthesis of building block BB-8

Synthesis of carbonic acid 3-methyl-oxetan-3-yl ester pentafluorophenyl ester (BB-8-1), carbonic acid oxetan-3-yl ester pentafluorophenyl ester (BB-8-2) and carbonic acid pentafluorophenyl ester 3-trifluoromethyl-oxetan-3-yl ester (BB-8-3)

- 5 A soln. of the appropriate alcohol (1 eq) and bis(pentafluorophenyl)carbonate (1.2 eq) in MeCN (0.55 mL/mmol) was cooled to 0°C and Et₃N (3.2 eq) was added dropwise. The rxn mixture was stirred ON allowing the temperature to reach RT (see Table 15). The mixture was concentrated in vacuo and the residue was purified by CC using DCM/MeOH.

Table 15

BB-8	Name	Reactant alcohol	t _R [min]	¹ H NMR (400 MHz, DMSO-d ₆) δ:
BB-8-1	Carbonic acid 3-methyl-oxetan-3-yl ester pentafluorophenyl ester	3-Methyl oxetan-3-ol	0.90	4.77 (d, <i>J</i> = 7.7 Hz, 2 H), 4.54 (d, <i>J</i> = 8.2 Hz, 2 H), 1.76 (s, 3 H)
BB-8-2	Carbonic acid oxetan-3-yl ester pentafluorophenyl ester	3-Hydroxy oxetane	0.86	5.65 (m, 1 H), 4.87 (m, 2 H), 4.65 (ddd, <i>J</i> ₁ = 0.9 Hz, <i>J</i> ₂ = 4.7 Hz, <i>J</i> ₃ = 8.1 Hz, 2 H)

10

The carbonic acid pentafluorophenyl ester 3-trifluoromethyl-oxetan-3-yl ester (BB-8-3) was prepared according to Med. Chem. Commun., 2013, 4, 95.

Synthesis of 4-(2-bromo-3-fluoro-phenyl)-morpholine (BB-8-4)

- 15 To a soln. of 2-fluoro-6-morpholinoaniline (100 mg, 0.51 mmol) in anh. MeCN was added tert-butyl nitrite (0.121 mL, 1.02 mmol) and copper (II) bromide (137 mg, 0.612 mmol). The rxn mixture was stirred for 30 min at RT and partitioned between water and EtOAc. The aq. phase was washed with EtOAc (2x) and the combined org. phases were washed with brine (1x), dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc and additionally by prep. LC-MS using method 2.

LC-MS: t_R=0.97 min, [M+H]⁺: 260.05

20 **Synthesis of 5-isopropyl-3H-[1,3,4]oxadiazol-2-one (BB-8-5)**

CDI (1228 mg, 7.34 mmol) was added to a soln. of isobutyric acid hydrazide (500 mg, 4.9 mmol) in anh. dioxane (21 mL) and the rxn mixture was heated at 85°C and stirred ON. Dioxane was evaporated off and the residue was partitioned between water and EtOAc. The org. phase was washed with brine (1x), dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

LC-MS: t_R =0.49 min, $[M+MeCN+H]^+$: 170.27

^1H NMR (400 MHz, DMSO- d_6) δ : 12.05 (m, 1 H), 2.86 (m, 1 H), 1.19 (d, J = 6.9 Hz, 6 H)

Synthesis of 3-chloro-4-methoxy-2-methyl-pyridine (BB-8-6)

To a soln. of 3,4-dichloro-2-methylpyridine (228 mg, 1.3 mmol) in MeOH (6.7 mL) was added a 25% soln. of NaOMe in MeOH (3.5 mL, 15.3 mmol) and the soln. was heated to 65°C for 18h. It was partitioned between DCM and water and the org. phase was washed with brine (1x), dried over $MgSO_4$ and concentrated in vacuo to give the title compound as white solid.

LC-MS: t_R =0.38 min, $[M+H]^+$: 158.43

^1H NMR (500 MHz, DMSO) δ : 8.28 (d, J = 5.6 Hz, 1 H), 7.07 (d, J = 5.7 Hz, 1 H), 3.92 (s, 3 H), 2.51 (s, 3 H)

10 Synthesis of (3-bromo-5-methoxy-pyridin-4-yl)-carbamic acid methyl ester (BB-10-1)

Step A (bromination): 3-bromo-5-methoxypyridin-4-amine

To a soln. of 4-amino-3-methoxypyridine (905 mg, 7 mmol) in MeCN (20 mL) was added N-bromosuccinimide (1384 mg, 7.7 mmol) and the soln. was stirred for 1h at RT. It was quenched with a sat. aq. soln. of $Na_2S_2O_3$ and extracted with EtOAc. The org. phase was washed with a sat. aq. soln. of $NaHCO_3$ (5x) and brine (1x), dried over $MgSO_4$ and concentrated in vacuo to give the title compound as brown oil.

LC-MS: t_R =0.38 min, $[M+H]^+$: 203.17

^1H NMR (500 MHz, DMSO) δ : 7.98 (s, 1 H), 7.89 (s, 1 H), 5.87 (s, 2 H), 3.86 (s, 4 H)

Step B (carbamate formation): (3-bromo-5-methoxy-pyridin-4-yl)-carbamic acid methyl ester (BB-10-1)

To a soln. of 3-bromo-5-methoxy-pyridin-4-ylamine (1140 mg, 5.61 mmol) and 2,6-lutidine (1.33 mL, 11.20 mmol) in DCM (40 mL) was added dropwise a soln. of methyl chloroformate (0.482 mL, 6.18 mmol) in DCM (5 mL) at 0°C. The rxn mixture was allowed to warm to RT and stirred for 18h. Additional amount of 2,6-lutidine (2.67 mL, 22.5 mmol) and methylchloroformate (0.876 mL, 11.2 mmol) was added at 0°C and the rxn mixture stirred for 1h at RT. It was quenched with a sat. aq. soln. of $NaHCO_3$ and extracted with DCM (2x). The combined org. phases were dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

25 LC-MS: t_R =0.62 min, $[M+H]^+$: 261.14

^1H NMR (400 MHz, DMSO) δ : 9.23 (s, 1 H), 8.40 (s, 1 H), 8.39 (s, 1 H), 3.91 (s, 3 H), 3.63 (s, 3 H)

Synthesis of intermediates of formula A-1

To a soln. of 1-fluoro/chloro-2-nitro-(hetero)arene (BB-2, 1 eq) and Boc-protected diamine (BB-1, 1 to 1.2 eq) in DMSO (1.5 mL/mmol) was added DIPEA (2 eq) and the soln. was heated at a given temperature for a given time (see Table 16). The rxn mixture was partitioned between EtOAc and water. The org. phase was washed with water (4x) and with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc and/or DCM/MeOH.

Table 16

A-1	Name	Reactant BB-2	Reactant BB-1	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
A-1-1	4-(3-Methoxy-2-nitro-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester	3-Fluoro-2-nitroanisole	1-N-Boc-4-aminopiperidine	100 24	0.96	352.16
A-1-2	(R)-3-(3-Methoxy-2-nitro-phenylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester	3-Fluoro-2-nitroanisole	(R)-(+)-1-Boc-3-aminopyrrolidine	100 24	0.92	338.74
A-1-3	(R)-3-(2-Methoxy-3-nitro-pyridin-4-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester	BB-2-1	(R)-(+)-1-Boc-3-aminopyrrolidine	80 24	0.88	339.11
A-1-4	(R)-3-(4-Methoxy-3-nitro-pyridin-2-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester	2-Chloro-4-methoxy-3-nitro-pyridine	(R)-(+)-1-Boc-3-aminopyrrolidine	85 24	0.87	339.13
A-1-5	4-(3-Methoxy-2-nitro-phenylamino)-2-methyl-piperidine-1-carboxylic acid tert-butyl ester	3-Fluoro-2-nitroanisole	1-N-Boc-4-amino-2-methyl-piperidine	100 24	0.98	366.22
A-1-6	4-(3-Methoxy-2-nitro-phenylamino)-3-methyl-piperidine-1-carboxylic acid tert-butyl ester	3-Fluoro-2-nitroanisole	1-N-Boc-4-amino-3-methyl-piperidine	100 24	0.98	366.39
A-1-7	4-(3-Methoxy-2-nitro-phenylamino)-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester	3-Fluoro-2-nitroanisole	1-N-Boc-4-aminopiperidine-3-carboxylic acid ethyl ester	90 24	0.97	424.14
A-1-8	4-(3-Methyl-2-nitro-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester	3-Fluoro-2-nitrotoluene	1-N-Boc-4-aminopiperidine	100 18	1.14	336.32

Synthesis of intermediates of formula A-2

To a soln. of intermediate A-1 (1 eq) in EtOAc (3 to 3.3 mL/mmol) was added 10% Pd/C moistened with ~50% water (0.01 to 0.05 eq) and the rxn mixture was hydrogenated under atmospheric pressure for a given time (see Table 17). It was filtered over a pad of celite and the filtrate was concentrated in vacuo. The crude was purified by

5 CC using Hept/EtOAc or DCM/MeOH.

Table 17

A-2	Name	Reactant A-1	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
A-2-1	4-(2-Amino-3-methoxy-phenylamino)- piperidine-1-carboxylic acid tert-butyl ester	A-1-1	24	0.68	322.00
A-2-2	(R)-3-(2-Amino-3-methoxy- phenylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester	A-1-2	10	0.67	308.13
A-2-3	(R)-3-(3-Amino-2-methoxy-pyridin-4- ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester	A-1-3	4,5	0.59	309.11
A-2-4	(R)-3-(3-Amino-4-methoxy-pyridin-2- ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester	A-1-4	3	0.58	309.18
A-2-5	4-(2-Amino-3-methoxy-phenylamino)- 2-methyl-piperidine-1-carboxylic acid tert-butyl ester	A-1-5	3.5	0.71	336.32
A-2-6	4-(2-Amino-3-methoxy-phenylamino)- 3-methyl-piperidine-1-carboxylic acid tert-butyl ester	A-1-6	1	0.72/0.73	336.23
A-2-7	4-(2-Amino-3-methoxy-phenylamino)- piperidine-1,3-dicarboxylic acid 1-tert- butyl ester 3-ethyl ester	A-1-7	1	0.76	394.09
A-2-8	4-(2-Amino-3-methyl-phenylamino)- piperidine-1-carboxylic acid tert-butyl ester	A-1-8	18	0.76	306.26

Synthesis of intermediates of formula A-3

To a soln. of intermediate A-2 (1 eq) in MeCN (3.7 mL/mmol) was added CDI (1.2 eq) and the rxn mixture was stirred at a given temperature for a given time (see Table 18). The solvent was evaporated off and the residue was partitioned between EtOAc or DCM and water. The org. phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH.

Table 18

A-3	Name	Reactant A-2	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
A-3-1	4-(4-Methoxy-2-oxo-2,3-dihydro-benzimidazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester	A-2-1	RT 2	0.82	348.14
A-3-2	(R)-3-(4-Methoxy-2-oxo-2,3-dihydro-benzimidazol-1-yl)-pyrrolidine-1-carboxylic acid tert-butyl ester	A-2-2	RT 0.2	0.80	334.15
A-3-3	(R)-3-(4-Methoxy-2-oxo-2,3-dihydro-imidazo[4,5-c]pyridine-1-yl)-pyrrolidine-1-carboxylic acid tert-butyl ester	A-2-3	RT 2	0.72	335.12
A-3-4	(R)-3-(7-Methoxy-2-oxo-1,2-dihydro-imidazo[4,5-b]pyridine-3-yl)-pyrrolidine-1-carboxylic acid tert-butyl ester	A-2-4	45°C 0.2	0.74	335.34
A-3-5	4-(4-Methoxy-2-oxo-2,3-dihydro-benzimidazol-1-yl)-2-methyl-piperidine-1-carboxylic acid tert-butyl ester	A-2-5	RT 0.25	0.86	362.21
A-3-6	4-(4-Methoxy-2-oxo-2,3-dihydro-benzimidazol-1-yl)-3-methyl-piperidine-1-carboxylic acid tert-butyl ester	A-2-6	RT 0.75	0.85	362.21
A-3-7	4-(4-Methoxy-2-oxo-2,3-dihydro-benzimidazol-1-yl)-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester	A-2-7	RT 0.75	0.84	420.13
A-3-8	4-(4-Methyl-2-oxo-2,3-dihydro-benzimidazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester	A-2-8	RT 21	0.97	332.31

Synthesis of compounds of formula Ia (from compounds of formula A-3)Method A (K₂CO₃ / DMF)

To a soln. of intermediate A-3 (1 eq) in anh. DMF (3.5 to 6 mL/mmol) was added K₂CO₃ (3 eq) at RT then reactant BB-3 (1.1 to 2 eq) at 0°C. The rxn mixture was allowed to reach RT and stirred at a given temperature for a given time (see Table 19). It was quenched with water and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH or by trituration in a mixture of Hept/EtOAc 1/1 and filtration.

Method B (NaH / THF)

To a soln. of intermediate A-3 (1 eq) in anh. THF (3 mL/mmol) was added NaH (2 eq, as a 60% dispersion in mineral oil) at RT followed by BB-3 (1.2 eq). When necessary in term of solubility, anh. DMF (0.1 to 2 mL/mmol) could be added. The rxn mixture was stirred at a given temperature for a given time (see Table 19), quenched with a sat. soln. of NaHCO₃ and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH

Table 19

Ia	Name	Reactant A-3	Reactant BB-3	Method T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
Ia-1	4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (Example 1)	A-3-1	2-(Trifluoromethyl) benzyl bromide	A RT 24	1.04	505.98
Ia-2	(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (Example 6)	A-3-2	2-(Trifluoromethyl) benzyl bromide	A RT 24	1.02	492.10
Ia-3	(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethoxy-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (Example 20)	A-3-2	2-(Trifluoromethoxy) benzyl bromide	B 50°C 24	1.03	507.95

la-4	(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-imidazo[4,5-c]pyridin-1-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (Example 39)	A-3-3	2-(Trifluoromethyl) benzyl bromide	A RT 1.5	1.01	493.15
la-5	(R)-3-[7-Methoxy-2-oxo-1-(2-trifluoromethyl-benzyl)-1,2-dihydro-imidazo[4,5-b]pyridine-3-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (Example 43)	A-3-4	2-(Trifluoromethyl) benzyl bromide	B 50°C 5	1.00	493.13
la-6	4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-pyridin-3-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester	A-3-1	BB-3-1	A RT 24	0.99	507.13
la-7	4-[4-Methoxy-2-oxo-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (Example 53)	A-3-1	BB-3-2	A RT 3	1.01	507.13
la-8	(R)-3-[4-Methoxy-3-(2-methoxy-benzyl)-2-oxo-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (Example 65)	A-3-2	2-Methoxybenzyl chloride	B RT 18 then 50°C 4	0.98	454.19
la-9	4-[4-Methoxy-2-oxo-3-(3-trifluoromethyl-pyridin-4-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester	A-3-1	BB-3-3	A RT 24	1.02	507.14

la-10	4-[4-Methoxy-2-oxo-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,3-dihydro-benzoimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (Example 64)	A-3-1	BB-3-4	A RT 24	0.99	507.12
la-11	(R)-3-[4-Methoxy-3-(2-methoxy-benzyl)-2-oxo-2,3-dihydro-imidazo[4,5-c]pyridine-1-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester	A-3-3	2-Methoxybenzyl chloride	A RT 24	0.95	455.21
la-12	4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-2-methyl-piperidine-1-carboxylic acid tert-butyl ester (Example 144)	A-3-5	2-(Trifluoromethyl) benzyl bromide	B RT 24	1.06	520.24
la-13	4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-3-methyl-piperidine-1-carboxylic acid tert-butyl ester (Example 146)	A-3-6	2-(Trifluoromethyl) benzyl bromide	A RT 1 then 50°C 18	1.06	520.13
la-14	4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (Example 164)	A-3-7	2-(Trifluoromethyl) benzyl bromide	A RT 8.5	1.04	578.05
la-24	4-[4-Methyl-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester	A-3-8	2-(Trifluoromethyl) benzyl bromide	A RT 18	1.21	490.29

Synthesis of intermediates of formula B-1

A mixture of BB-6 (1 eq) and BB-5 (8.3 eq) in DIPEA (2 eq) was heated to 180°C and stirred for a given temperature (see Table 20). It was partitioned between DCM and water and the org. phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

5 **Table 20**

B-1	Name	Reactant BB-6	Reactant BB-5	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
B-1-1	(2-Methoxy-6-nitro-phenyl)- (2-trifluoromethyl-benzyl)- amine	2-Chloro-3- nitroanisole	2- (Trifluoromethyl) benzylamine	3.5	0.99	327.04

Synthesis of intermediates of formula B-2

To a suspension of intermediate B-1 (1 eq) and zinc dust (10 eq) in MeOH (10 mL/mmol) was added ammonium formate (10 eq) at 0°C. The rxn mixture was stirred at a given temperature for a given time (see Table 21), filtered
 10 over a pad of celite and the filtrate was concentrated in vacuo. The crude was purified by CC using DCM/MeOH.

Table 21

B-2	Name	Reactant B-1	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
B-2-1	3-Methoxy-N2-(2-trifluoromethyl-benzyl)- benzene-1,2-diamine	B-1-1	0 0.5	0.74	297.07

Synthesis of intermediates of formula B-3

Intermediates B-3 were prepared using a similar protocol as for the synthesis of intermediates A-3 replacing
 15 intermediates A-2 by intermediates B-2 (see Table 22).

Table 22

B-3	Name	Reactant B-2	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
B-3-1	7-Methoxy-1-(2-trifluoromethyl-benzyl)-1,3- dihydro-benzimidazol-2-one	B-2-1	RT 2	0.87	323.06

Synthesis of compounds of formula Ia (from compounds of formula B-3)

To a soln. of intermediate B-3 (1 eq) and BB-7 (1.5 eq) in toluene (6.8 mL/mmol) was added a 1M soln. of (tributylphosphoranylidene)acetonitrile in toluene (2 eq) under argon. The rxn mixture was heated to 110°C and stirred for a given time (see Table 23). It was quenched with water and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc and/or DCM/MeOH. When necessary, an additional purification by prep. LC-MS Method 1 can be performed.

Table 23

Ia	Name	Reactant B-3	Reactant BB-7	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
Ia-15	4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-azepane-1-carboxylic acid tert-butyl ester (Example 179)	B-3-1	4-Hydroxy azepane-1-carboxylic acid tert-butyl ester	2	1.04	520.12
Ia-16	5-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (Example 188)	B-3-1	5-hydroxy-2-azabicyclo[2.2.1] heptane-2-carboxylic acid tert-butyl ester	8	1.04	518.10
Ia-17	6-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-3-aza-bicyclo[3.1.1]heptane-3-carboxylic acid tert-butyl ester (Example 191)	B-3-1	6-hydroxy-3-azabicyclo[3.1.1] heptane-3-carboxylic acid tert-butyl ester	18	1.04	518.11
Ia-18	(3R*,4S*)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester (Example 196)	B-3-1	cis-1-Boc-4-methylpyrrolidin-3-ol	18	1.03	506.13

la-19	(3R*,4R*)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester (Example 199)	B-3-1	trans-1-Boc-4-methylpyrrolidine-3-ol	18	1.03	506.12
la-20	3-Fluoro-4-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (Example 210)	B-3-1	3-Fluoro-4-hydroxypiperidine-1-carboxylic acid tert-butyl ester	18	1.03	524.04
la-21	3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (Example 214)	B-3-1	1-Boc-3-hydroxypiperidine	18	1.05	506.08
la-22	3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-azetidine-1-carboxylic acid tert-butyl ester (Example 213)	B-3-1	1-Boc-3-hydroxyazetidine	16	1.01	478.03
la-23	4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-3,3-dimethyl-piperidine-1-carboxylic acid tert-butyl ester (Example 228)	B-3-1	1-Boc-4-hydroxy-3,3-dimethylpiperidine	18	1.07	534.22

Synthesis of intermediates of formula C-1

To a soln. of intermediate la (1 eq) in DCM (2 to 10 mL/mmol) was added TFA (1.5 to 5 mL/mmol) and the rxn mixture was stirred at RT for a given time (see Table 24). It was quenched with a 1M soln. of NaOH until pH reached 12 to 13 and extracted with DCM (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using DCM/MeOH.

Table 24

C-1	Name	Reactant la	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
C-1-1	4-Methoxy-1-piperidin-4-yl-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-1	2.5	0.72	406.13
C-1-2	4-Methoxy-1-(R)-pyrrolidin-3-yl-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-2	0.5	0.73	392.17
C-1-3	4-Methoxy-1-(R)-pyrrolidin-3-yl-3-(2-trifluoromethoxy-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-3	2	0.73	407.93
C-1-4	4-Methoxy-1-(R)-pyrrolidin-3-yl-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridine-2-one	la-4	1	0.67	393.09
C-1-5	7-Methoxy-3-(R)-pyrrolidin-3-yl-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-b]pyridine-2-one	la-5	1.5	0.68	393.23
C-1-6	4-Methoxy-1-piperidin-4-yl-3-(2-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzoimidazol-2-one	la-6	1.5	0.65	407.20
C-1-7	4-Methoxy-1-piperidin-4-yl-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzoimidazol-2-one	la-7	0.7	0.65	407.19
C-1-8	4-Methoxy-3-(2-methoxy-benzyl)-1-(R)-pyrrolidin-3-yl-1,3-dihydro-benzoimidazol-2-one	la-8	2.5	0.66	354.10
C-1-9	4-Methoxy-1-piperidin-4-yl-3-(3-trifluoromethyl-pyridin-4-ylmethyl)-1,3-dihydro-benzoimidazol-2-one	la-9	0.5	0.66	407.19
C-1-10	4-Methoxy-1-piperidin-4-yl-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-benzoimidazol-2-one	la-10	2	0.66	407.17
C-1-11	4-Methoxy-3-(2-methoxy-benzyl)-1-(R)-pyrrolidin-3-yl-1,3-dihydro-imidazo[4,5-c]pyridine-2-one	la-11	2	0.62	355.14
C-1-12	4-Methoxy-1-(2-methyl-piperidin-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-12	18	0.73	420.15

C-1-13	4-Methoxy-1-(3-methyl-piperidin-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-13	1.5	0.73	420.14
C-1-14	1-Azepan-4-yl-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-15	0.5	0.74	420.11
C-1-15	2-Aza-bicyclo[2.2.1]hept-5-yl-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-16	1	0.76	418.09
C-1-16	1-(3-Aza-bicyclo[3.1.1]hept-6-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-17	0.5	0.75	418.10
C-1-17	trans-4-Methoxy-1-(4-methyl-pyrrolidin-3-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-18	1	0.74	406.18
C-1-18	cis-4-Methoxy-1-(4-methyl-pyrrolidin-3-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-19	1	0.74	406.11
C-1-19	1-(3-Fluoro-piperidin-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-20	0.5	0.73/0.74	424.07
C-1-20	4-Methoxy-1-piperidin-3-yl-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-21	2	0.73	406.15
C-1-21	1-Azetidin-3-yl-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-22	0.75	0.70	378.11
C-1-22	1-(3,3-Dimethyl-piperidin-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-23	0.5	0.75	434.05
C-1-23	4-Methyl-1-piperidin-4-yl-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	la-24	1	0.82	390.25

Synthesis of compounds of formula Ib

Method A (Buchwald-Hartwig)

To a mixture of C-1 (1 eq), BB-8 (1.3 eq) and sodium tert-butoxide (2 eq) in toluene (3 to 10 mL/mmol) under N₂,
 5 was added BINAP (0.2 eq) and Pd₂(dba)₃ (0.1 eq). The rxn mixture was flushed with N₂, heated at a given

temperature and stirred for a given time (see Table 25). It was partitioned between water and EtOAc and the org. phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc. When necessary an additional purification by prep. LC-MS was performed.

Method B (Reductive amination)

- 5 To a soln. of C-1 (1 eq) in THF (10 mL/mmol) was added BB-8 (3 eq) and the rxn mixture was stirred for 1h. AcOH (1.1 eq) and NaBH(OAc)₃ (3 eq) were added and the rxn mixture was stirred at RT for a given time (see Table 25). It was quenched with a 1M aq. soln. of NaOH and extracted with DCM (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 25

lb	Name	Reactant C-1	Reactant BB-8	Method T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lb-1	1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 2)	C-1-1	2-Bromo-1,3-dimethylbenzene	A 100 18	1.15	510.12
lb-2	4-Methoxy-1-(1-phenyl-piperidin-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 4)	C-1-1	Bromobenzene	A 100 18	0.91	481.94
lb-3	1-[1-(2,4-Dichloro-benzyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 5)	C-1-1	2,4-Dichloro benzaldehyde	B RT 4	0.85	563.96
lb-4	1-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 7)	C-1-2	2,6-Difluoro bromobenzene	A 100 18	1.09	504.07

lb-5	1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 8)	C-1-2	2-Bromo-1,3-dimethylbenzene	A 100 18	1.00	496.12
lb-6	1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 9)	C-1-1	2,6-Difluoro bromobenzene	A 100 18	1.11	518.10
lb-7	1-[1-(2,6-Dimethoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 10)	C-1-1	2-Bromo-1,3-dimethoxy benzene	A 100 18	0.87	542.08
lb-8	1-[1-(2-Fluoro-6-methoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 11)	C-1-1	2-Bromo-3-fluoroanisole	A 100 18	1.04	529.98
lb-9	4-Methoxy-1-[1-(2-methoxy-6-methyl-phenyl)-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 12)	C-1-1	2-Bromo-1-methoxy-3-methylbenzene	A 100 24	1.03	526.09
lb-10	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 13)	C-1-1	2-Bromo-3-fluorotoluene	A 100 18	1.14	514.04

lb-11	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 15)	C-1-2	2-Bromo-3-fluorotoluene	A 100 18	1.09	500.25
lb-12	4-Methoxy-1-[(R)-1-(2-methoxy-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 16)	C-1-2	2-Bromoanisole	A 100 18	0.90	497.99
lb-13	1-[(R)-1-(2,6-Dimethoxy-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 17)	C-1-2	2-Bromo-1,3-dimethoxy benzene	A 100 18	0.87	527.94
lb-14	4-Methoxy-1-[(R)-1-(2-methoxy-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 18)	C-1-2	2-Bromo-1-methoxy-3-methylbenzene	A 100 18	0.90	511.98
lb-15	1-[(R)-1-(2-Fluoro-6-methoxy-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 19)	C-1-2	2-Bromo-3-fluoroanisole	A 100 18	0.98	515.95
lb-16	1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethoxy-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 22)	C-1-3	2-Bromo-1,3-dimethylbenzene	A 100 18	0.99	511.95

lb-17	1-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethoxy-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 23)	C-1-3	2,6-Difluoro bromobenzene	A 100 18	1.09	519.90
lb-18	4-Methoxy-1-[(R)-1-(2-methoxy-4-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 33)	C-1-2	3-Bromo-2-methoxy-4-methylpyridine	A 100 18	1.00	513.12
lb-19	1-[(R)-1-(3,5-Difluoro-pyridin-4-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 34)	C-1-2	4-Bromo-3,5-difluoropyridine	A 100 18	0.83	505.08
lb-20	1-[(R)-1-(3,5-Dimethyl-pyridin-4-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 36)	C-1-2	4-Bromo-3,5-dimethylpyridine hydrochloride	A 100 18	0.81	497.13
lb-21	1-[(R)-1-(2-Fluoro-4-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 37)	C-1-2	3-Bromo-2-fluoro-4-methylpyridine	A 100 18	1.07	501.11
lb-22	1-[(R)-1-(3,5-Dimethoxy-pyridin-4-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 38)	C-1-2	4-Bromo-3,5-dimethoxypyridine	A 100 18	0.82	529.11
lb-23	1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 41)	C-1-4	2-Bromo-1,3-dimethylbenzene	A 100 18	1.03	497.12

lb-24	1-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 42)	C-1-4	2,6-Difluoro bromobenzene	A 100 18	1.08	505.06
lb-25	3-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-7-methoxy-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one (Example 45)	C-1-5	2-Bromo-1,3-dimethylbenzene	A 100 18	0.86	497.14
lb-26	3-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-7-methoxy-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one (Example 46)	C-1-5	2,6-Difluoro bromobenzene	A 100 18	1.04	505.11
lb-27	4-Methoxy-1-[(R)-1-(2-methoxy-4-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 47)	C-1-4	3-Bromo-2-methoxy-4-methylpyridine	A 100 18	1.05	514.13
lb-28	1-[(R)-1-(2-Fluoro-4-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 48)	C-1-4	3-Bromo-2-fluoro-4-methylpyridine	A 100 18	1.05	502.11
lb-29	1-[(R)-1-(2-Fluoro-6-methoxy-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 49)	C-1-4	2-Bromo-3-fluoroanisole	A 100 18	1.03	517.13

lb-30	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 50)	C-1-4	2-Bromo-3-fluorotoluene	A 100 18	1.10	501.12
lb-31	4-Methoxy-1-[(R)-1-(2-methoxy-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 51)	C-1-4	2-Bromo-1-methoxy-3-methylbenzene	A 100 18	0.88	513.05
lb-32	1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzoimidazol-2-one (Example 54)	C-1-6	2-Bromo-1,3-dimethylbenzene	A 100 18	1.11	511.15
lb-33	1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzoimidazol-2-one (Example 55)	C-1-6	2,6-Difluoro bromobenzene	A 100 18	1.07	519.11
lb-34	1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzoimidazol-2-one (Example 58)	C-1-7	2-Bromo-1,3-dimethylbenzene	A 100 18	1.14	511.19
lb-35	1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzoimidazol-2-one (Example 59)	C-1-7	2,6-Difluoro bromobenzene	A 100 24	1.09	519.15

lb-36	1-[(R)-1-(2,4-Dimethyl-pyridin-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 66)	C-1-2	3-Bromo-2,4-dimethylpyridine	A 105 18	0.81	497.12
lb-37	1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 67)	C-1-8	2-Bromo-1,3-dimethylbenzene	A 105 18	0.94	458.17
lb-38	1-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 68)	C-1-8	2,6-Difluoro bromobenzene	A 105 18	1.05	466.49
lb-39	1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-4-ylmethyl)-1,3-dihydro-benzimidazol-2-one (Example 73)	C-1-9	2-Bromo-1,3-dimethylbenzene	A 100 18	1.16	511.17
lb-40	1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-4-ylmethyl)-1,3-dihydro-benzimidazol-2-one (Example 74)	C-1-9	2,6-Difluoro bromobenzene	A 100 18	1.11	519.11
lb-41	1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one (Example 75)	C-1-10	2-Bromo-1,3-dimethylbenzene	A 100 18	1.10	511.20

lb-42	1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one (Example 76)	C-1-10	2,6-Difluoro bromobenzene	A 100 18	1.06	519.11
lb-43	1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 77)	C-1-11	2-Bromo-1,3- dimethylbenzene	A 100 18	0.98	459.16
lb-44	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 78)	C-1-11	2-Bromo-3- fluorotoluene	A 100 18	1.05	463.12
lb-45	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 110)	C-1-8	2-Bromo-3- fluorotoluene	A 100 18	1.04	462.24
lb-46	1-[1-(2-Fluoro-6-methyl-phenyl)-3-methyl-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 147)	C-1-13	2-Bromo-3- fluorotoluene	A 105 18	1.14	528.16
lb-47	1-[(R)-1-(2-Fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 160)	C-1-2	1-Bromo-2- fluorobenzene	A 105 18	1.07	486.07

lb-48	1-[(R)-1-(2-Fluoro-6-morpholin-4-yl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 161)	C-1-2	BB-8-4	A 105 18	0.92	571.03
lb-49	1-[1-(2-Fluoro-6-methyl-phenyl)-azepan-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 184)	C-1-14	2-Bromo-3-fluorotoluene	A 110 18	1.13	528.09
lb-50	1-[1-(2,6-Dimethyl-phenyl)-azepan-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 185)	C-1-14	2-Bromo-1,3-dimethylbenzene	A 110 18	1.14	524.13
lb-51	1-[2-(2-Fluoro-6-methyl-phenyl)-2-aza-bicyclo[2.2.1]hept-5-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 190)	C-1-15	2-Bromo-3-fluorotoluene	A 110 18	0.99	526.06
lb-52	1-[3-(2-Fluoro-6-methyl-phenyl)-3-aza-bicyclo[3.1.1]hept-6-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 197)	C-1-16	2-Bromo-3-fluorotoluene	A 110 2.5	1.12	526.14
lb-53	1-[(3R*,4S*)-1-(2-Fluoro-6-methyl-phenyl)-4-methyl-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 198)	C-1-17	2-Bromo-3-fluorotoluene	A 110 2	1.12	514.12

lb-54	1-[(3R*,4R*)-1-(2-Fluoro-6-methyl-phenyl)-4-methyl-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 200)	C-1-18	2-Bromo-3-fluorotoluene	A 110 18	1.05	514.10
lb-55	4-Methoxy-1-[(R)-1-(2-trifluoromethoxy-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 201)	C-1-2	2-(Trifluoromethoxy)bromobenzene	A 110 20	1.10	552.02
lb-56	4-Methoxy-1-[(R)-1-[2-(2-methoxy-ethoxy)-phenyl]-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 204)	C-1-2	1-Bromo-2-(2-methoxyethoxy)benzene	A 110 20	0.91	542.05
lb-57	1-[3-Fluoro-1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 211)	C-1-19	2-Bromo-3-fluorotoluene	A 110 2	1.09/1.11	532.02
lb-58	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 212)	C-1-20	2-Bromo-3-fluorotoluene	A 110 18	1.11	514.05
lb-59	1-[1-(2-Fluoro-6-methyl-phenyl)-azetidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 215)	C-1-21	2-Bromo-3-fluorotoluene	A 110 2	1.07	486.04

lb-60	1-[1-(2,6-Dimethyl-phenyl)-piperidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 217)	C-1-20	2-Bromo-1,3-dimethylbenzene	A 110 20	1.11	510.09
lb-61	1-[1-(2-Fluoro-6-methyl-phenyl)-3,3-dimethyl-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 227)	C-1-22	2-Bromo-3-fluorotoluene	A 110 18	1.16	542.18
lb-62	1-[1-(2-Benzyloxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 231)	C-1-1	2-Benzyloxy bromobenzene	A 100 5	0.96	588.15
lb-63	4-Methoxy-1-(3'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 232)	C-1-1	2-Bromo-3-methylpyridine	A 110 18	0.81	497.06
lb-64	4-Methoxy-1-(3'-methoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 233)	C-1-1	2-Bromo-3-methoxypyridine	A 110 18	0.82	513.06
lb-65	4-Methoxy-1-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 234)	C-1-1	3-Bromo-2-methoxy-4-methylpyridine	A 110 18	1.10	527.10

lb-66	1-(2'-Fluoro-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 235)	C-1-1	3-Bromo-2-fluoro-4-methylpyridine	A 110 18	1.08	515.09
lb-67	1-(3'-Fluoro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 236)	C-1-1	2-Bromo-3-fluoropyridine	A 110 18	1.00	501.12
lb-68	1-(2',4'-Dimethyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 237)	C-1-1	3-Bromo-2,4-dimethylpyridine	A 110 18	0.81	511.18
lb-69	1-(4'-Fluoro-2'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 244)	C-1-1	3-Bromo-4-fluoro-2-methylpyridine	A 110 6	0.84	515.16
lb-70	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methyl-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 245)	C-1-23	2-Bromo-3-fluorotoluene	A 100 2	1.32	498.17
lb-71	4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-2'-carbonitrile (Example 246)	C-1-1	3-Bromo-4-methylpicolinonitrile	A 110 18	1.06	522.18

lb-72	4-Methoxy-1-(4'-methoxy-2'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 247)	C-1-1	BB-8-6	A 110 18	0.83	527.18
lb-73	1-(2',4'-Dimethoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 248)	C-1-1	3-Bromo-2,4-dimethoxypyridine	A 110 18	0.87	543.06
lb-74	4-Methoxy-1-[1-(4-methoxy-6-methyl-pyrimidin-5-yl)-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 249)	C-1-1	5-Bromo-4-methoxy-6-methylpyrimidine	A 110 18	0.93	528.12
lb-75	1-[1-(4,6-Dimethoxy-pyrimidin-5-yl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 250)	C-1-1	5-Bromo-4,6-dimethoxypyrimidine	A 110 4	1.04	544.05

Synthesis of compounds of formula Ic

Method A (standard S_NAr /CsF)

To a soln. of C-1 (1 eq) and BB-8 (1 to 1.1 eq) in DMSO (3 mL/mmol) was added CsF (2 eq). The rxn mixture was heated at a given temperature for a given time (see Table 26) and was partitioned between EtOAc and water. The org. phase was washed with water (3x) and with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method B (PyBOP activated S_NAr)

C-1 (1 eq), BB-8 (1.5 eq) and DIPEA (3 eq) were dissolved in anh. DMF (5 mL/mmol) and the mixture was stirred for 5 min at RT. PyBOP (1.8 eq) was added portionwise and the rxn mixture was further stirred at RT for a given time (see Table 26). It was partitioned between EtOAc and a 5% aq. soln. of $KHSO_4$ and the org. phase was washed with a sat. aq. soln. of $NaHCO_3$ (2x) and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method C (standard S_NAr / K_2CO_3)

The procedure is similar to method A replacing CsF by K_2CO_3 (2 eq).

Method D (PyBOP activated S_NAr + cyclodehydration)

The procedure is similar to method B but the resulting open form product is additionally submitted to a cyclodehydration as follows:

The open form product (1 eq) was dissolved in anh. THF and Burgess' reagent (2.5 eq) was added portionwise at RT (see Table 26). The rxn mixture was stirred at 150°C for 30 min under microwave condition and partitioned between EtOAc and H₂O. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 26

lc	Name	Reactant C-1	Reactant BB-8	Method T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lc-1	3-Cyclopropyl-5-{4-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-piperidin-1-yl}-1-methyl-1H-pyrazole-4-carbaldehyde (Example 14)	C-1-1	5-Chloro-3-cyclopropyl-1-methyl-1H-pyrazole-4-carbaldehyde	A 100 96	1.04	554.09
lc-2	1-[(R)-1-(5-Isopropyl-[1,3,4]oxadiazol-2-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 69)	C-1-2	BB-8-5	B RT 18	0.98	502.14
lc-3	5-[(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-1,3-dimethyl-1H-pyrazole-4-carbaldehyde (Example 71)	C-1-2	5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde	A 100 18	0.99	514.16

lc-4	3-Fluoro-2-((R)-3-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidin-1-yl)-benzonitrile (Example 82)	C-1-2	2,3-Difluoro benzonitrile	C 80 18	1.06	511.13
lc-5	3-Fluoro-2-((R)-3-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidin-1-yl)-benzaldehyde (Example 83)	C-1-2	2,3-Difluoro benzaldehyde	C 100 18	1.06	514.16
lc-6	4-Methoxy-3-(2-trifluoromethyl-benzyl)-1-[(R)-1-(5-trifluoromethyl-[1,3,4]oxadiazol-2-yl)-pyrrolidin-3-yl]-1,3-dihydro-benzimidazol-2-one (Example 84)	C-1-2	5-(Trifluoromethyl)-1,3,4-oxadiazol-2-ol	D RT 24	1.00	528.10
lc-7	5-((R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbonitrile (Example 87)	C-1-2	5-chloro-1,3-dimethyl-1H-pyrazole-4-carbonitrile	A 80 24	1.00	511.34
lc-8	3-Fluoro-2-((R)-3-[4-methoxy-3-(2-methoxy-benzyl)-2-oxo-2,3-dihydro-benzimidazol-1-yl]-pyrrolidin-1-yl)-benzonitrile (Example 109)	C-1-8	2,3-Difluoro benzonitrile	C 105 3	1.02	473.21
lc-9	3-Fluoro-2-{4-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-2-methyl-piperidin-1-yl}-benzaldehyde (Example 145)	C-1-13	2,3-Difluoro benzaldehyde	C 105 72	1.10	542.13

lc-10	1-[(R)-1-(2-Fluoro-6-nitro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 154)	C-1-2	2,3-Difluoro nitrobenzene	C 100 18	1.07	530.98
lc-11	1-[(R)-1-(4,5-Dichloro-pyridazin-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 157)	C-1-2	3,4,5-Trichloro pyridazine	C RT 48 then 60 24	1.04	537.92
lc-12	1-[(R)-1-(3,5-Dichloro-pyridazin-4-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 158)	C-1-2	3,4,5-Trichloro pyridazine	C RT 48 then 60 24	1.03	538.00

Synthesis of compounds of formula Id

To a soln. of lc (1 eq) in MeOH (8 mL/mmol) was added toluene-4-sulfonic acid monohydrate (0.2 eq) and the rxn mixture was heated at 120°C under microwave condition for a given time (see Table 27). It was concentrated in vacuo and partitioned between EtOAc and a sat. aq. soln. of NaHCO₃. The org. phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 27

Id	Name	Reactant lc	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
ld-1	1-[1-(5-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 21)	lc-1	120 0.25	0.94	525.97
ld-2	1-[(R)-1-(2,5-Dimethyl-2H-pyrazol-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 79)	lc-3	120 0.35	0.84	486.33

Synthesis of compounds of formula le

To a soln. of Id (1 eq) in THF (4.5 mL/mmol) was added NCS (1.4 eq) and the rxn mixture was stirred at RT for a given time (see Table 28). It was partitioned between EtOAc and water and the org. phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

5 **Table 28**

le	Name	Reactant Id	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
le-1	1-[1-(4-Chloro-5-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 24)	Id-1	1	1.11	560.11
le-2	1-[(R)-1-(4-Chloro-2,5-dimethyl-2H-pyrazol-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 80)	Id-2	0.25	1.07	520.12

Synthesis of compounds of formula If

To a stirred soln. of Ic (1 eq) in a mixture of DMF (0.5 mL) was added toluene-4-sulfonic acid monohydrate (0.13 eq) and 4-toluenesulfonylhydrazide (1.3 eq) followed by sulfolane (0.5 mL) (see Table 29). The mixture was stirred at 100°C for 1h and cooled to RT. Sodium cyanoborohydride (4 eq) was added portionwise and the mixture was stirred at 100°C for 24h. It was quenched with a sat. aq. soln. of NaHCO₃ and extracted 3x with EtOAc. The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by prep. LC-MS using method 3.

10 **Table 29**

If	Name	Reactant Ic	t _R [min]	MS-data m/z [M+H] ⁺
If-1	1-[1-(5-Cyclopropyl-2,4-dimethyl-2H-pyrazol-3-yl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 25)	Ic-1	0.95	540.15

15 **Synthesis of compounds of formula Ig**

To a soln. of C-1 (1 eq) and TEA (3 eq) in a given solvent (5 mL/mmol) (see) was added at 0°C alkyl chloroformate or pentafluorophenylcarbonate BB-8 (1.2 eq). The rxn mixture was allowed to warm to RT and stirred at a given temperature for a given time (see Table 30). It was partitioned between DCM and a sat. aq. soln. of NaHCO₃. The org. phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC

using DCM/MeOH or Hept/EtOAc. If necessary a second purification by prep. LC-MS using method 2, 3 or 6 can be performed.

Table 30

Ig	Name	Reactant C-1	Reactant BB-8	Solvent T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
Ig-1	(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid methyl ester (Example 26)	C-1-2	Methyl chloroformate	DCM RT 2	0.95	450.04
Ig-2	4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-piperidine-1-carboxylic acid methyl ester (Example 29)	C-1-1	Methyl chloroformate	DCM RT 1	0.97	464.05
Ig-3	(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid ethyl ester (Example 60)	C-1-2	Ethyl chloroformate	DCM RT 18	0.97	464.06
Ig-4	(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid isopropyl ester (Example 61)	C-1-2	Isopropylchloroformate	DCM RT 18	1.00	478.09
Ig-5	(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid butyl ester (Example 62)	C-1-2	n-Butyl chloroformate	DCM RT 18	1.03	492.11
Ig-6	(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid phenyl ester (Example 63)	C-1-2	Phenyl chloroformate	DCM RT 18	1.01	512.10

lg-7	(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid 3-methyl-oxetan-3-yl ester (Example 70)	C-1-2	BB-8-1	DMF 110°C 0.25	0.95	506.13
lg-8	(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid oxetan-3-yl ester (Example 72)	C-1-2	BB-8-2	DMF 110°C 0.25	0.93	492.09
lg-9	(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid 3-trifluoromethyl-oxetan-3-yl ester (Example 86)	C-1-2	BB-8-3	DMF 110°C 0.5	1.00	560.13

Synthesis of compounds of formula lh

To a soln. of C-1 (1 eq) and TEA (3 eq) in DCM (5 mL/mmol) was added at 0°C acid chloride BB-8 (1 to 1.2 eq). The rxn mixture was stirred at RT for a given time (see Table 31) and partitioned between DCM and a sat. aq. soln. of NaHCO₃. The org. phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 31

lh	Name	Reactant C-1	Reactant BB-8	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lh-1	1-((R)-1-Benzoyl-pyrrolidin-3-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 27)	C-1-2	Benzoyl chloride	1.5	0.97	496.00
lh-2	1-[1-(2,2-Dimethyl-propionyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 28)	C-1-1	Pivaloyl chloride	1	1.00	490.12

lh-3	1-(1-Benzoyl-piperidin-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 30)	C-1-1	Benzoyl chloride	1	0.98	510.10
lh-4	1-(1-Cyclopropanecarbonyl-piperidin-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 222)	C-1-1	Cyclopropane carbonyl chloride	1.5	0.95	474.07

Synthesis of compounds of formula li

Method A (sodium triacetoxyborohydride)

To a soln. of C-1 (1 eq) in a mixture of DCM (25 mL/mmol) and MeOH (50 mL/mmol) were added AcOH (1.2 eq) and aldehyde BB-8 (1.3 eq) followed by NaBH(OAc)₃ (1.4 eq) portionwise. The rxn mixture was stirred at RT for a given time (see Table 32). It was quenched with a sat. aq. soln. of NaHCO₃ and extracted with DCM (3x). The combined org. phases were dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using DCM/MeOH.

Method B (indium(III) chloride/triethylsilane)

To a soln. of C-1 (1 eq) in MeOH (5 mL/mmol) was added BB-8 (1.1 eq) and the rxn mixture was stirred for 15 min. Triethylsilane (2 eq) and indium(III) chloride (0.3 eq) were added and the rxn mixture was stirred at RT for a given time (see Table 32). It was quenched with a sat. aq. soln. of K₂CO₃ and extracted with DCM (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by prep. LC-MS using method 6.

Method C (Alkylation)

To a soln. of C-1 (1 eq) in MeCN (5 mL/mmol) was added K₂CO₃ (4 eq) and BB-8 (5 eq) and the rxn mixture was stirred at 65°C for a given time (see Table 32). It was partitioned between EtOAc and water and the org. phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using DCM/MeOH.

Table 32

li	Name	Reactant C-1	Reactant BB-8	Method time [h]	t _R [min]	MS-data m/z [M+H] ⁺
li-1	4-Methoxy-1-((R)-1-methyl-pyrrolidin-3-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 31)	C-1-2	Formaldehyde (37% in H ₂ O)	A 18	0.75	406.15

li-2	1-((R)-1-Isopropyl-pyrrolidin-3-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 32)	C-1-2	Acetone	B 18	0.76	434.13
li-3	1-(1-Isopropyl-piperidin-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 35)	C-1-1	2-Iodopropane	C 2	0.76	448.13

Synthesis of compounds of formula lj

Method A (methyl ether cleavage with BBr₃)

To a soln. of lb (1 eq) in DCM (4 mL/mmol) was added dropwise at 0°C a 1M soln. of BBr₃ in DCM (3 eq). The rxn mixture was allowed to warm to RT and stirred for a given time (see Table 33). The mixture was quenched with chilled H₂O and extracted with DCM (3x). The combined org. phases were dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method B (methoxypyridine cleavage with BBr₃)

To a soln. of lb (1 eq) in DCM (20 to 35 mL/mmol) was added dropwise at -10°C a 1M soln. of BBr₃ in DCM (2 eq). The rxn mixture was stirred at -10°C for 30 min, allowed to warm to RT and stirred for a given time (see Table 33). The mixture was quenched with chilled H₂O, basified with a sat. aq. soln. of NaHCO₃ and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH.

Table 33

lj	Name	Reactant	Method time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lj-1	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-hydroxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 40)	lb-11	A 18	0.99	486.11
lj-2	1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-hydroxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 44)	lb-5	A 3	0.91	482.15

lj-3	1-[(R)-1-(2-Fluoro-6-methoxy-phenyl)-pyrrolidin-3-yl]-4-hydroxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (tautomeric form: 1-[(R)-1-(2-Fluoro-6-methoxy-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione) (Example 56)	lb-29	B 18	0.85	503.10
lj-4	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-hydroxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (tautomeric form 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione) (Example 57)	lb-30	B 42	0.94	487.22
lj-5	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-hydroxy-3-(2-methoxy-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (tautomeric form 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-methoxy-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione) (Example 81)	lb-44	B 24	0.88	449.14
lj-6	1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-hydroxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (tautomeric form 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione) (Example 93)	lb-23	B 36	0.85	483.15
lj-7	4-Hydroxy-1-[(R)-1-(2-methoxy-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (tautomeric form 1-[(R)-1-(2-Methoxy-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione) (Example 94)	lb-31	B 36	0.75	499.15

Synthesis of compounds of formula Ik

To a stirred soln. of Ij (1 eq) in DMSO (10 mL/mmol) was added K₂CO₃ (2 eq) followed by the corresponding halide (1.1 eq). The rxn mixture was stirred at a given temperature for a given time (see Table 34). It was partitioned between EtOAc and H₂O. The org. phase was washed with water (3x) and brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or by prep. LC-MS using method 3.

Table 34

Ik	Name	Reactant Ij	Reactant halide	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
Ik-1	1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-(2-hydroxy-ethoxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 52)	Ij-2	2-Bromoethanol	50 72	0.92	526.15
Ik-2	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(oxetan-3-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 149)	Ij-1	3-Bromoxetane	105 2 then 60 72	1.06	542.10
Ik-3	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(2-hydroxy-ethoxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 150)	Ij-1	2-Bromoethanol	100 1.5 then 80 18	1.00	529.99
Ik-4	4-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one (Example 151)	Ij-1	4-(Bromomethyl)-2,2-dimethyl-1,3-dioxolane	100 1.5 then 80 18	1.10	600.05

Synthesis of compounds of formula Ij

To a mixture of Ie (1 eq), boron species (3 eq) and K₂CO₃ (5 eq) in dioxane (4 mL/mmol) under N₂, was added PEPPSI-IPr (0.1 eq). The rxn mixture was flushed with N₂, heated at a given temperature and stirred for a given

time (see Table 35). It was partitioned between water and EtOAc and the org. phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc. When necessary an additional purification by prep. LC-MS was performed.

Table 35

lc	Name	Reactant le	Boron species	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lc-1	4-Methoxy-3-(2-trifluoromethyl-benzyl)-1-[(R)-1-(2,4,5-trimethyl-2H-pyrazol-3-yl)-pyrrolidin-3-yl]-1,3-dihydro-benzoimidazol-2-one (Example 85)	le-2	Trimethyl boroxine	115 5.5	0.90	500.98

5

Synthesis of compounds of formula Im

To a stirred soln. of lc (1 eq) in MeOH (4 mL/mmol) was added portionwise at 0°C NaBH₄ (2 eq). The rxn mixture was stirred at RT for a given time (see Table 36) and quenched with H₂O. It was extracted with DCM (3x) and the combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was

10

Table 36

Im	Name	Reactant lc	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
Im-1	1-[(R)-1-(2-Fluoro-6-hydroxymethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 88)	lc-5	1	0.99	516.15

Synthesis of compounds of formula In

To a stirred soln. of lc (1 eq) in THF (20 mL/mmol) under argon was added dropwise at 0°C a 3M soln. of MeMgBr in Et₂O (2 eq). The rxn mixture was stirred for a given time (see Table 37) allowing temperature to reach RT. The mixture was cooled to 0°C, quenched with a sat. aq. soln. of NH₄Cl and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

15

Table 37

In	Name	Reactant lc	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
In-1	1-((R)-1-[2-Fluoro-6-(1-hydroxy-ethyl)-phenyl]-pyrrolidin-3-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 89)	lc-5	0.25	1.00	530.05

Synthesis of compounds of formula lo

To a stirred soln. of In (1 eq) in DCM (3 mL/mmol) was added a 15% soln. of DMP in DCM (1.5 eq). The rxn mixture was stirred at RT for a given time (see Table 38). The mixture was quenched with a sat. aq. soln. of NaHCO₃ and extracted with DCM (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 38

lo	Name	Reactant lc	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lo-1	1-[(R)-1-(2-Acetyl-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 90)	In-1	4.5	1.04	528.15

10 **Synthesis of compounds of formula lp**

The procedure was similar to the one synthesizing compounds of formula In except that reactant lc were replaced by reactant lo (see Table 39).

Table 39

lp	Name	Reactant In	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lp-1	1-((R)-1-[2-Fluoro-6-(1-hydroxy-1-methyl-ethyl)-phenyl]-pyrrolidin-3-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 91)	lo-1	0.4	0.96	544.17

15 **Synthesis of intermediates of formula C-3**

Intermediates C-3 were prepared using a similar protocol as for the synthesis of intermediates A-1 replacing amine building blocks BB-1 by amine building blocks BB-4 (see Table 40).

Table 40

C-3	Name	Reactant BB-2	Reactant BB-4	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
C-3-1	[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-(3-methoxy-2-nitro-phenyl)-amine	3-Fluoro-2-nitroanisole	BB-4-1	105 24	1.03	346.08
C-3-2	3-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-ylamino]-2-nitro-benzoic acid methyl ester	Methyl 3-Fluoro-2-nitrobenzoate	BB-4-3	85 24	0.96	385.16
C-3-3	3-Fluoro-2-[(R)-3-(6-methoxy-5-nitro-pyrimidin-4-ylamino)-pyrrolidin-1-yl]-benzonitrile	BB-2-3	BB-4-3	105 3	0.95	359.13
C-3-4	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-(3-methoxy-2-nitro-phenyl)-amine	3-Fluoro-2-nitroanisole	BB-4-2	105 24	1.07	360.22
C-3-5	[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-(4-methoxy-6-methyl-3-nitro-pyridin-2-yl)-amine	2-Chloro-4-methoxy-6-methyl-3-nitropyridine	BB-4-1	50 48	1.01	361.05
C-3-6	(6-Bromo-3-methoxy-2-nitro-phenyl)-[1-(2,6-dimethyl-phenyl)-piperidin-4-yl]-amine	4-Bromo-3-fluoro-2-nitroanisole	BB-4-4	100 18	1.11	433.93

Synthesis of intermediates of formula C-4

Intermediates C-4 were prepared using a similar protocol (method A) as for the synthesis of intermediates A-2 replacing intermediates A-1 by intermediates C-3 (see Table 41).

Alternatively, intermediates C-4 were prepared using the protocol described below (method B).

Method B (ammonium formate / Zn dust)

To a suspension of intermediate C-3 (1 eq) in MeOH (18.7 mL/mmol) was added Zn dust (10 eq) and the rxn mixture was cooled to 0°C. Ammonium formate (10 eq) was added and the rxn mixture was stirred at RT for a given time (see Table 41). It was filtered over a pad of celite and the filtrate was concentrated in vacuo. The residue was diluted with EtOAc and washed with a sat. aq. soln. of NaHCO₃. The org. phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 41

C-4	Name	Reactant C-3	Method time [h]	t _R [min]	MS-data m/z [M+H] ⁺
C-4-1	N1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-methoxy-benzene-1,2-diamine	C-3-1	A 24	0.75	316.13
C-4-2	2-Amino-3-[(R)-1-(2-cyano-6-fluoro-phenyl)-pyrrolidin-3-ylamino]-benzoic acid methyl ester	C-3-2	A 2.5	0.97	355.14
C-4-3	2-[(R)-3-(5-Amino-6-methoxy-pyrimidin-4-ylamino)-pyrrolidin-1-yl]-3-fluoro-benzonitrile	C-3-3	A 1	0.75	329.11
C-4-4	N1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-methoxy-benzene-1,2-diamine	C-3-4	A 3	0.78	330.11
C-4-5	N2-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-6-methyl-pyridine-2,3-diamine	C-3-5	A 2	0.74 A	331.08
C-4-6	3-Bromo-N2-[1-(2,6-dimethyl-phenyl)-piperidin-4-yl]-6-methoxy-benzene-1,2-diamine	C-3-6	B 0.3	1.03	404.15

Synthesis of intermediates of formula C-6 (from intermediates of formula C-4)

Intermediates C-6 were prepared using a similar protocol as for the synthesis of intermediates A-3 replacing
 5 intermediates A-2 by intermediates C-4 (see Table 42).

Table 42

C-6	Name	Reactant C-4	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
C-6-1	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one	C-4-1	RT 1	0.88	342.15
C-6-2	1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-2,3-dihydro-1H-benzimidazole-4-carboxylic acid methyl ester	C-4-2	55 3	0.91	381.11

C-6-3	3-Fluoro-2-[(R)-3-(6-methoxy-8-oxo-7,8-dihydro-purin-9-yl)-pyrrolidin-1-yl]-benzonitrile	C-4-3	RT 24	0.82	355.13
C-6-4	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzoimidazol-2-one	C-4-4	RT 4.5	0.96	356.06
C-6-5	3-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-7-methoxy-5-methyl-1,3-dihydro-imidazo[4,5-b]pyridine-2-one	C-4-5	RT 2.5	0.73	357.05
C-6-6	7-Bromo-1-[1-(2,6-dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzoimidazol-2-one	C-4-6	up to 80 48	1.04	430.06

Synthesis of intermediates of formula C-5

Intermediates C-5 were prepared using a similar protocol as for the synthesis of intermediates C-1 replacing intermediates Ia by intermediates A-3 (see Table 43).

5 **Table 43**

C-5	Name	Reactant A-3	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
C-5-1	4-Methoxy-1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one	A-3-1	0.25	0.47	248.20
C-5-2	4-Methoxy-1-(R)-pyrrolidin-3-yl-1,3-dihydro-benzoimidazol-2-one	A-3-2	1	0.46	234.15

Synthesis of intermediate of formula C-6 (from C-5)

To a soln. of C-5 (1 eq) in DMSO (1.5 mL/mmol) was added K₂CO₃ (2 eq) and BB-8 (1.2 eq). The rxn mixture was heated at a given temperature for a given time (see Table 44) and was partitioned between DCM and water. The org. phase was washed with water (3x) and with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using EtOAc/MeOH.

10

Table 44

C-6	Name	Reactant C-5	Reactant BB-8	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
C-6-7	3-Fluoro-2-[4-(4-methoxy-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-benzonitrile	C-5-1	2,3-Difluorobenzonitrile	100 3	0.90	367.12

C-6-8	3-Fluoro-2-[(R)-3-(4-methoxy-2-oxo-2,3-dihydro-benzimidazol-1-yl)-pyrrolidin-1-yl]-benzonitrile	C-5-2	2,3-Difluorobenzonitrile	100 18	0.87	353.17
-------	---	-------	--------------------------	-----------	------	--------

Synthesis of compounds of formula Iq

Compounds of formula Iq were prepared using similar protocols (method A or B) as for the synthesis of intermediates or examples Ia replacing intermediates A-3 by intermediates C-6 (see Table 45).

- 5 Alternatively, intermediates or examples Iq were prepared using the protocol described below (method C).

Method C (Mitsunobu)

- To a soln. of intermediate C-6 (1 eq) and BB-3 (1 to 1.5 eq) in toluene (3.4 to 6.8 mL/mmol) was added a 1M soln. of (tributylphosphoranylidene)acetonitrile in toluene (2 eq) under argon. The rxn mixture was heated to 110°C and stirred for a given time (see Table 45). It was quenched with water and extracted with EtOAc (3x). The combined
10 org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc and/or DCM/MeOH. When necessary, an additional purification by prep. LC-MS using method 1 or 2 can be performed.

Table 45

Iq	Name	Reactant C-6	Reactant BB-3	Method T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
Iq-1	3-(6-Chloro-4-methoxy-pyridazin-3-ylmethyl)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one (Example 92)	C-6-1	BB-3-10	A RT to 45°C 40	0.96	498.14
Iq-2	1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid methyl ester (Example 98)	C-6-2	2-(Trifluoromethyl)benzyl bromide	A RT 24	1.05	539.24

lq-3	3-Fluoro-2-[(R)-3-[6-methoxy-8-oxo-7-(2-trifluoromethyl-benzyl)-7,8-dihydro-purin-9-yl]-pyrrolidin-1-yl]-benzonitrile (Example 104)	C-6-3	2-(Trifluoromethyl) benzyl bromide	A RT 3	1.05	513.19
lq-4	3-Fluoro-2-[(R)-3-[6-methoxy-7-(2-methoxy-benzyl)-8-oxo-7,8-dihydro-purin-9-yl]-pyrrolidin-1-yl]-benzonitrile (Example 105)	C-6-3	2-Methoxybenzyl chloride	A RT 4	1.01	475.11
lq-5	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(2-isopropoxy-benzyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one (Example 166)	C-6-4	1-(Chloromethyl)-2-(propan-2-yloxy)benzene	A RT to 60°C 24	1.13	504.11
lq-6	3-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-7-methoxy-5-methyl-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one (Example 171)	C-6-5	2-(Trifluoromethyl) benzyl bromide	A RT 1.5	1.03	515.03
lq-7	3-Fluoro-2-{4-[4-methoxy-2-oxo-3-(3-trifluoromethyl-pyrazin-2-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-piperidin-1-yl}-benzonitrile (Example 96)	C-6-7	BB-3-5	A RT 24	1.03	527.11
lq-8	3-Fluoro-2-{4-[4-methoxy-3-(3-methoxy-pyrazin-2-ylmethyl)-2-oxo-2,3-dihydro-benzimidazol-1-yl]-piperidin-1-yl}-benzonitrile (Example 97)	C-6-7	2-(Bromomethyl)-3-methoxypyrazine	A RT 24	0.99	489.11

lq-9	3-Fluoro-2-((R)-3-[4-methoxy-2-oxo-3-(3-trifluoromethyl-pyrazin-2-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidin-1-yl)-benzonitrile (Example 111)	C-6-8	BB-3-5	A RT 24	1.01	513.01
lq-10	3-Fluoro-2-((R)-3-[4-methoxy-3-(3-methoxy-pyrazin-2-ylmethyl)-2-oxo-2,3-dihydro-benzimidazol-1-yl]-pyrrolidin-1-yl)-benzonitrile (Example 112)	C-6-8	2-(Bromomethyl)-3-methoxy pyrazine hydrochloride	A RT 24	0.97	475.22
lq-11	3-Fluoro-2-{4-[4-methoxy-3-(4-methoxy-pyrimidin-5-ylmethyl)-2-oxo-2,3-dihydro-benzimidazol-1-yl]-piperidin-1-yl}-benzonitrile (Example 113)	C-6-7	BB-3-7	A RT 24	0.99	489.19
lq-12	3-Fluoro-2-((R)-3-[4-methoxy-3-(4-methoxy-pyrimidin-5-ylmethyl)-2-oxo-2,3-dihydro-benzimidazol-1-yl]-pyrrolidin-1-yl)-benzonitrile (Example 114)	C-6-8	BB-3-7	A RT 24	0.95	475.12
lq-13	3-Fluoro-2-{4-[4-methoxy-2-oxo-3-(4-trifluoromethyl-pyrimidin-5-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-piperidin-1-yl}-benzonitrile (Example 117)	C-6-7	BB-3-9	A RT 24	1.05	527.11

lq-14	3-Fluoro-2-[(R)-3-[4-methoxy-2-oxo-3-(4-trifluoromethyl-pyrimidin-5-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile (Example 153)	C-6-8	BB-3-9	A RT 48	1.01	512.96
lq-15	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-isopropoxy-benzyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one (Example 165)	C-6-1	1-(Chloromethyl)-2-(propan-2-yloxy)benzene	A RT 24 then 60 2	1.08	490.11
lq-16	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(3-trifluoromethyl-pyrazin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one (Example 167)	C-6-1	BB-3-5	A 60 24	1.03	502.04
lq-17	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyrazin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one (Example 168)	C-6-4	BB-3-5	A 60 24	1.08	516.01
lq-18	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(3-methoxy-pyrazin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one (Example 169)	C-6-1	2-(Bromomethyl)-3-methoxypyrazine hydrochloride	A 60 24 then 100 18	0.98	464.11

lq-19	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-methoxy-pyrazin-2-ylmethyl)-1,3-dihydro-benzoimidazol-2-one (Example 170)	C-6-4	2-(Bromomethyl)-3-methoxypyrazine hydrochloride	A 60 24 then 100 18	1.04	478.24
lq-20	3-(6-Chloro-4-isopropoxy-pyridazin-3-ylmethyl)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzoimidazol-2-one (Example 172)	C-6-1	BB-3-11	C 110 3	1.02	526.12
lq-21	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-methyl-pyridazin-3-ylmethyl)-1,3-dihydro-benzoimidazol-2-one (Example 174)	C-6-1	BB-3-12	C 110 1.5	0.88	448.14
lq-22	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-methoxy-pyrimidin-5-ylmethyl)-1,3-dihydro-benzoimidazol-2-one (Example 175)	C-6-1	BB-3-6	C 110 1.5	0.99	464.15
lq-23	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-trifluoromethyl-pyrimidin-5-ylmethyl)-1,3-dihydro-benzoimidazol-2-one (Example 176)	C-6-1	BB-3-8	C 110 4	1.04	502.06
lq-24	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(3-isopropoxy-pyrazin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzoimidazol-2-one (Example 177)	C-6-1	BB-3-13	C 110 2	1.05	492.17

lq-25	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(3-isopropoxy-pyrazin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzoimidazol-2-one (Example 178)	C-6-4	BB-3-13	C 2	1.10	506.19
lq-26	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(4-isopropyl-pyridin-3-ylmethyl)-4-methoxy-1,3-dihydro-benzoimidazol-2-one (Example 180)	C-6-1	BB-3-14	C 110 1.5	0.85	475.17
lq-27	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(4-isopropyl-pyridin-3-ylmethyl)-4-methoxy-1,3-dihydro-benzoimidazol-2-one (Example 181)	C-6-4	BB-3-14	C 110 1.5	0.89	489.20
lq-28	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(3-isopropoxy-pyridin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzoimidazol-2-one (Example 182)	C-6-1	BB-3-15	C 110 1.5	0.90	491.16
lq-29	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(3-isopropoxy-pyridin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzoimidazol-2-one (Example 183)	C-6-4	BB-3-15	C 110 1.5	0.94	505.13
lq-30	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(4-isopropyl-pyrimidin-5-ylmethyl)-4-methoxy-1,3-dihydro-benzoimidazol-2-one (Example 186)	C-6-1	BB-3-16	C 110 3	1.06	476.09

lq-31	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(3-isopropyl-pyrazin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzoimidazol-2-one (Example 187)	C-6-4	BB-3-17	C 110 1.5	1.07	490.16
lq-32	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(3-isopropyl-pyrazin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzoimidazol-2-one (Example 189)	C-6-1	BB-3-17	C 110 1.5	1.01	476.10
lq-33	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(4-isopropyl-pyrimidin-5-ylmethyl)-4-methoxy-1,3-dihydro-benzoimidazol-2-one (Example 192)	C-6-4	BB-3-16	C 110 24	1.13	490.17
lq-34	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzoimidazol-2-one (Example 195)	C-6-1	(2-(Trifluoromethyl) pyridin-3-yl) methanol	C 110 2	1.05	501.12
lq-35	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-benzoimidazol-2-one (Example 202)	C-6-1	(3-(Trifluoromethyl) pyridin-2-yl) methanol	C 110 18	1.03	501.05
lq-36	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzoimidazol-2-one (Example 203)	C-6-1	(4-(Trifluoromethyl) pyridin-3-yl) methanol	C 110 2	1.08	501.09

lq-37	3-(2-Cyclopropoxy-benzyl)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one (Example 208)	C-6-1	1-(Bromomethyl)-2-cyclopropyloxy benzene	A RT 6	1.06	488.12
lq-38	3-(2-Cyclopropoxy-benzyl)-1-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one (Example 209)	C-6-4	1-(Bromomethyl)-2-cyclopropyloxy benzene	A RT 18 then 60 3.5	1.13	502.15
lq-39	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one (Example 216)	C-6-4	[3-(trifluoromethyl)pyridin-2-yl] methanol	C 110 24	1.09	515.10
lq-40	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-thiazol-4-ylmethyl)-1,3-dihydro-benzimidazol-2-one (Example 218)	C-6-1	BB-3-18	C 110 18	1.04	507.00
lq-41	1-[1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-[(S)-1-(2-trifluoromethyl-phenyl)-ethyl]-1,3-dihydro-benzimidazol-2-one (Example 219)	C-6-1	1-(2-(trifluoromethyl)phenyl)ethan-1-ol	C 110 2.5	1.07	514.02
lq-42	3-(2,4-Difluoro-6-isopropoxy-benzyl)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one (Example 220)	C-6-1	BB-3-19	C 110 2.5	1.09	526.04

lq-43	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methyl-4-trifluoromethyl-thiazol-5-ylmethyl)-1,3-dihydro-benzimidazol-2-one (Example 221)	C-6-1	[2-methyl-4-(trifluoromethyl)-1,3-thiazol-5-yl]methanol	C 110 4	1.06	521.01
lq-44	3-(2-Cyclopropyl-benzyl)-1-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one (Example 223)	C-6-4	(2-Cyclopropylphenyl) methanol	C 110 2	1.14	486.13
lq-45	2-{3-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methoxy-2-oxo-2,3-dihydro-benzimidazol-1-ylmethyl}-phenyl acetate	C-6-4	2-(Chloromethyl)phenyl acetate	A 70 10	1.08	504.16
lq-46	4-Bromo-3-[1-(2,6-dimethyl-phenyl)-piperidin-4-yl]-7-methoxy-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one	C-6-6	2-(Trifluoromethyl) benzyl bromide	A RT 2	1.20	588.03

Synthesis of compounds of formula Ir

Method A

To a soln. of intermediate lq (1 eq) in EtOH (5 to 12 mL/mmol) was added ammonium formate (2 eq) and 10% Pd/C moistened with ~50% water (0.05 eq) and the rxn mixture was heated to 65°C for a given time (see Table 46). It was filtered over a pad of celite and the filtrate was concentrated in vacuo. The crude was purified by CC using EtOAc/MeOH or DCM/MeOH.

Method B

To a soln. of intermediate lq (1 eq) in a mixture of EtOAc (65 mL/mmol) and MeOH (89 mL/mmol) was added 10% Pd/C moistened with ~50% water (0.1 eq) and the rxn mixture was hydrogenated under an atmospheric pressure of deuterium for a given time (see Table 46). It was filtered over a pad of celite and the filtrate was concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 46

Ir	Name	Reactant Iq	Method time [h]	t _R [min]	MS-data m/z [M+H] ⁺
Ir-1	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-methoxy-pyridazin-3-ylmethyl)-1,3-dihydro-benzoimidazol-2-one (Example 95)	lq-1	A 24	0.81	464.18
Ir-2	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(4-isopropoxy-pyridazin-3-ylmethyl)-4-methoxy-1,3-dihydro-benzoimidazol-2-one (Example 173)	lq-20	A 1	0.87	492.16
Ir-3	1-(1-(2,6-dimethylphenyl)piperidin-4-yl)-4-methoxy-3-(2-(trifluoromethyl)benzyl)-1,3-dihydro-benzoimidazol-2-one-7- <i>d</i> (Example 3)	lq-46	B 4.5	1.14	511.18

Synthesis of acid intermediates of formula E-1

To a soln. of intermediates Iq (1 eq) in a 1/1/1 mixture of THF/MeOH/water (9 mL/mmol) was added lithium hydroxide hydrate (4 eq). The rxn mixture was heated to 50°C and stirred for a given time (see Table 47). It was diluted with water and extracted with Et₂O (3x). The aq. phase was acidified until pH 2-3 with a 1M soln. of HCl and extracted with DCM (3x). The combined org. phases were dried over MgSO₄ and concentrated in vacuo.

Table 47

E-1	Name	Reactant Iq	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
E-1-1	1-[(R)-1-(2-cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid	lq-2	2	0.97	525.10

10 **Synthesis of compounds of formula Is**

To a soln. of acids of formula E-1 (1 eq) in DMF (4 mL/mmol) was added DIPEA (3 eq) and HATU (1 eq). The rxn mixture was stirred for 5 min at RT and the appropriate amine (1.2 eq) pure or as soln. was added. The rxn mixture was further stirred ON at RT (see Table 48) and diluted with DCM. The org. phase was washed with water and brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 48

Is	Name	Reactant E-1	Amine	t _R [min]	MS-data m/z [M+H] ⁺
Is-1	1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid methylamide (Example 99)	E-1-1	2M soln. of methylamine in THF	0.94	538.21
Is-2	1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid amide (Example 100)	E-1-1	0.5 M soln. of ammonia in dioxane	0.91	524.16
Is-3	1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid dimethylamide (Example 101)	E-1-1	2M soln. of dimethylamine in THF	0.98	552.21
Is-4	1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid (2-hydroxy-ethyl)-amide (Example 193)	E-1-1	Ethanolamine	0.88	568.04
Is-5	1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid (2-methoxy-ethyl)-amide (Example 194)	E-1-1	2-Methoxy ethylamine	0.95	582.1

Synthesis of compounds of formula It

To a soln. of compounds of formula Iq (1 eq) and CaCl₂ (0.3 eq) in EtOH (15 mL/mmol) was added at 0°C a suspension of NaBH₄ (2.5 eq) in EtOH (8 mL/mmol). The rxn mixture was allowed to warm to RT and stirred at that temperature for a given time (see Table 49). It was quenched with water and extracted with DCM (3x). The combined org. phases were dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 49

It	Name	Reactant lq	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
It-1	3-Fluoro-2-((R)-3-[4-hydroxymethyl-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl)-benzonitrile (Example 102)	lq-2	24	0.97	511.24

Synthesis of compounds of formula luMethod A (Reductive amination I)

- 5 To a stirred soln. of lc (1 eq) in a mixture of DCM (25 mL/mmol), MeOH (50 mL/mmol) and AcOH (1.2 eq) was added the appropriate amine (1.3 eq) followed by NaBH(OAc)₃ (1.4 eq). The rxn mixture was stirred at RT for a given time (see Table 50) and the volatiles were evaporated in vacuo. The residue was partitioned between DCM and a sat. aq. soln. of NaHCO₃. The org. phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified by prep. LC-MS using method 4 and 5.

10 Method B (Reductive amination II)

To a stirred soln. of aldehyde lc (1 eq) and the appropriate amine (1.1 eq) in THF (4 mL/mmol) was added NaBH(OAc)₃ (1.5 eq). The rxn mixture was stirred at RT for a given time (see Table 50) and partitioned between DCM and a 1M aq. soln. of NaOH. The org. phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified by prep. LC-MS using method 2.

15 **Table 50**

lu	Name	Reactant lc	Reactant amine	Method time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lu-1	1-[(R)-1-(2-Fluoro-6-methylaminomethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 103)	lc-5	2M soln. of methylamine in THF	A 1	0.86	529.27
lu-2	1-[(R)-1-(2-Dimethylaminomethyl-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 106)	lc-5	2M soln. of dimethylamine in THF	A 24	0.90	543.30

lu-3	1-[(R)-1-(2-Fluoro-6-[(2-hydroxy-ethyl)-methyl-amino]-methyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 107)	lc-5	2-(Methylamino)ethanol	A 24	0.86	573.28
lu-4	1-[(R)-1-(2-Azetidin-1-ylmethyl-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 108)	lc-5	Azetidine	A 18	0.91	555.25
lu-5	1-[(R)-1-(2-Fluoro-6-morpholin-4-ylmethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 115)	lc-5	Morpholine	A 24	0.90	585.14
lu-6	1-[(R)-1-(2-Fluoro-6-pyrrolidin-1-ylmethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 116)	lc-5	Pyrrolidine	A 2	0.93	569.16
lu-7	1-[(R)-1-[2-Fluoro-6-(4-methyl-piperazin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 132)	lc-5	1-Methyl piperazine	B 1.5	0.76	598.30
lu-8	1-[(R)-1-(2-Fluoro-6-piperidin-1-ylmethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 133)	lc-5	Piperidine	B 18	0.94	583.26
lu-9	1-[(R)-1-[2-Fluoro-6-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 134)	lc-5	4-Hydroxy piperidine	B 18	0.87	599.27

lu-10	1-[(R)-1-(2-Fluoro-6-piperazin-1-ylmethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 135)	lc-5	Piperazine	B 18	0.73	584.24
lu-11	1-[(R)-1-[2-(4-Dimethylamino-piperidin-1-ylmethyl)-6-fluoro-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 136)	lc-5	4-Dimethyl amino piperidine	B 18	0.73	626.30
lu-12	1-[(R)-1-[2-Fluoro-6-(4-methoxy-piperidin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 137)	lc-5	4-Methoxy piperidine	B 3.5	0.92	613.08
lu-13	1-[(R)-1-[2-Fluoro-6-(3-methoxy-pyrrolidin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 138)	lc-5	3-Methoxy pyrrolidine	B 3.5	0.92	599.07
lu-14	1-[(R)-1-(2-Fluoro-6-[(2-methoxy-ethyl)-methyl-amino]-methyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 139)	lc-5	N-(2-Methoxy ethyl) methylami ne	B 3.5	0.91	587.10
lu-15	1-[(R)-1-(2-[(Ethyl-(2-hydroxy-ethyl)-amino]-methyl)-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 140)	lc-5	2- (Ethylamin o)ethanol	B 3.5	0.87	587.40

lu-16	1-[(R)-1-(2-[[Bis-(2-hydroxy-ethyl)-amino]-methyl]-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 141)	lc-5	Diethanol amine	B 72	0.83	603.14
lu-17	1-((R)-1-{2-Fluoro-6-[(2-methoxy-1-methyl-ethylamino)-methyl]-phenyl}-pyrrolidin-3-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 142)	lc-5	2-Amino-1-methoxy propane	B 3.5	0.90	587.27
lu-18	1-((R)-1-[2-Fluoro-6-(3-methoxy-azetidin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 143)	lc-5	3-Methoxy azetidine	B 3.5	0.92	585.20

Synthesis of intermediates of formula D-1

A suspension of lj (1eq) in POCl₃ (2 mL/mmol) was heated to 85°C and stirred ON (see Table 51). The rxn mixture was carefully quenched with a ice cold 2M aq. soln. of NaOH and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 51

D-1	Name	Reactant lj	t _R [min]	MS-data m/z [M+H] ⁺
D-1-1	4-Chloro-1-[(R)-1-(2,6-dimethyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one	lj-6	1.06	501.09
D-1-2	4-Chloro-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one	lj-4	1.09	505.03

Synthesis of compounds of formula Iv

10 Method A (amine as solvent)

A soln. of D-1 (1 eq) in the appropriate amine (5 mL/mmol) was heated to a given temperature and stirred for a given time (see Table 52). The rxn mixture was diluted with EtOAc and washed with a sat. aq. soln. of NaHCO₃ (2x)

and with brine. The org. phase was dried over MgSO_4 and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method B (alcohol/KOH/DMSO)

To a stirred soln. of D-1 (1 eq) in DMSO (8 mL/mmol) was added the appropriate alcohol (5 to 10 eq) and KOH (2.5 eq). The rxn mixture was heated to a given temperature for a given time (see Table 52). It was diluted with EtOAc and washed with H_2O (3x) and brine. The org. phase was dried over MgSO_4 and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH.

Method C (Buchwald)

An oven dried flask was charged with intermediate D-1 (1 eq), the appropriate amine (1.2 eq), Cs_2CO_3 (2.5 eq) RuPhos precatalyst (0.1 eq) and RuPhos (0.1 eq). The flask was evacuated and refilled with argon (3x) and *t*-BuOH (17 mL/mmol) was added. The rxn mixture was degassed under vacuum, refilled with argon (3x) and heated to a given temperature and stirred for a given time (see Table 52). It was partitioned between water and EtOAc and the org. phase was washed with brine, dried over MgSO_4 and concentrated in vacuo. The crude was purified by prep. LC-MS using method 2 and 5.

Table 52

lv	Name	Reactant D-1	Reactant amine / alcohol	Method T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lv-1	1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-(2-hydroxy-ethylamino)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 118)	D-1-1	Ethanol amine	A 100 72 then 130 72	0.81	526.28
lv-2	1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-(2-hydroxy-ethoxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 119)	D-1-1	Ethylene glycol	B 50 2.5	0.97	527.17
lv-3	4-(2-Dimethylamino-ethoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 120)	D-1-2	Dimethyl amino ethanol	B 50 1.5	0.85	558.14

lv-4	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(2-morpholin-4-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 121)	D-1-2	4-(2-Hydroxyethyl)morpholine	B 50 1.5	0.85	600.11
lv-5	4-[1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-imidazo[4,5-c]pyridin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester (Example 122)	D-1-2	tert-Butyl 4-hydroxy-1-piperidine carboxylate	B 50 2	1.15	670.17
lv-6	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-[(2-hydroxy-ethyl)-methyl-amino]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 123)	D-1-2	2-(Methylamino)ethanol	A 120 48 then 130 120	0.86	544.22
lv-7	4-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 125)	D-1-2	2,2-Dimethyl-4-hydroxy methyl-1,3-dioxolane	B 50 4	1.10	601.34
lv-8	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(oxetan-3-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 127)	D-1-2	3-Hydroxy oxetane	B 80 72 then 50 120	1.08	543.20

lv-9	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-morpholin-4-yl-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 129)	D-1-2	Morpholine	A 100 770	0.97	556.25
lv-10	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(1-methyl-pyrrolidin-3-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 130)	D-1-2	1-Methyl-3-pyrrolidinol	B 50 2	0.85	570.13
lv-11	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(3-methoxy-azetidin-1-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 205)	D-1-2	3-Methoxyazetidine hydrochloride	C 110 2	0.91	556.13
lv-12	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(4-methyl-piperazin-1-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 206)	D-1-2	1-Methylpiperazine	A 120 48 140 120	0.82	569.14
lv-13	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(2-methoxy-ethylamino)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 207)	D-1-2	2-Methoxyethylamine	A 140 144	0.87	544.15

Synthesis of intermediates of formula D-2

A suspension of (methoxymethyl)triphenylphosphonium chloride (1.2 eq) in anh. THF (12.5 mL/mmol) was cooled to -78°C. A 1.6 M soln. of n-butyllithium in hexanes (1.2 eq) was dropwise added at -78°C and the mixture was stirred for 30 min at -78°C. A solution of aldehyde lc (1 eq) in anh. THF (6.25 mL/mmol) was dropwise added at -78°C and the rxn mixture was stirred for a given time (see Table 53) at RT. It was quenched with a sat. aq. soln. of NH₄Cl and extracted with DCM (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using DCM/MeOH and/or by prep. LC-MS using method 1.

Table 53

D-2	Name	Reactant lc	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
D-2-1	1-((R)-1-[2-Fluoro-6-((E)-2-methoxy-vinyl)-phenyl]-pyrrolidin-3-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one	lc-5	18	1.08-1.09	542.27

Synthesis of compounds of formula lw

To a soln. of enol ether D-2 (1 eq) in anh. THF (8.7 mL/mmol) was added a 5M aq. soln. of HCl (1.8 mL/mmol) and the rxn mixture was heated to 70°C and stirred for a given time (see Table 54). The mixture was diluted with Et₂O and washed with H₂O and a sat. aq. soln. of NaHCO₃. The org. phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using DCM/MeOH.

Table 54

lw	Name	Reactant D-2	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lw-1	(3-Fluoro-2-((R)-3-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidin-1-yl)-phenyl)-acetaldehyde (Example 126)	D-2-1	0.6	0.89	528.13

10 **Synthesis of compounds of formula lx**Method A (Boc cleavage)

To a solution of intermediate lv (1 eq) in DCM (4 mL/mmol) was added dropwise TFA (1 mL/mmol) and the rxn mixture was stirred at RT for a given time (see Table 55). It was basified with a 1M solution of NaOH until pH 12-13 and extracted with DCM (3x). The combined org. phases were dried over MgSO₄ and concentrated in vacuo. The crude was purified by prep. LC-MS using method 4.

Method B (ketal cleavage)

To a soln. of ketal lv or lk (1 eq) in anh. THF (9 mL/mmol) was added a 25% aq. soln. of HCl (3 mL/mmol) at 0°C and the rxn mixture was stirred for a given time (see Table 55) at RT. The rxn mixture was quenched with a sat. aq. soln. of NaHCO₃ and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 55

lx	Name	Reactant lv or lk	Method time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lx-1	1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(piperidin-4-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 124)	lv-5	A 1.5	0.83	570.27
lx-2	4-(2,3-Dihydroxy-propoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (Example 128)	lv-7	B 1	0.94	561.21
lx-3	4-(2,3-Dihydroxy-propoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 152)	lk-4	B 18	0.94	560.10

Synthesis of compounds of formula ly

- To a stirred soln. of lw (1 eq) in DCM (4 mL/mmol) was added AcOH (1.5 eq) and the appropriate amine (1.1 eq) followed by NaBH(OAc)₃ (1.5 eq). The rxn mixture was stirred at RT for a given time (see Table 56) and partitioned between DCM and a sat. aq. soln. of NaHCO₃. The org. phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using EtOAc/MeOH.

Table 56

ly	Name	Reactant lw	Reactant amine	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
ly-1	1-[(R)-1-[2-Fluoro-6-(2-morpholin-4-yl-ethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 131)	lw-1	morpholine	2	0.89	599.32

10 **Synthesis of compounds of formula lz**

To a stirred suspension of alcohol ln (1 eq) in THF (15 mL/mmol) was added at 0°C NaH (5 eq). The mixture was stirred for 10 min and the corresponding halide (1.5 eq) was added. The rxn mixture was allowed to reach RT and stirred at a given temperature for a given time (see Table 57). It was quenched with water and extracted with DCM

(3x). The combined org. phases were dried over MgSO_4 and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH.

Table 57

lz	Name	Reactant In	Reactant halide	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lz-1	1-[(R)-1-[2-Fluoro-6-(1-methoxy-ethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 148)	In-1	Methyl iodide	RT 4	1.09	543.92

5

Synthesis of compounds of formula laa

To a soln. of intermediate lc (1 eq) in EtOAc (3 mL/mmol) was added 10% Pd/C moistened with ~50% water (0.01 eq) and the rxn mixture was hydrogenated under atmospheric pressure for a given time (see Table 58). It was filtered over a pad of celite and the filtrate was concentrated in vacuo. The crude was purified by CC using

10

Table 58

laa	Name	Reactant lc	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
laa-1	1-[(R)-1-(2-Amino-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 155)	lc-10	1	1.01	501.03

Synthesis of compounds of formula lab

A stirred soln. of aniline laa (1 eq) in a 48% aq. soln. of HBr (2.7 mL/mmol) was cooled to -20°C and a soln. of NaNO_2 (1 eq) in H_2O (0.4 mL/mmol) was dropwise added. The mixture was stirred for 30 min at 0°C and a soln. of CuBr (0.55 eq) in a 48% aq. soln. of HBr (0.8 mL/mmol) was dropwise added. The rxn mixture was heated to 60°C and stirred for a given time (see Table 59). The pH was adjusted to around 7 by the addition of a 2M aq. soln. of NaOH and the mixture was extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO_4 and concentrated in vacuo. The crude was purified by prep. LC-MS using method 1.

15

Table 59

lab	Name	Reactant laa	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lab-1	1-[(R)-1-(2-Bromo-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 156)	laa-1	1	1.11	563.96

Synthesis of compounds of formula lac

To a degassed mixture of bromide laa (1 eq) and alkyne (1.6 eq) in anh. THF (24 mL/mmol) was added under argon CuI (0.06 eq), bis(tri-tert-butylphosphine)palladium(0) (0.05 eq) and DBU (1.3 eq). The mixture was heated to 70°C and stirred for 2h (see Table 60). The volatiles were evaporated off and the residue was purified by prep. LC-MS using method 3.

Table 60

lac	Name	Reactant lab	Reactant alkyne	t _R [min]	MS-data m/z [M+H] ⁺
lac-1	1-[(R)-1-[2-Fluoro-6-(3-morpholin-4-yl-prop-1-ynyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 159)	lab-1	4-(Prop-2-yn-1-yl)morpholine	0.87	609.04

10 **Synthesis of compounds of formula lad**

To a soln. of alkyne lac (1 eq) in EtOAc (3 mL/mmol) was added 10% Pd/C moistened with ~50% water (0.01 eq) and the rxn mixture was hydrogenated under atmospheric pressure for a given time (see Table 61). It was filtered over a pad of celite and the filtrate was concentrated in vacuo. The crude was purified by prep. LC-MS using method 5.

15 **Table 61**

lad	Name	Reactant lac	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lad-1	1-[(R)-1-[2-Fluoro-6-(3-morpholin-4-yl-propyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 162)	lac-1	7	0.87	613.09

Synthesis of compounds of formula lae

A soln. of alcohol In (1 eq) in DCM (3 mL/mmol) was cooled to 0°C and thionyl chloride (1.1 eq) was dropwise added. The rxn mixture was stirred for 30 min at RT and the volatiles were evaporated off. The residue was taken in DCM (5 mL/mmol) and TEA (5 eq) followed by the appropriate amine (1.1 eq) were added at 0°C. The mixture was allowed to warm to RT and stirred for a given time (see Table 62). It was diluted with DCM and washed with a 1M aq. soln. of NaOH. The org. phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified by prep. LC-MS using method 2 and 5.

Table 62

lae	Name	Reactant In	Reactant amine	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lae-1	1-((R)-1-{2-Fluoro-6-[1-(3-methoxy-azetidin-1-yl)-ethyl]-phenyl}-pyrrolidin-3-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 163)	In-1	3-Methoxy azetidine	4	0.91/0.93	599.04

Synthesis of intermediates of formula E-2

To a soln. of carboxylic ester Iq (1 eq) in THF (7.2 mL/mmol) was added a 2M aq. soln. of NaOH (10 eq) and the rxn mixture was stirred at RT for a given time (see Table 63). It was acidified with a 1M aq. soln. of HCl until pH~4-5 and extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 63

E-2	Name	Reactant Iq	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
E-2-1	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(2-hydroxy-benzyl)-4-methoxy-1,3-dihydro-benzoimidazol-2-one	Iq-45	4	1.09	462.11

Synthesis of compounds of formula Iaf**Method A (NaH / THF)**

To a stirred suspension of phenol E-2 (1 eq) in THF (15 mL/mmol) was added at 0°C NaH (5 eq). The mixture was stirred for 10 min and the corresponding halide (1.5 eq) was added. The rxn mixture was stirred at a given temperature for a given time (see Table 64). It was quenched with water and extracted with EtOAc (3x). The combined org. phases were dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method B (K₂CO₃ / DMF)

To a stirred soln. of phenol E-2 (1 eq) in anh. DMF (8 mL/mmol) was added K₂CO₃ (2 eq) and the corresponding halide (2 eq). The rxn mixture was stirred for a given time and a given temperature (see Table 64). Additional amount of halide (3 x 2 eq) were added to bring the rxn to completion. It was partitioned between EtOAc and H₂O and the org. phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 64

Iaf	Name	Reactant E-2	Reactant halide	Method T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
Iaf-1	3-(2-Cyclopropylmethoxy-benzyl)-1-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one (Example 224)	E-2-1	(Bromo methyl) cyclo propane	A 60°C 18h	1.14	516.20
Iaf-2	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-[2-(oxetan-3-yloxy)-benzyl]-1,3-dihydro-benzimidazol-2-one (Example 225)	E-2-1	3-Bromo oxetane	B up to 90°C 120	1.08	518.17
Iaf-3	3-(2-Cyclobutoxy-benzyl)-1-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one (Example 226)	E-2-1	Bromo cyclo butane	B up to 100°C 120	1.15	516.18

Synthesis of intermediates of formula C-2

To a soln. of methyl carbamate BB-10 (1 eq) in MeCN (4.3 mL/mmol) was added K₂CO₃ (2.2 eq) and the corresponding halide (1.05 eq). The rxn mixture was heated to a given temperature and stirred for a given time

(see Table 65). It was filtered and the filtrate was concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 65

C-2	Name	Reactant BB-10	Reactant halide	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
C-2-1	(3-Bromo-5-methoxy-pyridin-4-yl)- (2-trifluoromethyl-benzyl)-carbamic acid methyl ester	BB-10-1	2- (Trifluoromethyl) ethyl benzyl bromide	80 2	1.09	419.05

5 Synthesis of compounds of formula lag

Sodium tert-butoxide (6 eq), BrettPhos precatalyst (0.3 eq) and BrettPhos (0.3 eq) were placed in a sealed cap vial and a soln. of intermediate C-2 (3 eq) and amine BB-4 (1 eq) in anh. dioxane were added. The rxn mixture was flushed with N₂, heated at a given temperature and stirred for a given time (see Table 66). It was quenched with water and extracted with DCM (3x). The combined org. phases were dried over MgSO₄ and concentrated in vacuo.

10 The crude was purified by prep. LC-MS using method 1.

Table 66

lag	Name	Reactant C-2	Reactant BB-4	T [°C] time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lag-1	3-[1-(2-Fluoro-6-methyl-phenyl)- piperidin-4-yl]-7-methoxy-1-(2- trifluoromethyl-benzyl)-1,3-dihydro- imidazo[4,5-c]pyridin-2-one (Example 229)	C-2-1	BB-4-2	80 2	1.01	515.23

Synthesis of compounds of formula lah

To a soln. of intermediate lb (1 eq) in EtOH (20 mL/mmol) was added 20% palladium hydroxide on carbon (0.1 eq) and the rxn mixture was hydrogenated under atmospheric pressure for a given time (see Table 67). It was filtered over a pad of celite and the filtrate was concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

15

Table 67

lah	Name	Reactant lb	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lah-1	1-[1-(2-Hydroxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 230)	lb-62	96	0.83	498.02

Synthesis of compounds of formula lai

To a soln. of intermediate lah (1 eq) and alcohol R¹⁵-OH (1 to 1.5 eq) in toluene (10 mL/mmol) was added a 1M soln. of (tributylphosphoranylidene)acetonitrile in toluene (2 eq) under argon. The rxn mixture was heated to 110°C and stirred for a given time (see Table 68). It was quenched with water and extracted with DCM (3x). The combined org. phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH. When necessary, an additional purification by prep. LC-MS using method 5 can be performed.

Table 68

lai	Name	Reactant lah	Alcohol R ¹⁵ -OH	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
lai-1	1-(1-{2-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-phenyl}-piperidin-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one	lah-1	2-(t-Butyl dimethylsiloxy) ethanol	4.5	1.00	656.18
lai-2	4-Methoxy-1-[1-[2-(tetrahydro-pyran-4-yloxy)-phenyl]-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 239)	lah-1	Tetrahydro-2H-pyran-4-ol	4.5	0.89	582.17
lai-3	1-[1-(2-Cyclopropylmethoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 240)	lah-1	Hydroxymethyl cyclopropane	4.5	0.92	552.20

lai-4	1-[1-(2-Cyclobutoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 241)	lah-1	Cyclobutanol	4.5	0.91	552.11
lai-5	4-Methoxy-1-{1-[2-(oxetan-3-yloxy)-phenyl]-piperidin-4-yl}-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 242)	lah-1	Oxetan-3-ol	18	0.88	554.18
lai-6	1-[1-(2-Butoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 243)	lah-1	1-Butanol	18	0.94	554.22

Synthesis of compounds of formula lai

To a soln. of lai (1 eq) in THF (20 mL/mmol) was added dropwise a 1M soln. of TBAF in THF (1.2 eq) and the rxn mixture was stirred at RT for a given time (see Table 69). It was partitioned between EtOAc and a sat. aq. soln. of NaHCO₃. The org. phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified by prep. LC-MS using method 6.

Table 69

laij	Name	Reactant lai	time [h]	t _R [min]	MS-data m/z [M+H] ⁺
laij-1	1-{1-[2-(2-Hydroxy-ethoxy)-phenyl]-piperidin-4-yl}-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one (Example 238)	lai-1	18	0.82	542.18

II. Biological Assays

10 In vitro assay

hC5a DISCO IC₅₀ assay

Adherent cells (CHO-K1 C5AR1 beta-arrestin cell line, DiscoverX, CA USA) are washed with PBS, detached by incubation with Dissociation Buffer (Gibco Cat# 13151-014, 2 ml per 165 cm² dish) for 3 minutes, then washed with 10 ml PBS (without Mg⁺⁺ and Ca⁺⁺) and counted. 7'500 cells/384-well are seeded out in 384-well plates (Cell

culture plate MTP384 white Polystyrene, Corning, Cat# 3570) in 20 μ l/well Cell plating medium (F12 HAMs/10% FCS/1% P/S) and incubated at 37°C / 5% CO₂ / 24h.

5 μ l Antagonist at 6-fold end concentration or DMSO control is added to assay medium and subsequently 5 μ l 1 - 10 nM C5a agonist at 6 fold end concentration. Cells are centrifuged for 1 min at 1000 rpm and incubated for 1.5 hour in at 37°C. Plates are equilibrated at room temperature for several minutes before adding 12 μ l/well Detection Reagent (PathHunter Detection Kit, DiscoverX, Cat# 93-0001). Plates are centrifuged for 1 min at 1000 rpm and incubated for 45 minutes at RT before being measured on a Fluostar Optima, BMG Labtech. IC₅₀ values are calculated from a serial dilution range of antagonist using inhouse software and given in nmol/l.

10 The calculated IC₅₀ values may fluctuate depending on the daily cellular assay performance. Fluctuations of this kind are known to those skilled in the art. Average IC₅₀ values from several measurements are given as geometric mean values.

Antagonistic activities of exemplified compounds are displayed in Table 70 below.

Table 70: list of examples and their antagonistic activities

Example Number	Compound N°	C5aR IC ₅₀ (nM)	Example Number	Compound N°	C5aR IC ₅₀ (nM)	Example Number	Compound N°	C5aR IC ₅₀ (nM)
1	la-1	621	85	lz-1	712	169	lq-18	17
2	lb-1	18	86	lg-9	229	170	lq-19	45
3	lr-3	23	87	lc-7	629	171	lq-6	64
4	lb-2	131	88	lm-1	39	172	lq-20	275
5	lb-3	284	89	ln-1	44	173	lr-2	107
6	la-2	66	90	lo-1	38	174	lq-21	544
7	lb-4	11	91	lp-1	70	175	lq-22	221
8	lb-5	14	92	lq-1	2024	176	lq-23	48
9	lb-6	32	93	lj-6	149	177	lq-24	24
10	lb-7	23	94	lj-7	313	178	lq-25	49
11	lb-8	29	95	lr-1	191	179	la-15	122
12	lb-9	10	96	lq-7	231	180	lq-26	9
13	lb-10	16	97	lq-8	1351	181	lq-27	22
14	lc-1	216	98	lq-2	165	182	lq-28	9
15	lb-11	13	99	ls-1	391	183	lq-29	14
16	lb-12	19	100	ls-2	1428	184	lb-49	36

17	lb-13	22	101	ls-3	1580	185	lb-50	36
18	lb-14	13	102	lt-1	759	186	lq-30	14
19	lb-15	12	103	lu-1	669	187	lq-31	26
20	la-3	36	104	lq-3	863	188	la-16	313
21	ld-1	3442	105	lq-4	4483	189	lq-32	13
22	lb-16	30	106	lu-2	227	190	lb-51	118
23	lb-17	8	107	lu-3	1318	191	la-17	114
24	le-1	330	108	lu-4	360	192	lq-33	42
25	lf-1	185	109	lc-8	61	193	ls-4	632
26	lg-1	459	110	lb-45	6	194	ls-5	1485
27	lh-1	3344	111	lq-9	264	195	lq-34	20
28	lh-2	1326	112	lq-10	511	196	la-18	139
29	lg-2	182	113	lq-11	2240	197	lb-52	74
30	lh-3	1523	114	lq-12	1543	198	lb-53	15
31	li-1	3454	115	lu-5	21	199	la-19	119
32	li-2	642	116	lu-6	165	200	lb-54	19
33	lb-18	8	117	lq-13	308	201	lb-55	31
34	lb-19	27	118	lv-1	201	202	lq-35	2
35	li-3	4510	119	lv-2	12	203	lq-36	6
36	lb-20	450	120	lv-3	659	204	lb-56	30
37	lb-21	7	121	lv-4	270	205	lv-11	45
38	lb-22	470	122	lv-5	509	206	lv-12	2298
39	la-4	2434	123	lv-6	42	207	lv-13	508
40	lj-1	6	124	lx-1	5220	208	lq-37	19
41	lb-23	18	125	lv-7	124	209	lq-38	34
42	lb-24	75	126	lw-1	20	210	la-20	2294
43	la-5	393	127	lv-8	17	211	lb-57	27
44	lj-2	13	128	lx-2	207	212	lb-58	2079
45	lb-25	16	129	lv-9	53	213	la-22	469
46	lb-26	39	130	lv-10	3908	214	la-21	205

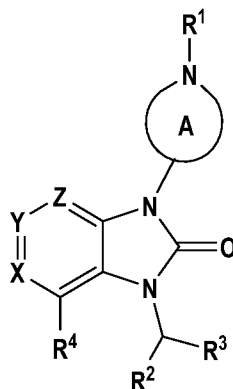
47	lb-27	95	131	ly-1	53	215	lb-59	27
48	lb-28	165	132	lu-7	314	216	lq-39	12
49	lb-29	132	133	lu-8	70	217	lb-60	158
50	lb-30	42	134	lu-9	2265	218	lq-40	346
51	lb-31	62	135	lu-10	5764	219	lq-41	34
52	lk-1	30	136	lu-11	1586	220	lq-42	109
53	la-7	1845	137	lu-12	133	221	lq-43	175
54	lb-32	43	138	lu-13	156	222	lh-4	2651
55	lb-33	178	139	lu-14	227	223	lq-44	130
56	lj-3	717	140	lu-15	1034	224	laf-1	18
57	lj-4	89	141	lu-16	2128	225	laf-2	40
58	lb-34	25	142	lu-17	108	226	laf-3	36
59	lb-35	49	143	lu-18	108	227	lb-61	30
60	lg-3	84	144	la-12	312	228	la-23	259
61	lg-4	65	145	lc-9	16	229	lag-1	268
62	lg-5	99	146	la-13	201	230	lah-1	129
63	lg-6	729	147	lb-46	20	231	lb-62	66
64	la-10	2916	148	lz-1	28	232	lb-63	82
65	la-8	396	149	lk-2	14	233	lb-64	195
66	lb-36	60	150	lk-3	11	234	lb-65	17
67	lb-37	36	151	lk-4	31	235	lb-66	28
68	lb-38	84	152	lx-3	38	236	lb-67	171
69	lc-2	2819	153	lq-14	215	237	lb-68	90
70	lg-7	538	154	lc-10	23	238	laj-1	133
71	lc-3	133	155	laa-1	15	239	lai-2	82
72	lg-8	397	156	lab-1	21	240	lai-3	46
73	lb-39	272	157	lc-11	630	241	lai-4	36
74	lb-40	1330	158	lc-12	683	242	lai-5	74
75	lb-41	27	159	lac-1	73	243	lai-6	61
76	lb-42	38	160	lb-47	35	244	lb-69	227

161

77	lb-43	89	161	lb-48	69	245	lb-70	111
78	lb-44	121	162	lad-1	135	246	lb-71	39
79	ld-2	911	163	lae-1	591	247	lb-72	563
80	le-2	157	164	la-14	179	248	lb-73	182
81	lj-5	2427	165	lq-15	6	249	lb-74	273
82	lc-4	28	166	lq-5	17	250	lb-75	853
83	lc-5	23	167	lq-16	6			
84	lc-6	2035	168	lq-17	10			

Claims

1. A compound of formula (I)



Formula (I)

5 wherein

- ring **A** represents a saturated 4- to 7-membered mono-cyclic carbocyclic ring containing the ring nitrogen atom to which **R**¹ is attached, wherein said ring independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from (C₁₋₃)alkyl, fluoro, or (C₁₋₄)alkoxy-carbonyl; or
- ring **A** represents a saturated 7- or 8-membered bridged bi-cyclic carbocyclic ring containing the ring nitrogen atom to which **R**¹ is attached, wherein said ring is unsubstituted;

X and **Z** independently represent CR⁵ or N; and **Y** represents CR⁵; or, in case both **X** and **Z** represent CH, **Y** may in addition represent N; wherein each **R**⁵ independently represents hydrogen, or (C₁₋₃)alkyl;

R¹ represents

- (C₁₋₄)alkyl;
- -CO-**R**¹¹ wherein **R**¹¹ represents (C₁₋₄)alkyl; (C₁₋₄)alkoxy; phenyl, phenoxy; (C₃₋₆)cycloalkyl; or (C₃₋₆)cycloalkoxy optionally containing one ring oxygen and optionally mono-substituted with methyl or trifluoromethyl;
- benzyl wherein the phenyl ring of said benzyl is optionally mono- or di-substituted with halogen; or
- phenyl, or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from
 - (C₁₋₄)alkyl;
 - (C₁₋₄)alkoxy;
 - (C₁₋₃)fluoroalkyl;
 - (C₁₋₃)fluoroalkoxy;
 - halogen;
 - cyano;
 - nitro;
 - hydroxy;

- hydroxy-(C₁₋₃)alkyl;
- (C₁₋₄)alkoxy-(C₁₋₃)alkyl;
- hydroxy-(C₂₋₃)alkoxy;
- (C₁₋₄)alkoxy-(C₂₋₃)alkoxy;
- 5 ➤ (C₃₋₆)cycloalkyl-**X**¹²-, wherein **X**¹² represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen;
- **R**¹³-CO-**X**¹³-, wherein **X**¹³ represents a direct bond or (C₁₋₃)alkylene, and **R**¹³ represents hydrogen or (C₁₋₄)alkyl);
- 3-(morpholin-4-yl)-prop-1-ynyl;
- 10 ➤ **R**^{14a}**R**^{14b}N-**X**¹⁴-, wherein **X**¹⁴ represents a direct bond or (C₁₋₃)alkylene; and wherein **R**^{14a} and **R**^{14b} independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R**^{14a} and **R**^{14b} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl, hydroxy, (C₁₋₄)alkoxy, or dimethylamino; or
- 15 ➤ benzyloxy, wherein the phenylring of benzyloxy is optionally mono- or di-substituted with halogen or methyl;

R² 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

- (C₁₋₄)alkyl;
- 20 ➤ (C₁₋₄)alkoxy;
- (C₁₋₃)fluoroalkyl;
- (C₁₋₃)fluoroalkoxy;
- halogen; or
- (C₃₋₆)cycloalkyl-**X**²¹-, wherein **X**²¹ represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen;
- 25

R³ represents hydrogen, or (C₁₋₃)alkyl; and

R⁴ represents

- (C₁₋₄)alkyl;
- hydroxy-(C₁₋₃)alkyl;
- 30 • -O-**R**⁴¹, wherein **R**⁴¹ represents
 - hydrogen;
 - (C₁₋₄)alkyl;
 - (C₂₋₄)alkyl which is substituted with one or two hydroxy;
 - **R**^{41a}**R**^{41b}N-(C₂₋₃)alkylene-, wherein **R**^{41a} and **R**^{41b} independently represent hydrogen or (C₁₋₄)alkyl; or
 - 35 ➤ (C₄₋₇)heterocyclyl-**X**⁴¹-, wherein **X**⁴¹ represents a direct bond or (C₁₋₃)alkylene, and wherein the (C₄₋₇)heterocyclyl independently contains one or two ring heteroatoms independently selected from

nitrogen and oxygen; wherein said (C₄₋₇)heterocyclyl independently is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from:

- (C₁₋₄)alkyl; and/or
 - (C₁₋₄)alkoxy-carbonyl attached to a ring nitrogen atom having a free valency;
- 5 • -NR^{42a}R^{42b} wherein R^{42a} and R^{42b} independently represent hydrogen, (C₁₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₃)alkyl, hydroxy-(C₂₋₃)alkyl, or R^{42a} and R^{42b} together with the nitrogen to which they are attached form a 4- to 7-membered saturated ring optionally containing one further ring heteroatom selected from oxygen and nitrogen, wherein said ring is unsubstituted or mono-substituted with (C₁₋₃)alkyl or (C₁₋₃)alkoxy; or
- 10 • -CO-R⁴³ wherein R⁴³ represents (C₁₋₄)alkoxy, or -NR^{43a}R^{43b} wherein R^{43a} and R^{43b} independently represent hydrogen, (C₁₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₃)alkyl or hydroxy-(C₂₋₃)alkyl;
- or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

- ring **A** represents a saturated 4- to 7-membered mono-cyclic carbocyclic ring containing the ring nitrogen atom to which R¹ is attached, wherein said ring independently is unsubstituted, or mono-substituted with (C₁₋₃)alkyl, fluoro, or (C₁₋₄)alkoxy-carbonyl, or di-substituted wherein the substituents are two (C₁₋₃)alkyl substituents, or two fluoro substituents; or
 - ring **A** represents a saturated 7- or 8-membered bridged bi-cyclic carbocyclic ring containing the ring nitrogen atom to which R¹ is attached, wherein said ring is unsubstituted;
- 20 or a pharmaceutically acceptable salt thereof.

3. A compound according to claims 1 or 2; wherein ring **A** represents a saturated 4- to 7-membered mono-cyclic carbocyclic ring containing the ring nitrogen atom to which R¹ is attached, wherein said ring independently is unsubstituted, or mono-substituted with (C₁₋₃)alkyl, fluoro, or (C₁₋₄)alkoxy-carbonyl, or di-substituted wherein the substituents are two (C₁₋₃)alkyl substituents, or two fluoro substituents, or a pharmaceutically acceptable salt thereof.

4. A compound according to any one of claims 1 to 3; wherein

- **X** represents CR⁵; **Z** represents CR⁵; and **Y** represents CR⁵; wherein each R⁵ independently represents hydrogen, or (C₁₋₃)alkyl; wherein preferably at maximum one R⁵ is different from hydrogen;
- **X** represents CH; **Z** represents N; and **Y** represents CR⁵; wherein each R⁵ independently represents hydrogen, or (C₁₋₃)alkyl;
- **X** represents N; **Z** represents CR⁵; and **Y** represents CR⁵; wherein each R⁵ independently represents hydrogen or (C₁₋₃)alkyl; wherein preferably at maximum one R⁵ is different from hydrogen;
- **X** represents N; **Z** represents N; and **Y** represents CR⁵; wherein R⁵ represents hydrogen, or (C₁₋₃)alkyl;

or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 4; wherein one of **X** and **Z** represents CH or N; the other represents CH; and **Y** represents CR⁵, wherein **R**⁵ represents hydrogen or (C₁₋₃)alkyl; or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 5;

wherein **R**¹ represents

- (C₁₋₄)alkyl;
- 10 • -CO-**R**¹¹ wherein **R**¹¹ represents (C₁₋₄)alkyl; (C₁₋₄)alkoxy; phenyl, phenoxy; or (C₃₋₆)cycloalkoxy optionally containing one ring oxygen and optionally mono-substituted with methyl or trifluoromethyl;
- benzyl wherein the phenyl ring of said benzyl is optionally mono- or di-substituted with halogen;
- phenyl which is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from
- 15 ➤ (C₁₋₄)alkyl;
- (C₁₋₄)alkoxy;
- (C₁₋₃)fluoroalkyl;
- (C₁₋₃)fluoroalkoxy;
- halogen;
- 20 ➤ cyano;
- nitro;
- hydroxy;
- hydroxy-(C₁₋₃)alkyl;
- (C₁₋₄)alkoxy-(C₁₋₃)alkyl;
- 25 ➤ hydroxy-(C₂₋₃)alkoxy;
- (C₁₋₄)alkoxy-(C₂₋₃)alkoxy;
- (C₃₋₆)cycloalkyl-**X**¹²-, wherein **X**¹² represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen;
- **R**¹³-CO-**X**¹³-, wherein **X**¹³ represents a direct bond or (C₁₋₃)alkylene, and **R**¹³ represents hydrogen or (C₁₋₄)alkyl;
- 30 ➤ 3-(morpholin-4-yl)-prop-1-ynyl;
- **R**^{14a}**R**^{14b}N-**X**¹⁴-, wherein **X**¹⁴ represents a direct bond or (C₁₋₃)alkylene; and wherein **R**^{14a} and **R**^{14b} independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R**^{14a} and **R**^{14b} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is
- 35 optionally mono-substituted with (C₁₋₄)alkyl, hydroxy, (C₁₋₄)alkoxy, or dimethylamino;

- benzyloxy; or
- 5- or 6-membered heteroaryl; wherein said 5- or 6-membered heteroaryl independently is mono-, di- or tri-substituted, wherein the substituents are independently selected from
 - (C₁₋₄)alkyl;
 - (C₁₋₄)alkoxy;
 - (C₁₋₃)fluoroalkyl;
 - (C₁₋₃)fluoroalkoxy;
 - halogen;
 - cyano;
 - (C₃₋₆)cycloalkyl-**X**¹², wherein **X**¹² represents a direct bond, -O-, or -(C₁₋₃)alkylene-O; or
 - **R**¹³-CO-**X**¹³-, wherein **X**¹³ represents a direct bond or (C₁₋₃)alkylene, and **R**¹³ represents hydrogen or (C₁₋₄)alkyl;

or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 6; wherein

R¹ represents

- -CO-**R**¹¹ wherein **R**¹¹ represents (C₁₋₄)alkyl; or (C₁₋₄)alkoxy;
- phenyl which is mono-, or di- or tri-substituted, wherein the substituents are independently selected from
 - (C₁₋₄)alkyl;
 - (C₁₋₄)alkoxy;
 - (C₁₋₃)fluoroalkyl;
 - (C₁₋₃)fluoroalkoxy;
 - halogen;
 - cyano;
 - nitro;
 - hydroxy-(C₁₋₃)alkyl;
 - (C₁₋₄)alkoxy-(C₁₋₃)alkyl;
 - hydroxy-(C₂₋₃)alkoxy;
 - (C₁₋₄)alkoxy-(C₂₋₃)alkoxy;
 - (C₃₋₆)cycloalkyl-**X**¹²-, wherein **X**¹² represents a direct bond, -O-, or -(C₁₋₃)alkylene-O;
 - **R**^{14a}**R**^{14b}N-**X**¹⁴-, wherein **X**¹⁴ represents a direct bond or (C₁₋₃)alkylene; and wherein **R**^{14a} and **R**^{14b} independently represent hydrogen, (C₁₋₄)alkyl, hydroxy-(C₂₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₄)alkyl; or **R**^{14a} and **R**^{14b} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally containing one additional ring heteroatom selected from oxygen and nitrogen; and wherein said ring is optionally mono-substituted with (C₁₋₄)alkyl, hydroxy, (C₁₋₄)alkoxy, or dimethylamino; or

- 5- or 6-membered heteroaryl; wherein said 5- or 6-membered heteroaryl independently is mono-, di- or tri-substituted, wherein the substituents are independently selected from
 - (C₁₋₄)alkyl;
 - (C₁₋₄)alkoxy;
 - 5 ➤ (C₁₋₃)fluoroalkyl;
 - halogen;
 - cyano; or
 - (C₃₋₆)cycloalkyl-**X**¹², wherein **X**¹² represents a direct bond;

or a pharmaceutically acceptable salt thereof.

10

8. A compound according to any one of claims 1 to 7; wherein **R**² represents phenyl, or 6-membered heteroaryl; wherein said phenyl or 6-membered heteroaryl independently is mono-, or di-substituted, wherein the substituents are independently selected from

- (C₁₋₄)alkyl;
- 15 ➤ (C₁₋₄)alkoxy;
- (C₁₋₃)fluoroalkyl;
- (C₁₋₃)fluoroalkoxy;
- halogen; or
- (C₃₋₆)cycloalkyl-**X**²¹, wherein **X**²¹ represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen;
- 20

or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 8; wherein **R**² represents phenyl, or 6-membered heteroaryl; wherein said phenyl or 6-membered heteroaryl is mono-substituted in *ortho* position with regard to the point of attachment of the rest of the molecule, wherein the substituent is independently selected from

- (C₁₋₄)alkyl;
- (C₁₋₄)alkoxy;
- (C₁₋₃)fluoroalkyl;
- (C₁₋₃)fluoroalkoxy; or
- 30 ➤ (C₃₋₆)cycloalkyl-**X**²¹, wherein **X**²¹ represents a direct bond, -O-, or -(C₁₋₃)alkylene-O-, and wherein the (C₃₋₆)cycloalkyl independently contains one optional ring oxygen;

or a pharmaceutically acceptable salt thereof.

10. A compound according to any one of claims 1 to 9; wherein

R^4 represents

- (C_{1-4}) alkyl;
- hydroxy- (C_{1-3}) alkyl;
- 5 • -O- R^{41} , wherein R^{41} represents
 - hydrogen;
 - (C_{1-4}) alkyl;
 - (C_{2-4}) alkyl which is substituted with one or two hydroxy;
 - $R^{41a}R^{41b}N-(C_{2-3})$ alkylene-, wherein R^{41a} and R^{41b} independently represent hydrogen or (C_{1-4}) alkyl; or
 - 10 ➤ (C_{4-7}) heterocyclyl- X^{41} -, wherein X^{41} represents a direct bond or (C_{1-3}) alkylene, and wherein the (C_{4-7}) heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen and oxygen; wherein the oxygen atom of such group (C_{4-7}) heterocyclyl- X^{41} -O- is separated by at least two (ring and/or chain) carbon atoms from such ring heteroatom; wherein said (C_{4-7}) heterocyclyl independently is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently
 - 15 selected from:
 - (C_{1-4}) alkyl; and/or
 - (C_{1-4}) alkoxy-carbonyl attached to a ring nitrogen atom having a free valency;
- - $NR^{42a}R^{42b}$ wherein R^{42a} represents hydrogen or (C_{1-4}) alkyl, and R^{42b} independently represents hydrogen, (C_{1-4}) alkyl, (C_{1-3}) alkoxy- (C_{2-3}) alkyl, hydroxy- (C_{2-3}) alkyl, or R^{42a} and R^{42b} together with the nitrogen to which they
 - 20 are attached form a 4- to 7-membered saturated ring optionally containing one further ring heteroatom selected from oxygen and nitrogen, wherein said ring is unsubstituted or mono-substituted with (C_{1-3}) alkyl, or (C_{1-3}) alkoxy; or
- -CO- R^{43} wherein R^{43} represents (C_{1-4}) alkoxy; or - $NR^{43a}R^{43b}$ wherein R^{43a} represents hydrogen or (C_{1-4}) alkyl, and R^{43b} independently represents hydrogen, (C_{1-4}) alkyl, (C_{1-3}) alkoxy- (C_{2-3}) alkyl, or hydroxy- (C_{2-3}) alkyl;
- 25 or a pharmaceutically acceptable salt thereof.

11. A compound according to any one of claims 1 to 10; wherein

R^4 represents

- (C_{1-4}) alkyl;
- 30 • hydroxy- (C_{1-3}) alkyl;
- -O- R^{41} , wherein R^{41} represents
 - hydrogen;
 - (C_{1-4}) alkyl;
 - (C_{2-4}) alkyl which is substituted with one or two hydroxy;
 - 35 ➤ $R^{41a}R^{41b}N-(C_{2-3})$ alkylene-, wherein R^{41a} and R^{41b} independently represent hydrogen or (C_{1-4}) alkyl; or

- (C₄₋₇)heterocyclyl-**X**⁴¹-, wherein **X**⁴¹ represents a direct bond or -CH₂-, and wherein the (C₄₋₇)heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen and oxygen; wherein the oxygen atom of such group (C₄₋₇)heterocyclyl-**X**⁴¹-O- is separated by at least two (ring and/or chain) carbon atoms from such ring heteroatom; wherein said (C₄₋₇)heterocyclyl independently is unsubstituted, or mono-substituted with (C₁₋₄)alkyl at a ring nitrogen atom having a free valency, or di-substituted with methyl;
- -NR^{42a}R^{42b} wherein **R**^{42a} represents hydrogen or (C₁₋₄)alkyl, and **R**^{42b} independently represents (C₁₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₃)alkyl, hydroxy-(C₂₋₃)alkyl; or **R**^{42a} and **R**^{42b} together with the nitrogen to which they are attached form a 4- to 7-membered saturated ring optionally containing one further ring heteroatom selected from oxygen and nitrogen, wherein said ring is unsubstituted, or mono-substituted with (C₁₋₃)alkyl attached to a ring nitrogen atom having a free valency, or (C₁₋₃)alkoxy attached to a ring carbon; or
 - -CO-**R**⁴³ wherein **R**⁴³ represents (C₁₋₄)alkoxy; or -NR^{43a}R^{43b} wherein **R**^{43a} represents hydrogen or (C₁₋₄)alkyl, and **R**^{43b} independently represents hydrogen, (C₁₋₄)alkyl, (C₁₋₃)alkoxy-(C₂₋₃)alkyl, or hydroxy-(C₂₋₃)alkyl;
- or a pharmaceutically acceptable salt thereof.

12. A compound according to claim 1 selected from the group consisting of:

- 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester;
- 1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-(1-(2,6-dimethylphenyl)piperidin-4-yl)-4-methoxy-3-(2-(trifluoromethyl)benzyl)-1,3-dihydro-benzoimidazol-2-one-7-d;
- 4-Methoxy-1-(1-phenyl-piperidin-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[1-(2,4-Dichloro-benzyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 1-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[1-(2,6-Dimethoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[1-(2-Fluoro-6-methoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 4-Methoxy-1-[1-(2-methoxy-6-methyl-phenyl)-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;

- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 3-Cyclopropyl-5-{4-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-piperidin-1-yl}-1-methyl-1H-pyrazole-4-carbaldehyde;
- 5 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-Methoxy-1-[(R)-1-(2-methoxy-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2,6-Dimethoxy-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 10 4-Methoxy-1-[(R)-1-(2-methoxy-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methoxy-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 15 (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethoxy-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 1-[1-(5-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethoxy-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 20 2-one;
- 1-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethoxy-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(4-Chloro-5-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 25 1-[1-(5-Cyclopropyl-2,4-dimethyl-2H-pyrazol-3-yl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid methyl ester;
- 1-[(R)-1-Benzoyl-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 30 1-[1-(2,2-Dimethyl-propionyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid methyl ester;
- 1-(1-Benzoyl-piperidin-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 35 4-Methoxy-1-[(R)-1-methyl-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-Isopropyl-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

- 4-Methoxy-1-[(R)-1-(2-methoxy-4-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(3,5-Difluoro-pyridin-4-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 5 1-(1-Isopropyl-piperidin-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(3,5-Dimethyl-pyridin-4-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-4-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 10 1-[(R)-1-(3,5-Dimethoxy-pyridin-4-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-imidazo[4,5-c]pyridin-1-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-hydroxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 15 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 20 (R)-3-[7-Methoxy-2-oxo-1-(2-trifluoromethyl-benzyl)-1,2-dihydro-imidazo[4,5-b]pyridin-3-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-hydroxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 3-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-7-methoxy-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one;
- 25 3-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-7-methoxy-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one;
- 4-Methoxy-1-[(R)-1-(2-methoxy-4-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 30 1-[(R)-1-(2-Fluoro-4-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methoxy-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 35 4-Methoxy-1-[(R)-1-(2-methoxy-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;

- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-(2-hydroxy-ethoxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-[4-Methoxy-2-oxo-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester;
- 5 1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methoxy-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione;
- 10 c]pyridine-2,4-dione;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione;
- 1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 15 1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid ethyl ester;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid isopropyl ester;
- 20 (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid butyl ester;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid phenyl ester;
- 25 4-[4-Methoxy-2-oxo-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester;
- (R)-3-[4-Methoxy-3-(2-methoxy-benzyl)-2-oxo-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 1-[(R)-1-(2,4-Dimethyl-pyridin-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 30 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2,6-Difluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(5-Isopropyl-[1,3,4]oxadiazol-2-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 35 (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidine-1-carboxylic acid 3-methyl-oxetan-3-yl ester;

- 5-[(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-1,3-dimethyl-1H-pyrazole-4-carbaldehyde;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid oxetan-3-yl ester;
- 5 1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-4-ylmethyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-4-ylmethyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-
- 10 benzoimidazol-2-one;
- 1-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 15 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2,5-Dimethyl-2H-pyrazol-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(4-Chloro-2,5-dimethyl-2H-pyrazol-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-
- 20 benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-methoxy-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione;
- 3-Fluoro-2-[(R)-3-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile;
- 25 3-Fluoro-2-[(R)-3-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzaldehyde;
- 4-Methoxy-3-(2-trifluoromethyl-benzyl)-1-[(R)-1-(5-trifluoromethyl-[1,3,4]oxadiazol-2-yl)-pyrrolidin-3-yl]-1,3-dihydro-benzoimidazol-2-one;
- 4-Methoxy-3-(2-trifluoromethyl-benzyl)-1-[(R)-1-(2,4,5-trimethyl-2H-pyrazol-3-yl)-pyrrolidin-3-yl]-1,3-dihydro-
- 30 benzoimidazol-2-one;
- (R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidine-1-carboxylic acid 3-trifluoromethyl-oxetan-3-yl ester;
- 5-[(R)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-1,3-dimethyl-1H-pyrazole-4-carbonitrile;
- 35 1-[(R)-1-(2-Fluoro-6-hydroxymethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;

- 1-[(R)-1-[2-Fluoro-6-(1-hydroxy-ethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Acetyl-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 5 1-[(R)-1-[2-Fluoro-6-(1-hydroxy-1-methyl-ethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 3-(6-Chloro-4-methoxy-pyridazin-3-ylmethyl)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione;
- 10 1-[(R)-1-(2-Methoxy-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-3,5-dihydro-1H-imidazo[4,5-c]pyridine-2,4-dione;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-methoxy-pyridazin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 15 3-Fluoro-2-{4-[4-methoxy-2-oxo-3-(3-trifluoromethyl-pyrazin-2-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-piperidin-1-yl}-benzonitrile;
- 3-Fluoro-2-{4-[4-methoxy-3-(3-methoxy-pyrazin-2-ylmethyl)-2-oxo-2,3-dihydro-benzimidazol-1-yl]-piperidin-1-yl}-benzonitrile;
- 1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid methyl ester;
- 20 1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid methylamide;
- 1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid amide;
- 25 1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzimidazole-4-carboxylic acid dimethylamide;
- 3-Fluoro-2-{(R)-3-[4-hydroxymethyl-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-pyrrolidin-1-yl}-benzonitrile;
- 1-[(R)-1-(2-Fluoro-6-methylaminomethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 30 3-Fluoro-2-{(R)-3-[6-methoxy-8-oxo-7-(2-trifluoromethyl-benzyl)-7,8-dihydro-purin-9-yl]-pyrrolidin-1-yl}-benzonitrile;
- 3-Fluoro-2-{(R)-3-[6-methoxy-7-(2-methoxy-benzyl)-8-oxo-7,8-dihydro-purin-9-yl]-pyrrolidin-1-yl}-benzonitrile;
- 1-[(R)-1-(2-Dimethylaminomethyl-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 35 1-[(R)-1-(2-Fluoro-6-[[2-hydroxy-ethyl]-methyl-amino]-methyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

- 1-[(R)-1-(2-Azetidin-1-ylmethyl-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 3-Fluoro-2-[(R)-3-[4-methoxy-3-(2-methoxy-benzyl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile;
- 5 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methoxy-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 3-Fluoro-2-[(R)-3-[4-methoxy-2-oxo-3-(3-trifluoromethyl-pyrazin-2-ylmethyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile;
- 3-Fluoro-2-[(R)-3-[4-methoxy-3-(3-methoxy-pyrazin-2-ylmethyl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile;
- 10 3-Fluoro-2-[4-[4-methoxy-3-(4-methoxy-pyrimidin-5-ylmethyl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-piperidin-1-yl]-benzonitrile;
- 3-Fluoro-2-[(R)-3-[4-methoxy-3-(4-methoxy-pyrimidin-5-ylmethyl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile;
- 15 1-[(R)-1-(2-Fluoro-6-morpholin-4-ylmethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-pyrrolidin-1-ylmethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 3-Fluoro-2-[4-[4-methoxy-2-oxo-3-(4-trifluoromethyl-pyrimidin-5-ylmethyl)-2,3-dihydro-benzoimidazol-1-yl]-piperidin-1-yl]-benzonitrile;
- 20 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-(2-hydroxy-ethylamino)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-4-(2-hydroxy-ethoxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 25 4-(2-Dimethylamino-ethoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(2-morpholin-4-yl-ethoxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 4-[1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-imidazo[4,5-c]pyridin-4-yloxy]-piperidine-1-carboxylic acid tert-butyl ester;
- 30 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-[(2-hydroxy-ethyl)-methyl-amino]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(piperidin-4-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 35 4-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;

- (3-Fluoro-2-((R)-3-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl)-phenyl)-acetaldehyde;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(oxetan-3-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 5 4-(2,3-Dihydroxy-propoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-morpholin-4-yl-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(1-methyl-pyrrolidin-3-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 10 1-[(R)-1-[2-Fluoro-6-(2-morpholin-4-yl-ethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-[2-Fluoro-6-(4-methyl-piperazin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 15 1-[(R)-1-(2-Fluoro-6-piperidin-1-ylmethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-[2-Fluoro-6-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-piperazin-1-ylmethyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 20 1-[(R)-1-[2-(4-Dimethylamino-piperidin-1-ylmethyl)-6-fluoro-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-[2-Fluoro-6-(4-methoxy-piperidin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 25 1-[(R)-1-[2-Fluoro-6-(3-methoxy-pyrrolidin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-[[[2-methoxy-ethyl]-methyl-amino]-methyl]-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-[[[Ethyl-(2-hydroxy-ethyl)-amino]-methyl]-6-fluoro-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 30 1-[(R)-1-(2-[[[Bis-(2-hydroxy-ethyl)-amino]-methyl]-6-fluoro-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-[2-Fluoro-6-[(2-methoxy-1-methyl-ethylamino)-methyl]-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 35 1-[(R)-1-[2-Fluoro-6-(3-methoxy-azetidin-1-ylmethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;

- 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-2-methyl-piperidine-1-carboxylic acid tert-butyl ester;
- 3-Fluoro-2-{4-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-2-methyl-piperidin-1-yl}-benzaldehyde;
- 5 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzoimidazol-1-yl]-3-methyl-piperidine-1-carboxylic acid tert-butyl ester;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-3-methyl-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-[2-Fluoro-6-(1-methoxy-ethyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 10 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(oxetan-3-yloxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(2-hydroxy-ethoxy)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 15 4-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 4-(2,3-Dihydroxy-propoxy)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 3-Fluoro-2-[(R)-3-[4-methoxy-2-oxo-3-(4-trifluoromethyl-pyrimidin-5-ylmethyl)-2,3-dihydro-benzoimidazol-1-yl]-pyrrolidin-1-yl]-benzonitrile;
- 20 1-[(R)-1-(2-Fluoro-6-nitro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Amino-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 25 1-[(R)-1-(2-Bromo-6-fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(4,5-Dichloro-pyridazin-3-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(3,5-Dichloro-pyridazin-4-yl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 30 1-[(R)-1-(2-Fluoro-6-(3-morpholin-4-yl-prop-1-ynyl)-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-morpholin-4-yl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;
- 35 1-[(R)-1-[2-Fluoro-6-(3-morpholin-4-yl-propyl)-phenyl]-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzoimidazol-2-one;

- 1-((R)-1-(2-Fluoro-6-[1-(3-methoxy-azetidin-1-yl)-ethyl]-phenyl)-pyrrolidin-3-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester;
- 5 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(2-isopropoxy-benzyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(2-isopropoxy-benzyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(3-trifluoromethyl-pyrazin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 10 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyrazin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(3-methoxy-pyrazin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 15 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-methoxy-pyrazin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 3-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-7-methoxy-5-methyl-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one;
- 3-(6-Chloro-4-isopropoxy-pyridazin-3-ylmethyl)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 20 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(4-isopropoxy-pyridazin-3-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-methyl-pyridazin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 25 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-methoxy-pyrimidin-5-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-trifluoromethyl-pyrimidin-5-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(3-isopropoxy-pyrazin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 30 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(3-isopropoxy-pyrazin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-azepane-1-carboxylic acid tert-butyl ester;
- 35 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(4-isopropyl-pyridin-3-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;

- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(4-isopropyl-pyridin-3-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(3-isopropoxy-pyridin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 5 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(3-isopropoxy-pyridin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-azepan-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2,6-Dimethyl-phenyl)-azepan-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 10 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(4-isopropyl-pyrimidin-5-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(3-isopropyl-pyrazin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 5-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester;
- 15 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-3-(3-isopropyl-pyrazin-2-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[2-(2-Fluoro-6-methyl-phenyl)-2-aza-bicyclo[2.2.1]hept-5-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 20 6-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-3-aza-bicyclo[3.1.1]heptane-3-carboxylic acid tert-butyl ester;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(4-isopropyl-pyrimidin-5-ylmethyl)-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-
- 25 benzoimidazole-4-carboxylic acid (2-hydroxy-ethyl)-amide;
- 1-[(R)-1-(2-Cyano-6-fluoro-phenyl)-pyrrolidin-3-yl]-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-1H-benzoimidazole-4-carboxylic acid (2-methoxy-ethyl)-amide;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 30 (3R*,4S*)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 1-[3-(2-Fluoro-6-methyl-phenyl)-3-aza-bicyclo[3.1.1]hept-6-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(3R*,4S*)-1-(2-Fluoro-6-methyl-phenyl)-4-methyl-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-
- 35 dihydro-benzimidazol-2-one;
- (3R*,4R*)-3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester;

- 1-[(3R*,4R*)-1-(2-Fluoro-6-methyl-phenyl)-4-methyl-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-Methoxy-1-[(R)-1-(2-trifluoromethoxy-phenyl)-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 5 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(4-trifluoromethyl-pyridin-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 4-Methoxy-1-[(R)-1-[2-(2-methoxy-ethoxy)-phenyl]-pyrrolidin-3-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 10 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(3-methoxy-azetidin-1-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(4-methyl-piperazin-1-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 15 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-(2-methoxy-ethylamino)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 3-(2-Cyclopropoxy-benzyl)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 3-(2-Cyclopropoxy-benzyl)-1-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 20 3-Fluoro-4-[4-methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester;
- 1-[3-Fluoro-1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 25 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-azetidine-1-carboxylic acid tert-butyl ester;
- 3-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester;
- 30 1-[1-(2-Fluoro-6-methyl-phenyl)-azetidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 35 1-[1-(2,6-Dimethyl-phenyl)-piperidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-trifluoromethyl-thiazol-4-ylmethyl)-1,3-dihydro-benzimidazol-2-one;

- 1-[1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-[(S)-1-(2-trifluoromethyl-phenyl)-ethyl]-1,3-dihydro-benzimidazol-2-one;
- 3-(2,4-Difluoro-6-isopropoxy-benzyl)-1-[(R)-1-(2-fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 5 1-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-4-methoxy-3-(2-methyl-4-trifluoromethyl-thiazol-5-ylmethyl)-1,3-dihydro-benzimidazol-2-one;
- 1-(1-Cyclopropanecarbonyl-piperidin-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 3-(2-Cyclopropyl-benzyl)-1-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 10 3-(2-Cyclopropylmethoxy-benzyl)-1-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-3-[2-(oxetan-3-yloxy)-benzyl]-1,3-dihydro-benzimidazol-2-one;
- 3-(2-Cyclobutoxy-benzyl)-1-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methoxy-1,3-dihydro-benzimidazol-2-one;
- 15 1-[1-(2-Fluoro-6-methyl-phenyl)-3,3-dimethyl-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-3,3-dimethyl-piperidine-1-carboxylic acid tert-butyl ester;
- 20 3-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methoxy-1-(2-trifluoromethyl-benzyl)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-[1-(2-Hydroxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-[1-(2-Benzyloxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-Methoxy-1-(3'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 25 4-Methoxy-1-(3'-methoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 4-Methoxy-1-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 30 1-(2'-Fluoro-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-(3'-Fluoro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 1-(2',4'-Dimethyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;
- 35 1-[1-[2-(2-Hydroxy-ethoxy)-phenyl]-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

4-Methoxy-1-[1-[2-(tetrahydro-pyran-4-yloxy)-phenyl]-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

1-[1-(2-Cyclopropylmethoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

5 1-[1-(2-Cyclobutoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

4-Methoxy-1-[1-[2-(oxetan-3-yloxy)-phenyl]-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

1-[1-(2-Butoxy-phenyl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

10 1-(4'-Fluoro-2'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methyl-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

15 4-[4-Methoxy-2-oxo-3-(2-trifluoromethyl-benzyl)-2,3-dihydro-benzimidazol-1-yl]-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-2'-carbonitrile;

4-Methoxy-1-(4'-methoxy-2'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

1-(2',4'-Dimethoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one;

20 4-Methoxy-1-[1-(4-methoxy-6-methyl-pyrimidin-5-yl)-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one; or

1-[1-(4,6-Dimethoxy-pyrimidin-5-yl)-piperidin-4-yl]-4-methoxy-3-(2-trifluoromethyl-benzyl)-1,3-dihydro-benzimidazol-2-one ;

or a pharmaceutically acceptable salt thereof.

25

13. A pharmaceutical composition comprising, as active principle, a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

14. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use as a medicament.

30 **15.** A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in the prevention or treatment of vasculitic diseases or disorders, inflammatory diseases or disorders involving intravascular microvesicle release, immune complex (IC) diseases or disorders, neurodegenerative diseases or disorders, complement related inflammatory diseases or disorders, bullous diseases or disorders, diseases or disorders related to ischemia and/or ischemic reperfusion injury, inflammatory bowel diseases or disorders,
35 autoimmune diseases or disorders, or cancer.

16. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of deleterious consequences of contact sensitivity and inflammation caused by contact with artificial surfaces; the prevention or treatment of increased leukocyte and platelet activation (and infiltration to tissues thereof); the prevention or treatment of pathologic sequelae associated to an intoxication or an injury such as a trauma, an hemorrhage, a shock, or surgery including transplantation; the prevention or treatment of pathologic sequelae associated with insulin-dependent diabetes mellitus; the prevention of / the reduction of the risk of myocardial infarction or thrombosis; prevention or treatment of edema or increased capillary permeability; or the prevention of / the reduction of coronary endothelial dysfunction induced by cardiopulmonary bypass and/or cardioplegia.

17. Use of a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the prevention or treatment of vasculitic diseases or disorders; inflammatory diseases or disorders involving intravascular microvesicle release, immune complex (IC) diseases or disorders; neurodegenerative diseases or disorders; complement related inflammatory diseases or disorders; bullous diseases or disorders; diseases or disorders related to ischemia and/or ischemic reperfusion injury; inflammatory bowel diseases or disorders; cancers; autoimmune diseases or disorders; deleterious consequences of contact sensitivity and inflammation caused by contact with artificial surfaces; increased leukocyte and platelet activation (and infiltration to tissues thereof); pathologic sequelae associated to an intoxication or an injury such as a trauma, an hemorrhage, a shock, or surgery including transplantation; pathologic sequelae associated with insulin-dependent diabetes mellitus; the risk of myocardial infarction or thrombosis; edema or increased capillary permeability; or coronary endothelial dysfunction induced by cardiopulmonary bypass and/or cardioplegia.

18. A method of treatment of vasculitic diseases or disorders; inflammatory diseases or disorders involving intravascular microvesicle release, immune complex (IC) diseases or disorders; neurodegenerative diseases or disorders; complement related inflammatory diseases or disorders; bullous diseases or disorders; diseases or disorders related to ischemia and/or ischemic reperfusion injury; inflammatory bowel diseases or disorders; autoimmune diseases or disorders; cancer; deleterious consequences of contact sensitivity and inflammation caused by contact with artificial surfaces; increased leukocyte and platelet activation (and infiltration to tissues thereof); pathologic sequelae associated to an intoxication or an injury such as a trauma, an hemorrhage, a shock, or surgery including transplantation; pathologic sequelae associated with insulin-dependent diabetes mellitus; the risk of myocardial infarction or thrombosis; edema or increased capillary permeability; or coronary endothelial dysfunction induced by cardiopulmonary bypass and/or cardioplegia; comprising administering to a patient an effective amount of a compound of formula (I) as defined in any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/051230

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/04 C07D487/04 A61K31/4439 A61K31/437 A61P25/00
A61P35/00 A61P37/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/05770 A1 (FUJISAWA PHARMACEUTICAL CO [JP]; SAWADA KOZO [JP]; INOUE TAKAYUKI [JP]) 25 January 2001 (2001-01-25) pages 65, 71, 73, 92, 102, 103, 110: compounds (4), (27), (39), (18), (19), (60), (61), (94); page 22, line 28; examples 8-28 -----	1-18
A	WO 03/103669 A1 (SCHERING CORP [US]) 18 December 2003 (2003-12-18) pages 35-36, compounds 1T-1Z; page 1, line 19; claims -----	1-18
A	WO 03/037890 A2 (ICAGEN INC [US]; GROSS MICHAEL FRANCIS [US]; ATKINSON ROBERT NELSON [U]) 8 May 2003 (2003-05-08) page 28; examples ----- -/-	1-18

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

4 April 2019

Date of mailing of the international search report

16/04/2019

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Beyss-Kahana, Ellen

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/051230

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2013/079327 A1 (YAMAMOTO SHINGO [JP] ET AL) 28 March 2013 (2013-03-28) paragraph [0002]; examples -----	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2019/051230

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0105770	A1	25-01-2001	BR	0013041	A	16-07-2002
			CA	2379554	A1	25-01-2001
			CN	1374952	A	16-10-2002
			EP	1196391	A1	17-04-2002
			HU	0202186	A2	28-12-2002
			JP	2003505376	A	12-02-2003
			KR	20020020788	A	15-03-2002
			MX	PA02000340	A	21-06-2002
			TR	200200161	T2	21-05-2002
			US	6582351	B1	24-06-2003
			WO	0105770	A1	25-01-2001

WO 03103669	A1	18-12-2003	AR	040406	A1	06-04-2005
			AT	529112	T	15-11-2011
			AU	2003223631	A1	22-12-2003
			CA	2482551	A1	18-12-2003
			CN	1658875	A	24-08-2005
			EP	1494671	A1	12-01-2005
			IL	164583	A	17-05-2010
			JP	4563800	B2	13-10-2010
			JP	2005529161	A	29-09-2005
			JP	2006206603	A	10-08-2006
			KR	20040099449	A	26-11-2004
			MX	PA04010172	A	03-02-2005
			NZ	535764	A	26-10-2007
			PE	04642004	A1	24-07-2004
			TW	200305409	A	01-11-2003
			US	2004048843	A1	11-03-2004
			WO	03103669	A1	18-12-2003
			ZA	200407985	B	19-10-2005

WO 03037890	A2	08-05-2003	CA	2465328	A1	08-05-2003
			EP	1451173	A2	01-09-2004
			US	2003171360	A1	11-09-2003
			US	2008058376	A1	06-03-2008
			WO	03037890	A2	08-05-2003

US 2013079327	A1	28-03-2013	AU	2011260961	A1	10-01-2013
			BR	112012030711	A2	01-11-2016
			CA	2800523	A1	08-12-2011
			CN	102918040	A	06-02-2013
			CY	1118088	T1	28-06-2017
			DK	2578585	T3	14-11-2016
			EP	2578585	A1	10-04-2013
			EP	3112368	A1	04-01-2017
			ES	2592152	T3	28-11-2016
			HK	1178882	A1	18-08-2017
			HR	P20161027	T1	04-11-2016
			HU	E030720	T2	28-06-2017
			IL	223361	A	30-11-2015
			JP	5648686	B2	07-01-2015
			JP	5924393	B2	25-05-2016
			JP	6176353	B2	09-08-2017
			JP	2015052000	A	19-03-2015
			JP	2016185954	A	27-10-2016
			JP	W02011152351	A1	01-08-2013
			KR	20130109941	A	08-10-2013
			LT	2578585	T	10-10-2016

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2019/051230

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		NZ 603643 A	25-07-2014
		PL 2578585 T3	31-01-2017
		PT 2578585 T	23-09-2016
		RU 2012157072 A	20-07-2014
		SG 185617 A1	28-12-2012
		SG 10201503991S A	30-07-2015
		SM T201600360 B	10-11-2016
		TW 201209057 A	01-03-2012
		TW 201533046 A	01-09-2015
		US 2013079327 A1	28-03-2013
		US 2013217880 A1	22-08-2013
		US 2015094299 A1	02-04-2015
		US 2017313705 A1	02-11-2017
		US 2018170933 A1	21-06-2018
		WO 2011152351 A1	08-12-2011
		ZA 201208900 B	25-09-2013
