

1-(Piperazin-1-yl)-2-([1,2,4]triazol-1-yl)-ethanone derivatives

The present invention relates to novel 1-(piperazin-1-yl)-2-([1,2,4]triazol-1-yl)-ethanone derivatives of Formula (I), and their use as pharmaceuticals. The invention also concerns
5 related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of Formula (I), and especially their use as CXCR3 receptor modulators.

Chemokine receptors are a group of G-protein coupled receptors (GPCRs) that bind peptidic chemokine ligands with high affinity. The predominant function of chemokine
10 receptors is to guide leukocyte trafficking to lymphoid organs and tissues under resting conditions as well as during inflammation, but a role for certain chemokine receptors on non-hematopoietic cells and their progenitors has also been recognized.

The chemokine receptor CXCR3 is a G-protein coupled receptor binding to the inflammatory chemokines CXCL9 (initially called MIG, monokine induced by interferon- γ [INF- γ]), CXCL10 (IP-10, INF- γ -inducible protein 10), and CXCL11 (I-TAC, INF- γ -inducible T
15 cell α chemo-attractant). CXCR3 is mainly expressed on activated T helper type 1 (Th1) lymphocytes, but is also present on natural killer cells, macrophages, dendritic cells and a subset of B lymphocytes. The three CXCR3 ligands are expressed mainly under inflammatory conditions, expression in healthy tissue is very low. Cells that can express
20 CXCR3 ligands, for instance after exposure to inflammatory cytokines such as interferon- γ or TNF- α , include diverse stromal cells such as endothelial cells, fibroblasts, epithelial cells, keratinocytes but also includes hematopoietic cells such as macrophages and monocytes. The interaction of CXCR3 and its ligands (henceforth referred to as the CXCR3 axis) is involved in guiding receptor bearing cells to specific locations in the body, particularly to
25 sites of inflammation, immune injury and immune dysfunction and is also associated with tissue damage, the induction of apoptosis, cell growth, and angiostasis. CXCR3 and its ligands are upregulated and highly expressed in diverse pathological situations including autoimmune disorders, inflammation, infection, transplant rejection, fibrosis, neurodegeneration and cancer.

A role of the CXCR3 axis in autoimmune disorders is corroborated by several preclinical and clinical observations. Autoimmune disorders in which histological analysis of inflammatory lesions or serum levels of patients revealed elevated levels of CXCR3 ligands or increased numbers of CXCR3 positive cells include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), lupus nephritis, multiple sclerosis (MS), inflammatory bowel
35 disease (IBD; comprising Crohn's disease and ulcerative colitis), and type I diabetes mellitus (Groom, J. R. & Luster, A. D. Immunol Cell Biol 2011, 89, 207; Groom, J. R. &

Luster, A. D. *Exp Cell Res* 2011, 317, 620; Lacotte, S., Brun, S., Muller, S. & Dumortier, H. *Ann N Y Acad Sci* 2009, 1173, 310). As expression of CXCR3 ligands is very low in healthy tissue, the above cited correlative evidence strongly suggest a role for CXCR3 in human autoimmune diseases.

- 5 Preclinical disease models performed with CXCR3 deficient mice, mice deficient for one of the CXCR3 ligands or the use of antibodies blocking the function of either CXCR3 or one of its ligands further corroborate a role for the CXCR3 axis in immune pathology. For instance, it has been shown that mice deficient for either CXCR3 or the CXCR3 ligand CXCL9 show reduced pathology in a model for lupus nephritis (Menke, J. *et al. J Am Soc*
- 10 *Nephrol* 2008, 19, 1177). In an animal model for another form of kidney inflammation, interstitial cystitis, administration of an antibody blocking CXCL10 function was shown to reduce pathology in cyclophosphamide-induced cystitis (Sakthivel, S. K. *et al. J Immune Based Ther Vaccines* 2008, 6, 6). Similarly, blocking CXCL10 with an antibody reduced pathology in a rat model of rheumatoid arthritis (Mohan, K. & Issekutz, T. B. *J Immunol*
- 15 2007, 179, 8463). Similarly, in a murine model of inflammatory bowel disease, a blocking antibody against CXCL10 could prevent pathology in a therapeutic setting (Singh, U. P. *et al. J Interferon Cytokine Res* 2008, 28, 31). Further, experiments performed with tissue from CXCR3 deficient mice suggests a role for CXCR3 in celiac disease, another autoimmune type disorder (Lammers, K. M. *et al. Gastroenterology* 2008, 135, 194).
- 20 Inflammatory diseases that are associated with an elevated expression of the CXCR3 axis include chronic obstructive pulmonary disorder (COPD), asthma, sarcoidosis, atherosclerosis and myocarditis (Groom, J. R. & Luster, A. D. *Immunol Cell Biol* 2011, 89, 207; Groom, J. R. & Luster, A. D. *Exp Cell Res* 2011, 317, 620).

One study has shown that CXCR3 positive cells are increased in the lungs of smokers with

25 COPD compared to healthy subjects and immunoreactivity for the CXCR3-ligand CXCL10 was present in the bronchiolar epithelium of smokers with COPD but not in the bronchiolar epithelium of smoking and nonsmoking control subjects (Saetta, M. *et al. Am J Respir Crit Care Med* 2002, 165, 1404). These findings suggest that the CXCR3 axis may be involved in the immune cell recruitment that occurs in peripheral airways of smokers with COPD. In

30 agreement with these observations, a preclinical study of COPD revealed an attenuation of acute lung inflammation induced by cigarette smoke in CXCR3 deficient mice (Nie, L. *et al. Respir Res* 2008, 9, 82).

In one investigation of atherosclerosis, CXCR3 expression was found on all T cells within human atherosclerotic lesions. CXCR3 ligands CXCL9, CXCL10 and CXCL11 were all

35 found in endothelial and smooth muscle cells associated with those lesions, suggesting that they are involved in the recruitment and retention of CXCR3 positive cells, particularly

activated T lymphocytes, observed within vascular wall lesions during atherogenesis (Mach, F. *et al.* J Clin Invest 1999, 104, 1041).

Preclinical studies further support a role of CXCR3 in the development of atherosclerosis. CXCR3 genetic deletion in mice lacking ApoE results in a significantly reduced
5 atherosclerotic lesion development within abdominal aortas (Veillard, N. R. *et al.* Circulation 2005, 112, 870).

A pivotal role for the CXCR3 axis has also been suggested in rejection reactions after organ transplantation and bone marrow transplantation related toxicity (Groom, J. R. & Luster, A. D. Exp Cell Res 2011, 317, 620.). Preclinically, CXCR3 deficient mice show a significant
10 resistance to allograft rejection (Hancock, W. W. *et al.* J Exp Med 2000, 192, 1515).

CXCR3 ligand plasma concentrations also positively correlate with diverse liver pathologies, including liver cirrhosis and fibrosis in humans (Tacke, F., *et al.* Liver Int 2011, 31, 840).

In the field of oncology, blocking the CXCR3 axis has been proposed to help limit the metastatic spread of cancer cells. For instance, administration of the small molecule
15 CXCR3 receptor antagonist AMG487 could limit the metastasis of tumor cells to the lungs (Pradelli, E. *et al.* Int J Cancer 2009, 125, 2586). Functional evidence for a role of CXCR3 in regulating B-cell chronic lymphocytic leukemia (CLL) was reported by Trentin and coworkers (Trentin, L. *et al.* J Clin Invest 1999, 104, 115).

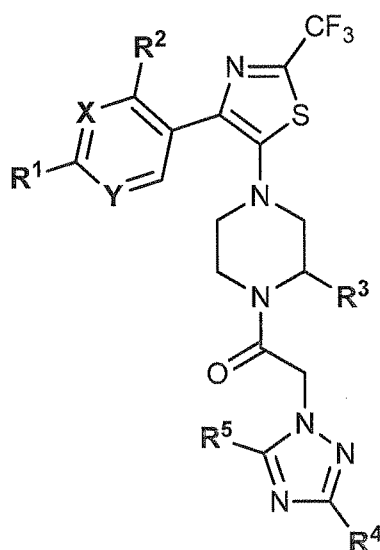
In the central nervous system, blocking the CXCR3 axis may have beneficial effects and
20 prevent neurodegeneration. Increased expression of CXCL10 in the CNS has been demonstrated in ischemia, Alzheimer's disease, multiple sclerosis (MS), and human immunodeficiency virus (HIV)-encephalitis. For example, ex vivo experiments have shown that tissue derived from either CXCR3 or CXCL10 deficient mice, neuronal cell death was diminished after neurotoxic NMDA-treatment when compared to tissue derived from wild
25 type mice (van Weering, H. R. *et al.* Hippocampus 2011, 21, 220). In a study looking to indentify drug-like molecules that provide neuroprotection against HTT fragment-induced neurodegeneration in a model for Huntington's disease, two CXCR3 receptor antagonists were identified (Reinhart, P. H. *et al.* Neurobiol Dis 2011, 43, 248.)

Different 1-(piperazin-1-yl)-2-heteroaryl-ethanone derivatives have been disclosed in WO
30 2010/126811. A more detailed structure-activity-relationship with respect to important drug-related properties of such compounds has been discussed on a poster presentation (A. Prokopowicz *et al.*, *Optimization of a biaryl series of CXCR3 antagonists*, 244th ACS National Meeting, Philadelphia, US, August 19-23, 2012). 4-(Benzoimidazol-2-yl)-thiazole derivatives have been disclosed in WO 2013/114332.

35 It has now been found that particular 2-([1,2,4]triazol-1-yl)-1-[4-(2-trifluoromethyl-thiazol-5-yl)-piperazin-1-yl]-ethanone derivatives have surprisingly high plasma concentrations after

oral administration and are potent CXCR3 modulators which may be useful for the treatment of diseases that are mediated or sustained through the CXCR3 axis, including autoimmune disorders (e.g. rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, systemic lupus erythematosus, lupus nephritis, interstitial cystitis, celiac disease), inflammatory disorders (e.g. asthma, COPD, atherosclerosis, myocarditis, sarcoidosis), transplantation rejection, fibrosis (e.g. liver cirrhosis), neurodegeneration and conditions involving neuronal death (e.g. Alzheimer's disease, Huntington's disease), and cancer.

1) In a first embodiment, the present invention relates to compounds of Formula (I)



Formula (I)

wherein

X represents N or CH;

Y represents N or CR⁶;

R¹ represents (C₁₋₄)alkyl; (C₃₋₆)cycloalkyl; (C₁₋₄)alkoxy; (C₃₋₆)cycloalkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; cyano; (C₁₋₂)alkoxy-(C₂₋₃)alkoxy; (C₁₋₃)alkyl which is mono-substituted with -NR⁷R⁸; (C₂₋₃)alkoxy which is mono-substituted with -NR⁷R⁸; heterocyclyl, wherein the heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one or two heteroatoms independently selected from nitrogen and oxygen and wherein said heterocyclyl is unsubstituted or mono-substituted with (C₁₋₂)alkyl; or heterocycloxy, wherein the heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one oxygen atom;

R² represents hydrogen, (C₁₋₄)alkoxy or fluoro;

R³ represents hydrogen or (C₁₋₄)alkyl;

R⁴ represents (C₁₋₄)alkyl, (C₁₋₄)alkyl which is mono-substituted with hydroxy, or (C₁₋₂)alkyl which is mono-substituted with -NR⁷R⁸;

R⁵ represents (C₁₋₄)alkyl or (C₁₋₄)alkyl which is mono-substituted with hydroxy;

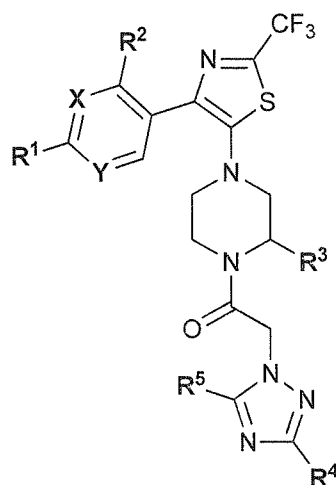
to the **R**⁶ bearing carbon atom;

R⁷ represents (C₁₋₂)alkyl; and

R⁸ represents (C₁₋₂)alkyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

In an aspect, the invention relates to a compound of Formula (I_P)



Formula (I_P)

wherein

X represents N or CH:

Y represents N or CR⁶:

15 **R¹** represents (C₁₋₄)alkyl; (C₃₋₆)cycloalkyl; (C₁₋₄)alkoxy; (C₃₋₆)cycloalkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; cyano; (C₁₋₂)alkoxy-(C₂₋₃)alkoxy; (C₁₋₃)alkyl which is mono-substituted with -NR⁷R⁸; (C₂₋₃)alkoxy which is mono-substituted with -NR⁷R⁸; heterocyclyl, wherein the heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one or two heteroatoms independently selected from nitrogen and oxygen and wherein said
20 heterocyclyl is unsubstituted or mono-substituted with (C₁₋₂)alkyl; or heterocycloxy, wherein the heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one oxygen atom;

R² represents hydrogen, (C₁₋₄)alkoxy or fluoro;

R³ represents hydrogen or methyl;

25 R^4 represents (C_{1-4}) alkyl, or (C_{1-2}) alkyl which is mono-substituted with $-NR^7R^8$.

R⁵ represents (C₁₋₄)alkyl;

R^6 represents hydrogen, (C_{1-4}) alkyl or fluoro; or R^1 and R^6 form, together with the carbon atoms to which they are attached, a 5- or 6-membered heterocyclic ring, wherein the moiety needed to complete said heterocyclic ring is selected from $-OCH_2CH_2^*$, $-OCH_2O^*$, $-OCH_2CH_2CH_2^*$ and $-OCH_2CH_2O^*$, wherein the asterisks indicate the bond which is linked

5 to the R^6 bearing carbon atom;

R^7 represents (C_{1-2}) alkyl; and

R^8 represents (C_{1-2}) alkyl;

or a pharmaceutically acceptable salt thereof.

10 Another aspect of the invention relates to a pharmaceutical composition comprising, as active principle, a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

Another aspect relates to a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use as a medicament.

15 Another aspect relates to the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a disease selected from the group consisting of Crohn's disease, ulcerative colitis, systemic lupus erythematosus, psoriasis, psoriatic arthritis, lupus nephritis, interstitial cystitis, celiac disease, myasthenia gravis, type I diabetes, uveitis, asthma, chronic obstructive pulmonary disorder, atherosclerosis, myocarditis, inflammatory myopathies, dry eye disease,
20 sarcoidosis, influenza, cerebral malaria, transplant rejection, liver cirrhosis, systemic sclerosis, pulmonary arterial hypertension, neurodegeneration, Alzheimer's disease, HIV associated dementia, Huntington's chorea, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, brain tumor, colon cancer, breast cancer, or metastatic spread of those cancers.

25 Definitions provided herein are intended to apply uniformly to the compounds of Formulae (I), (I_P), (II), (III), (IV) and (V) as defined in any one of embodiments 1) to 45), 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
30 (and in combination with) any definition or preferred definition of any or all other terms as defined herein.

The compounds of Formula (I) as defined in any one of embodiments 1) to 45), may contain one or more stereogenic or asymmetric centers, such as one or more asymmetric carbon

atoms. The compounds of Formula (I) may thus be present as mixtures of stereoisomers or in stereoisomerically enriched form, preferably as pure stereoisomers. Mixtures of stereoisomers may be separated in a manner known to a person skilled in the art.

5 The term "enriched", for example when used in the context of enantiomers, is understood in the context of the present invention to mean especially that the respective enantiomer is present in a ratio (*mutatis mutandis*: purity) of at least 70:30, and notably of at least 90:10 (*mutatis mutandis*: purity of 70% / 90%) with respect to the respective other enantiomer. Preferably the term refers to the respective essentially pure enantiomer. The term "essentially", for example when used in a term such as "essentially pure" is understood in
10 the context of the present invention to mean especially that the respective stereoisomer / composition / compound etc. consists in an amount of at least 90, especially of at least 95, and notably of at least 99 per cent by weight of the respective pure stereoisomer / composition / compound etc..

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

15 The term "alkyl", used alone or in combination, refers to a straight or branched saturated hydrocarbon chain containing one to four 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 (C₁₋₄)alkyl group contains from one to four carbon atoms. Examples of (C₁₋₄)alkyl groups are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec.*-butyl and *tert.*-

butyl. Examples of (C₁₋₃)alkyl groups are methyl, ethyl, *n*-propyl and *iso*-propyl. Examples of (C₁₋₂)alkyl groups are methyl and ethyl. In case **R**¹ represents "(C_{x-y})alkyl" the term means preferably methyl, ethyl and *n*-propyl, and more preferably ethyl and *n*-propyl. In case **R**¹ represents "(C_{x-y})alkyl which is mono-substituted with -**NR**⁷**R**⁸" the term "(C_{x-y})alkyl" means preferably ethyl. In case **R**³ represents "(C_{x-y})alkyl" the term means preferably methyl and ethyl, and more preferably methyl. In case **R**⁴ represents "(C_{x-y})alkyl" the term means preferably methyl and ethyl, and more preferably methyl. In case **R**⁴ represents "(C_{x-y})alkyl which is mono-substituted with hydroxy" the term "(C_{x-y})alkyl" means preferably methyl or *iso*-propyl and more preferably methyl. In case **R**⁴ represents "(C_{x-y})alkyl which is mono-substituted with -**NR**⁷**R**⁸" the term "(C_{x-y})alkyl" means preferably methyl. In case **R**⁵ represents "(C_{x-y})alkyl" the term means preferably methyl and ethyl, and more preferably methyl. In case **R**⁵ represents "(C_{x-y})alkyl which is mono-substituted with hydroxy" the term "(C_{x-y})alkyl" means preferably methyl. In case **R**⁶ represents "(C_{x-y})alkyl" the term means preferably methyl. In case **R**⁷ represents "(C_{x-y})alkyl" the term means preferably methyl. In case **R**⁸ represents "(C_{x-y})alkyl" the term means preferably methyl. In case a "(C_{x-y})alkyl" group is a substituent to a "heterocyclyl group" representing "**R**¹", the term "(C_{x-y})alkyl" means preferably methyl.

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 (C₁₋₄)alkoxy groups are methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *sec*.-butoxy and *tert*.-butoxy. Examples of (C₁₋₃)alkoxy groups are methoxy, ethoxy, *n*-propoxy and *iso*-propoxy. Examples of (C₂₋₃)alkoxy groups are ethoxy, *n*-propoxy and *iso*-propoxy. Examples of (C₁₋₂)alkoxy groups are methoxy and ethoxy. In case **R**¹ represents "(C_{x-y})alkoxy" the term means preferably methoxy, ethoxy and *iso*-propoxy and more preferably ethoxy. In case **R**² represents "(C_{x-y})alkoxy" the term means preferably ethoxy. In case **R**¹ represents "(C_{x-y})alkoxy which is mono-substituted with -**NR**⁷**R**⁸" the term "(C_{x-y})alkoxy" means preferably ethoxy; it is preferred that the oxygen-atom of the (C_{x-y})alkoxy group and the substituent -**NR**⁷**R**⁸ are attached to different carbon-atoms of the (C_{x-y})alkoxy group.

The term "(C_{xa-ya})alkoxy-(C_{x-y})alkoxy" (x, xa, y and ya each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms wherein one hydrogen atom has been replaced with (C_{xa-ya})alkoxy as defined before containing xa to ya carbon atoms. For example a "(C₁₋₂)alkoxy-(C₂₋₃)alkoxy group" refers to an (C₂₋₃)alkoxy group as defined before containing two or three carbon atoms wherein one hydrogen atom has been replaced with (C₁₋₂)alkoxy as defined before containing one or two carbon atoms. It is

preferred that the oxygen-atom of the (C_{x-y})alkoxy group and the oxygen atom of the (C_{xa-y_a})alkoxy group are attached to different carbon-atoms of the (C_{x-y})alkoxy group. Representative examples of (C₁₋₂)alkoxy-(C₂₋₃)alkoxy groups include 2-methoxy-ethoxy, 1-methoxy-prop-2-oxy, 2-methoxy-prop-1-oxy, 3-methoxy-prop-1-oxy, 2-ethoxy-ethoxy, 1-ethoxy-prop-2-oxy, 2-ethoxy-prop-1-oxy and 3-ethoxy-prop-1-oxy. In case **R**¹ represents "(C₁₋₂)alkoxy-(C₂₋₃)alkoxy" the term means preferably 2-methoxy-ethoxy and 2-ethoxy-ethoxy and more preferably 2-methoxy-ethoxy.

The term "(C₁₋₃)fluoroalkyl" 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 (C₁₋₃)fluoroalkyl groups include difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, and 2,2,2-trifluoroethyl. Another representative example of (C₁₋₃)fluoroalkyl is 1,1-difluoroethyl. Preferred are (C₁)fluoroalkyl groups such as trifluoromethyl or difluoromethyl. In case **R**¹ represents "(C_{x-y})fluoroalkyl" the term means preferably trifluoromethyl and 1,1-difluoroethyl and more preferably trifluoromethyl.

The term "(C₁₋₃)fluoroalkoxy" 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 (C₁₋₃)fluoroalkoxy groups include trifluoromethoxy, difluoromethoxy and 2,2,2-trifluoroethoxy. In case **R**¹ represents "(C_{x-y})fluoroalkoxy" the term means preferably 2,2,2-trifluoroethoxy.

The term "cycloalkyl", used alone or in combination, refers to a saturated carbocyclic 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, and cyclohexyl. In case **R**¹ represents "(C_{x-y})cycloalkyl" the term means preferably cyclopropyl.

The term "cycloalkoxy", used alone or in combination, refers to a cycloalkyl-O- group wherein the cycloalkyl group is as defined before. The term "(C_{x-y})cycloalkoxy" (x and y each being an integer) refers to a cycloalkoxy group as defined before containing x to y carbon atoms. For example a (C₃₋₆)cycloalkoxy group means a group of the formula (C₃₋

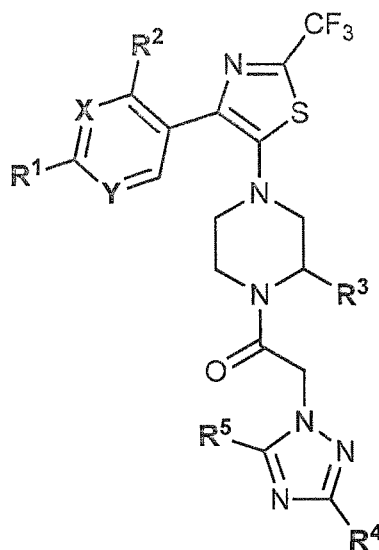
₆)cycloalkyl-O- in which the term "(C₃₋₆)cycloalkyl" has the previously given significance. Examples of (C₃₋₆)cycloalkoxy groups are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, and cyclohexyloxy. In case **R**¹ represents "(C_{x-y})cycloalkoxy" the term means preferably cyclobutyloxy.

- 5 The term "heterocyclyl", wherein the "heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one or two heteroatoms independently selected from nitrogen and oxygen", as used for substituents **R**¹, means for example azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, tetrahydrofurany and tetrahydropyrany groups, and preferably pyrrolidiny and piperaziny groups; wherein said heterocyclyl is unsubstituted or mono-
- 10 substituted with (C₁₋₂)alkyl. Particular examples are pyrrolidin-1-yl, and 4-methyl-piperazin-1-yl.

The term "heterocyclyloxy", used alone or in combination, refers to a heterocyclyl-O- group; the term "heterocyclyloxy", wherein the "heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one oxygen atom", as used for substituents **R**¹, means for

15 example oxetanyloxy, tetrahydrofuranyloxy and tetrahydropyranyloxy groups, and preferably an oxetan-3-yloxy group.

1P) A further embodiment of the invention relates to compounds of Formula (I) according to embodiment 1) which are also compounds of Formula (I_P)



Formula (I_P)

wherein

X represents N or CH;

Y represents N or CR⁶;

- R**¹ represents (C₁₋₄)alkyl; (C₃₋₆)cycloalkyl; (C₁₋₄)alkoxy; (C₃₋₆)cycloalkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; cyano; (C₁₋₂)alkoxy-(C₂₋₃)alkoxy; (C₁₋₃)alkyl which is mono-
- 25 substituted with -NR⁷R⁸; (C₂₋₃)alkoxy which is mono-substituted with -NR⁷R⁸; heterocyclyl,

wherein the heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one or two heteroatoms independently selected from nitrogen and oxygen and wherein said heterocyclyl is unsubstituted or mono-substituted with (C₁₋₂)alkyl; or heterocycloxy, wherein the heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one

5 oxygen atom;

R² represents hydrogen, (C₁₋₄)alkoxy or fluoro;

R³ represents hydrogen or methyl;

R⁴ represents (C₁₋₄)alkyl, or (C₁₋₂)alkyl which is mono-substituted with -**NR**⁷**R**⁸;

R⁵ represents (C₁₋₄)alkyl;

10 **R**⁶ represents hydrogen, (C₁₋₄)alkyl or fluoro; or **R**¹ and **R**⁶ form, together with the carbon atoms to which they are attached, a 5- or 6-membered heterocyclic ring, wherein the moiety needed to complete said heterocyclic ring is selected from -OCH₂CH₂-, -OCH₂O-, -OCH₂CH₂CH₂- and -OCH₂CH₂O-, wherein the asterisks indicate the bond which is linked to the **R**⁶ bearing carbon atom;

15 **R**⁷ represents (C₁₋₂)alkyl; and

R⁸ represents (C₁₋₂)alkyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

2) A further embodiment of the invention relates to compounds of formula (I) according to any one of embodiments 1) or 1P), wherein

20 **X** represents N or CH;

Y represents N or CR⁶;

R¹ represents (C₁₋₃)alkyl; cyclopropyl; (C₁₋₃)alkoxy; cyclobutyloxy; trifluoromethyl; trifluoromethoxy; 2,2,2-trifluoroethoxy; chloro; cyano; 2-methoxy-ethoxy; pyrrolidin-1-yl; 4-methyl-piperazin-1-yl; or oxetan-3-yloxy;

25 **R**² represents hydrogen or ethoxy;

R³ represents hydrogen or methyl;

R⁴ represents methyl or ethyl;

R⁵ represents methyl or ethyl; and

30 **R**⁶ represents hydrogen or fluoro; or **R**¹ and **R**⁶ form, together with the carbon atoms to which they are attached, a 5- or 6-membered heterocyclic ring, wherein the moiety needed to complete said heterocyclic ring is selected from -OCH₂CH₂- and -OCH₂CH₂CH₂-, wherein the asterisks indicate the bond which is linked to the **R**⁶ bearing carbon atom; and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

3) A further embodiment of the invention relates to compounds of formula (I) according to
35 any one of embodiments 1), 1P) or 2), wherein

R¹ represents ethyl; *n*-propyl; cyclopropyl; ethoxy; *iso*-propoxy; cyclobutyloxy; trifluoromethyl; trifluoromethoxy; or 2,2,2-trifluoroethoxy;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

4) A further embodiment of the invention relates to compounds of formula (I) according to any one of embodiments 1) or 1P) to 3), wherein

R² represents hydrogen;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

5) A further embodiment of the invention relates to compounds of formula (I) according to any one of embodiments 1) or 1P) to 4), wherein

R⁴ and **R⁵** represent methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

6) A further embodiment of the invention relates to compounds of formula (I) according to any one of embodiments 1) or 1P) to 5), wherein

R⁶ represents hydrogen;

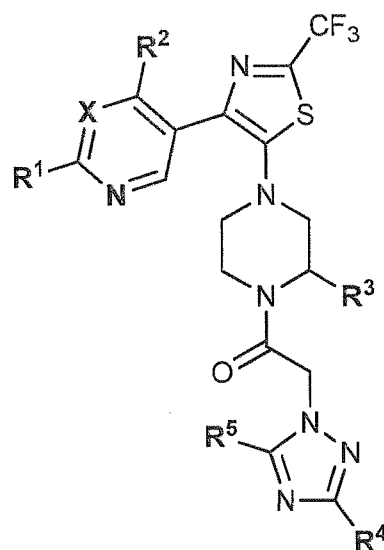
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

7) A further embodiment of the invention relates to compounds of formula (I) according to any one of embodiments 1), 1P) or 3) to 5), wherein

R¹ and **R⁶** form, together with the carbon atoms to which they are attached, a 5- or 6-membered heterocyclic ring, wherein the moiety needed to complete said heterocyclic ring is selected from -OCH₂CH₂-, -OCH₂O-, -OCH₂CH₂CH₂- and -OCH₂CH₂O-, wherein the asterisks indicate the bond which is linked to the **R⁶** bearing carbon atom;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

8) A further embodiment of the invention relates to compounds of Formula (I) according to any one of embodiments 1) or 1P) which are also compounds of Formula (II)



Formula (II)

wherein

X represents N or CH;

R¹ represents (C₁₋₄)alkyl; (C₃₋₆)cycloalkyl; (C₁₋₄)alkoxy; (C₃₋₆)cycloalkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; (C₁₋₂)alkoxy-(C₂₋₃)alkoxy; (C₁₋₃)alkyl which is mono-substituted with
5 -**NR**⁷**R**⁸; (C₂₋₃)alkoxy which is mono-substituted with -**NR**⁷**R**⁸; heterocyclyl, wherein the heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one or two heteroatoms independently selected from nitrogen and oxygen and wherein said heterocyclyl is unsubstituted or mono-substituted with (C₁₋₂)alkyl; or heterocycliloxy, wherein the heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one

10 oxygen atom;

R² represents hydrogen or (C₁₋₄)alkoxy;

R³ represents hydrogen or methyl;

R⁴ represents (C₁₋₄)alkyl, or (C₁₋₂)alkyl which is mono-substituted with -**NR**⁷**R**⁸;

R⁵ represents (C₁₋₄)alkyl;

15 **R**⁷ represents (C₁₋₂)alkyl; and

R⁸ represents (C₁₋₂)alkyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

9) A further embodiment of the invention relates to compounds of Formula (II) according to embodiment 8), wherein

20 **X** represents N or CH;

R¹ represents (C₁₋₄)alkyl; (C₃₋₆)cycloalkyl; (C₁₋₄)alkoxy; (C₃₋₆)cycloalkoxy; (C₁₋₂)fluoroalkyl; or (C₁₋₂)fluoroalkoxy;

R² represents hydrogen or ethoxy;

R³ represents hydrogen or methyl;

25 **R**⁴ represents methyl or ethyl; and

R⁵ represents methyl or ethyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

10) A further embodiment of the invention relates to compounds of Formula (II) according to any one of embodiments 8) or 9), wherein

30 **X** represents N;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

11) A further embodiment of the invention relates to compounds of Formula (II) according to any one of embodiments 8) to 10), wherein

35 **R**¹ represents ethyl; *n*-propyl; cyclopropyl; ethoxy; *iso*-propoxy; cyclobutyloxy; trifluoromethyl; or 2,2,2-trifluoroethoxy;

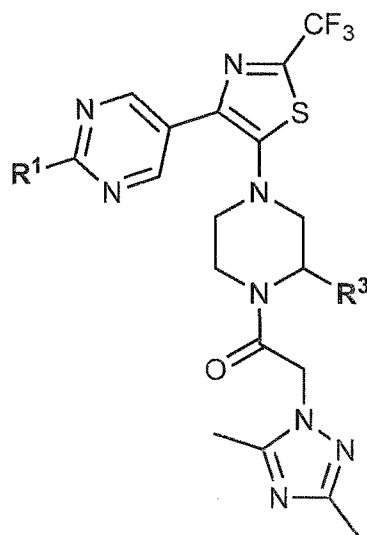
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

12) A further embodiment of the invention relates to compounds of Formula (II) according to any one of embodiments 8) to 11), wherein

R^3 represents methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

- 5 13) A further embodiment of the invention relates to compounds of Formula (I) according to any one of embodiments 1) or 1P) which are also compounds of Formula (III)



Formula (III)

wherein

- 10 R^1 represents (C₁₋₄)alkyl; (C₃₋₆)cycloalkyl; (C₁₋₄)alkoxy; (C₃₋₆)cycloalkoxy; (C₁₋₂)fluoroalkyl; or (C₁₋₂)fluoroalkoxy; and

R^3 represents hydrogen or methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

- 14) A further embodiment of the invention relates to compounds of Formula (III) according to embodiment 13), wherein

R^1 represents ethyl; *n*-propyl; cyclopropyl; ethoxy; *iso*-propoxy; cyclobutyloxy; trifluoromethyl; or 2,2,2-trifluoroethoxy;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

- 15) A further embodiment of the invention relates to compounds of Formula (III) according to embodiment 13), wherein

R^1 represents (C₁₋₄)alkoxy; or (C₁₋₂)fluoroalkyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

- 16) A further embodiment of the invention relates to compounds of Formula (III) according to embodiment 13), wherein

- 25 R^1 represents ethoxy; or trifluoromethyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

17) A further embodiment of the invention relates to compounds of Formula (III) according to embodiment 13), wherein

R¹ represents (C₁₋₄)alkyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

5 18) A further embodiment of the invention relates to compounds of Formula (III) according to embodiment 13), wherein

R¹ represents (C₃₋₆)cycloalkyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

10 19) A further embodiment of the invention relates to compounds of Formula (III) according to embodiment 13), wherein

R¹ represents (C₁₋₄)alkoxy;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

20) A further embodiment of the invention relates to compounds of Formula (III) according to embodiment 13), wherein

15 **R¹** represents (C₃₋₆)cycloalkoxy;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

21) A further embodiment of the invention relates to compounds of Formula (III) according to embodiment 13), wherein

R¹ represents (C₁₋₂)fluoroalkyl;

20 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

22) A further embodiment of the invention relates to compounds of Formula (III) according to embodiment 13), wherein

R¹ represents (C₁₋₂)fluoroalkoxy;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

25 23) A further embodiment of the invention relates to compounds of Formula (III) according to any one of embodiments 13) to 22), wherein

R³ represents hydrogen;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

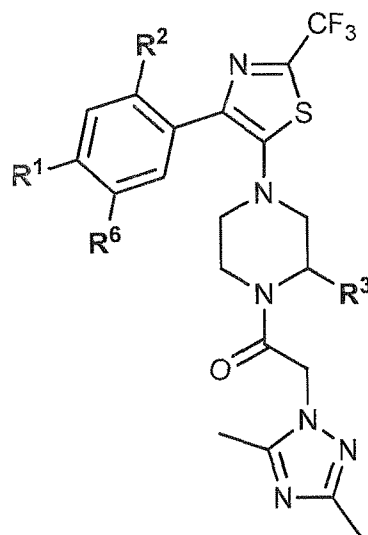
30 24) A further embodiment of the invention relates to compounds of Formula (III) according to any one of embodiments 13) to 22), wherein

R³ represents methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

25) A further embodiment of the invention relates to compounds of Formula (I) according to any one of embodiments 1) or 1P) which are also compounds of Formula (IV)

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Formula (IV)

wherein

R¹ represents (C₁₋₄)alkyl; (C₁₋₄)alkoxy; (C₁₋₃)fluoroalkoxy; halogen; or cyano;

5 **R**² represents hydrogen or fluoro;

R³ represents hydrogen or methyl; and

R⁶ represents hydrogen, (C₁₋₄)alkyl or fluoro; or **R**¹ and **R**⁶ form, together with the carbon atoms to which they are attached, a 5- or 6-membered heterocyclic ring, wherein the moiety needed to complete said heterocyclic ring is selected from -OCH₂CH₂-, -OCH₂O-,
10 -OCH₂CH₂CH₂- and -OCH₂CH₂O-, wherein the asterisks indicate the bond which is linked to the **R**⁶ bearing carbon atom;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

26) A further embodiment of the invention relates to compounds of Formula (IV) according to embodiment 25), wherein

15 **R**² and **R**⁶ represent hydrogen;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

27) A further embodiment of the invention relates to compounds of Formula (IV) according to embodiment 25), wherein

R² represents hydrogen; and

20 **R**¹ and **R**⁶ form, together with the carbon atoms to which they are attached, a 5- or 6-membered heterocyclic ring, wherein the moiety needed to complete said heterocyclic ring is selected from -OCH₂CH₂-, -OCH₂O-, -OCH₂CH₂CH₂- and -OCH₂CH₂O-, wherein the asterisks indicate the bond which is linked to the **R**⁶ bearing carbon atom;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

25 28) A further embodiment of the invention relates to compounds of Formula (IV) according to any one of embodiments 25) to 27), wherein

R³ represents methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

29) A further embodiment of the invention relates to compounds of formula (I) according to any one of embodiments 1) or 1P) to 22) or 24) to 28), wherein, in case **R**³ represents methyl, the carbon atom attached to **R**³ is (*R*)-configured;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

30) A further embodiment of the invention relates to compounds of formula (I) according to any one of embodiments 1) or 1P) to 22) or 24) to 28), wherein, in case **R**³ represents methyl, the carbon atom attached to **R**³ is (*S*)-configured;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

31) Examples of compounds of formula (I) as defined in embodiment 1) are selected from the group consisting of:

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(*R*)-4-[4-(4-methoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(*R*)-4-[4-(4-isopropoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(*R*)-2-methyl-4-[4-(4-trifluoromethoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(*R*)-2-methyl-4-[4-[4-(2,2,2-trifluoro-ethoxy)-phenyl]-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl]-ethanone;

4-(5-[(*R*)-4-[2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-acetyl]-3-methyl-piperazin-1-yl]-2-trifluoromethyl-thiazol-4-yl)-benzonitrile;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(*R*)-4-[4-(4-fluoro-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

1-[(*R*)-4-[4-(4-Chloro-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(*R*)-2-methyl-4-(4-p-tolyl-2-trifluoromethyl-thiazol-5-yl)-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(*R*)-4-[4-(4-ethyl-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(*R*)-4-[4-(3-fluoro-4-methoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(*R*)-4-[4-(2-fluoro-4-methoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(*R*)-4-[4-(4-methoxy-3-methyl-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

- 1-[(R)-4-(4-Benzo[1,3]dioxol-5-yl-2-trifluoromethyl-thiazol-5-yl)-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;
- 1-[(R)-4-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;
- 5 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(6-ethoxy-pyridin-3-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;
- 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(6-methoxy-pyridin-3-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;
- 2-(3-Dimethylaminomethyl-5-methyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;
- 10 1-[(R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-2-(3-ethyl-5-methyl-[1,2,4]triazol-1-yl)-ethanone;
- 1-[(R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-2-(5-ethyl-3-methyl-[1,2,4]triazol-1-yl)-ethanone;
- 15 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;
- 1-[(R)-4-(4-Chroman-6-yl-2-trifluoromethyl-thiazol-5-yl)-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;
- 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[4-(2-propyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl]-ethanone;
- 20 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[4-(2-methyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl]-ethanone;
- 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone;
- 25 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-[2-(2-methoxy-ethoxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;
- 1-[(R)-4-[4-[2-(2-Dimethylamino-ethoxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;
- 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(2-isopropoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;
- 30 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[4-[2-(2,2,2-trifluoro-ethoxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl]-ethanone;
- 1-[(R)-4-[4-(2,4-Diethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;
- 35 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[4-[2-(oxetan-3-yloxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(4-ethoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-methoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;

5 1-((R)-4-[4-(2-Cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((S)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;

10 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[4-(2-pyrrolidin-1-yl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone;

15 1-((R)-4-[4-(2-Cyclobutoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

1-((R)-4-[4-(3,4-Dihydro-2H-pyrano[2,3-b]pyridin-6-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

20 1-((R)-4-[4-(2,3-Dihydro-benzofuran-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2,2-dideuterium-ethanone;

1-((R)-4-[4-[2-(2-Dimethylamino-ethyl)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone; and

25 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-ethyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;

or salts (in particular pharmaceutically acceptable salts) of such compounds.

32) Preferred examples of compounds of formula (I) as defined in embodiment 1) are selected from the group consisting of:

30 1-((R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3-ethyl-5-methyl-[1,2,4]triazol-1-yl)-ethanone;

1-((R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(5-ethyl-3-methyl-[1,2,4]triazol-1-yl)-ethanone;

35 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[4-(2-propyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-isopropoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;

5 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-{4-[2-(2,2,2-trifluoro-ethoxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl}-piperazin-1-yl)-ethanone;

1-((R)-4-[4-(2-Cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((S)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;

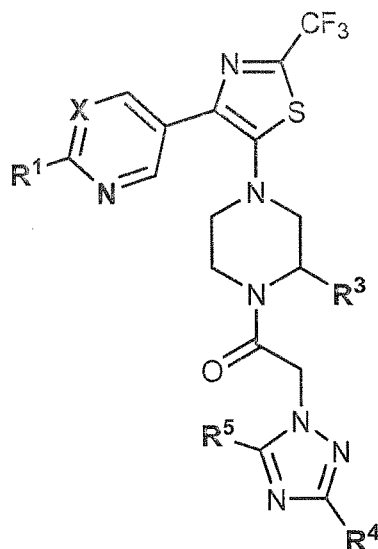
10 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone;

1-((R)-4-[4-(2-Cyclobutoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone; and

15 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-ethyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;

or salts (in particular pharmaceutically acceptable salts) of such compounds.

33) A further embodiment of the invention relates to compounds of Formula (I) according to embodiment 1) which are also compounds of Formula (V)



Formula (V)

wherein

X represents N or CH;

R¹ represents (C₁₋₄)alkyl, (C₃₋₆)cycloalkyl, (C₁₋₄)alkoxy, (C₃₋₆)cycloalkoxy, (C₁₋₃)fluoroalkyl, or (C₁₋₃)fluoroalkoxy;

R³ represents hydrogen, or (C₁₋₄)alkyl;

R⁴ represents (C₁₋₄)alkyl, or (C₁₋₄)alkyl which is mono-substituted with hydroxy;
R⁵ represents (C₁₋₄)alkyl, or (C₁₋₄)alkyl which is mono-substituted with hydroxy;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

34) A further embodiment of the invention relates to compounds of Formula (V) according to
5 embodiment 33), wherein

X represents N;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

35) A further embodiment of the invention relates to compounds of Formula (V) according to
any one of embodiments 33) or 34), wherein

10 **R¹** represents ethyl, *n*-propyl, cyclopropyl, ethoxy, *iso*-propoxy, cyclobutyloxy,
trifluoromethyl, 1,1-difluoroethyl, or 2,2,2-trifluoroethoxy;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

36) A further embodiment of the invention relates to compounds of Formula (V) according to
any one of embodiments 33) or 34), wherein

15 **R¹** represents ethoxy, trifluoromethyl, or 1,1-difluoroethyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

37) A further embodiment of the invention relates to compounds of Formula (V) according to
any one of embodiments 33) or 34), wherein

R¹ represents trifluoromethyl;
20 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

38) A further embodiment of the invention relates to compounds of Formula (V) according to
any one of embodiments 33) to 37), wherein

R³ represents hydrogen, methyl, or ethyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

25 39) A further embodiment of the invention relates to compounds of Formula (V) according to
any one of embodiments 33) to 37), wherein

R³ represents methyl, or ethyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

40) A further embodiment of the invention relates to compounds of Formula (V) according to
30 any one of embodiments 33) to 39), wherein

R⁴ represents methyl, ethyl, hydroxy-methyl, or 2-hydroxy-prop-2yl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

41) A further embodiment of the invention relates to compounds of Formula (V) according to
any one of embodiments 33) to 39), wherein

R⁴ represents methyl, or hydroxy-methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

42) A further embodiment of the invention relates to compounds of Formula (V) according to any one of embodiments 33) to 41), wherein

5 **R⁵** represents methyl, ethyl, or hydroxy-methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

43) A further embodiment of the invention relates to compounds of Formula (V) according to any one of embodiments 33) to 41), wherein

R⁵ represents methyl, or hydroxy-methyl;

10 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

44) Further examples of compounds of formula (I) as defined in embodiment 1) are selected from the group consisting of:

2-(3-Hydroxymethyl-5-methyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone;

15 2-(5-Hydroxymethyl-3-methyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone;

2-(3-Ethyl-5-methyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone;

20 2-(5-Ethyl-3-methyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone;

2-[3-(1-Hydroxy-1-methyl-ethyl)-5-methyl-[1,2,4]triazol-1-yl]-1-[(R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[2-trifluoromethyl-4-(6-trifluoromethyl-pyridin-3-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone;

25 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(S)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-ethyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone; and

1-[(R)-4-{4-[2-(1,1-Difluoro-ethyl)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl}-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

30 or salts (in particular pharmaceutically acceptable salts) of such compounds.

45) The invention, thus, relates to compounds of the Formula (I) as defined in embodiment 1), compounds of the Formula (I_P) as defined in embodiment 1P), compounds of the Formula (II) as defined in embodiment 8), compounds of the Formula (III) as defined in
35 embodiment 13), compounds of the formula (IV) as defined in embodiment 25), compounds of the formula (V) as defined in embodiment 33); and to such compounds further limited by

the characteristics of any one of embodiments 2) to 7), 9) to 12), 14) to 24), 26) to 32), and 34) to 44), all 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 a dysfunction of the CXCR3 receptor or dysfunction of ligands signalling through CXCR3, such as especially autoimmune disorders, inflammatory diseases, infectious diseases, transplant rejection, fibrosis, neurodegenerative disorders and cancer. Especially the following embodiments relating to the compounds of formulae (I), (I_P), (II), (III), (IV), and (V) are thus possible and intended and herewith specifically disclosed in individualized form:

- 10 1, 1P+1, 2+1P+1, 3+1P+1, 3+2+1P+1, 4+1P+1, 4+2+1P+1, 4+3+1P+1, 4+3+2+1P+1, 5+1P+1, 5+2+1P+1, 5+3+1P+1, 5+3+2+1P+1, 5+4+1P+1, 5+4+2+1P+1, 5+4+3+1P+1, 5+4+3+2+1P+1, 6+1P+1, 6+2+1P+1, 6+3+1P+1, 6+3+2+1P+1, 6+4+1P+1, 6+4+2+1P+1, 6+4+3+1P+1, 6+4+3+2+1P+1, 6+5+1P+1, 6+5+2+1P+1, 6+5+3+1P+1, 6+5+3+2+1P+1, 6+5+4+1P+1, 6+5+4+2+1P+1, 6+5+4+3+1P+1, 6+5+4+3+2+1P+1, 7+1P+1, 7+3+1P+1,
- 15 7+3+2+1P+1, 7+4+1P+1, 7+4+2+1P+1, 7+4+3+1P+1, 7+4+3+2+1P+1, 7+5+1P+1, 7+5+2+1P+1, 7+5+3+1P+1, 7+5+3+2+1P+1, 7+5+4+1P+1, 7+5+4+2+1P+1, 7+5+4+3+1P+1, 7+5+4+3+2+1P+1, 8+1P+1, 9+8+1P+1, 10+8+1P+1, 10+9+8+1P+1, 11+8+1P+1, 11+9+8+1P+1, 11+10+8+1P+1, 11+10+9+8+1P+1, 12+8+1P+1, 12+9+8+1P+1, 12+10+8+1P+1, 12+10+9+8+1P+1, 12+11+8+1P+1, 12+11+9+8+1P+1, 12+11+10+8+1P+1,
- 20 12+11+10+9+8+1P+1, 13+1P+1, 14+13+1P+1, 15+13+1P+1, 16+13+1P+1, 17+13+1P+1, 18+13+1P+1, 19+13+1P+1, 20+13+1P+1, 21+13+1P+1, 22+13+1P+1, 23+13+1P+1, 23+14+13+1P+1, 23+15+13+1P+1, 23+16+13+1P+1, 23+17+13+1P+1, 23+18+13+1P+1, 23+19+13+1P+1, 23+20+13+1P+1, 23+21+13+1P+1, 23+22+13+1P+1, 24+13+1P+1, 24+14+13+1P+1, 24+15+13+1P+1, 24+16+13+1P+1, 24+17+13+1P+1, 24+18+13+1P+1,
- 25 24+19+13+1P+1, 24+20+13+1P+1, 24+21+13+1P+1, 24+22+13+1P+1, 25+1P+1, 26+25+1P+1, 27+25+1P+1, 28+25+1P+1, 28+26+25+1P+1, 28+27+25+1P+1, 29+1P+1, 29+2+1P+1, 29+3+1P+1, 29+3+2+1P+1, 29+4+1P+1, 29+4+2+1P+1, 29+4+3+1P+1, 29+4+3+2+1P+1, 29+5+1P+1, 29+5+2+1P+1, 29+5+3+1P+1, 29+5+3+2+1P+1, 29+5+4+1P+1, 29+5+4+2+1P+1, 29+5+4+3+1P+1, 29+5+4+3+2+1P+1, 29+6+1P+1,
- 30 29+6+2+1P+1, 29+6+3+1P+1, 29+6+3+2+1P+1, 29+6+4+1P+1, 29+6+4+2+1P+1, 29+6+4+3+1P+1, 29+6+4+3+2+1P+1, 29+6+5+1P+1, 29+6+5+2+1P+1, 29+6+5+3+1P+1, 29+6+5+3+2+1P+1, 29+6+5+4+1P+1, 29+6+5+4+2+1P+1, 29+6+5+4+3+1P+1, 29+6+5+4+3+2+1P+1, 29+7+1P+1, 29+7+3+1P+1, 29+7+3+2+1P+1, 29+7+4+1P+1, 29+7+4+2+1P+1, 29+7+4+3+1P+1, 29+7+4+3+2+1P+1, 29+7+5+1P+1, 29+7+5+2+1P+1,
- 35 29+7+5+3+1P+1, 29+7+5+3+2+1P+1, 29+7+5+4+1P+1, 29+7+5+4+2+1P+1, 29+7+5+4+3+1P+1, 29+7+5+4+3+2+1P+1, 29+8+1P+1, 29+9+8+1P+1, 29+10+8+1P+1, 29+10+9+8+1P+1, 29+11+8+1P+1, 29+11+9+8+1P+1, 29+11+10+8+1P+1, 29+11+10+9+8+1P+1,

29+12+8+1P+1, 29+12+9+8+1P+1, 29+12+10+8+1P+1, 29+12+10+9+8+1P+1,
 29+12+11+8+1P+1, 29+12+11+9+8+1P+1, 29+12+11+10+8+1P+1, 29+12+11+10+9+
 8+1P+1, 29+13+1P+1, 29+14+13+1P+1, 29+15+13+1P+1, 29+16+13+1P+1,
 29+17+13+1P+1, 29+18+13+1P+1, 29+19+13+1P+1, 29+20+13+1P+1, 29+21+13+1P+1,
 5 29+22+13+1P+1, 29+24+13+1P+1, 29+24+14+13+1P+1, 29+24+15+13+1P+1,
 29+24+16+13+1P+1, 29+24+17+13+1P+1, 29+24+18+13+1P+1, 29+24+19+13+1P+1,
 29+24+20+13+1P+1, 29+24+21+13+1P+1, 29+24+22+13+1P+1, 29+25+1P+1,
 29+26+25+1P+1, 29+27+25+1P+1, 29+28+25+1P+1, 29+28+26+25+1P+1,
 29+28+27+25+1P+1, 30+1P+1, 30+2+1P+1, 30+3+1P+1, 30+3+2+1P+1, 30+4+1P+1,
 10 30+4+2+1P+1, 30+4+3+1P+1, 30+4+3+2+1P+1, 30+5+1P+1, 30+5+2+1P+1,
 30+5+3+1P+1, 30+5+3+2+1P+1, 30+5+4+1P+1, 30+5+4+2+1P+1, 30+5+4+3+1P+1,
 30+5+4+3+2+1P+1, 30+6+1P+1, 30+6+2+1P+1, 30+6+3+1P+1, 30+6+3+2+1P+1,
 30+6+4+1P+1, 30+6+4+2+1P+1, 30+6+4+3+1P+1, 30+6+4+3+2+1P+1, 30+6+5+1P+1,
 30+6+5+2+1P+1, 30+6+5+3+1P+1, 30+6+5+3+2+1P+1, 30+6+5+4+1P+1, 30+6+5+4+
 15 2+1P+1, 30+6+5+4+3+1P+1, 30+6+5+4+3+2+1P+1, 30+7+1P+1, 30+7+3+1P+1,
 30+7+3+2+1P+1, 30+7+4+1P+1, 30+7+4+2+1P+1, 30+7+4+3+1P+1, 30+7+4+3+2+1P+1,
 30+7+5+1P+1, 30+7+5+2+1P+1, 30+7+5+3+1P+1, 30+7+5+3+2+1P+1, 30+7+5+4+1P+1,
 30+7+5+4+2+1P+1, 30+7+5+4+3+1P+1, 30+7+5+4+3+2+1P+1, 30+8+1P+1, 30+9+8+
 1P+1, 30+10+8+1P+1, 30+10+9+8+1P+1, 30+11+8+1P+1, 30+11+9+8+1P+1, 30+11+10+
 20 8+1P+1, 30+11+10+9+8+1P+1, 30+12+8+1P+1, 30+12+9+8+1P+1, 30+12+10+8+1P+1,
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 25 30+24+15+13+1P+1, 30+24+16+13+1P+1, 30+24+17+13+1P+1, 30+24+18+13+1P+1,
 30+24+19+13+1P+1, 30+24+20+13+1P+1, 30+24+21+13+1P+1, 30+24+22+13+1P+1,
 30+25+1P+1, 30+26+25+1P+1, 30+27+25+1P+1, 30+28+25+1P+1, 30+28+26+25+1P+1,
 30+28+27+25+1P+1, 31+1P+1, 32+1P+1, 33+1, 34+33+1, 35+33+1, 35+34+33+1,
 36+33+1, 36+34+33+1, 37+33+1, 37+34+33+1, 38+33+1, 38+34+33+1, 38+35+33+1,
 30 38+35+34+33+1, 38+36+33+1, 38+36+34+33+1, 38+37+33+1, 38+37+34+33+1, 39+33+1,
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10 42+40+35+33+1, 42+40+35+34+33+1, 42+40+36+33+1, 42+40+36+34+33+1,
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33+1, 42+40+38+37+33+1, 42+40+38+37+34+33+1, 42+40+39+33+1, 42+40+39+34+
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35+33+1, 43+40+38+35+34+33+1, 43+40+38+36+33+1, 43+40+38+36+34+33+1,
30 43+40+38+37+33+1, 43+40+38+37+34+33+1, 43+40+39+33+1, 43+40+39+34+33+1,
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34+33+1, 43+40+39+37+33+1, 43+40+39+37+34+33+1, 43+41+33+1, 43+41+34+33+1,
43+41+35+33+1, 43+41+35+34+33+1, 43+41+36+33+1, 43+41+36+34+33+1, 43+41+37+
33+1, 43+41+37+34+33+1, 43+41+38+33+1, 43+41+38+34+33+1, 43+41+38+35+33+1,
35 43+41+38+35+34+33+1, 43+41+38+36+33+1, 43+41+38+36+34+33+1, 43+41+38+37+
33+1, 43+41+38+37+34+33+1, 43+41+39+33+1, 43+41+39+34+33+1, 43+41+39+35+
33+1, 43+41+39+35+34+33+1, 43+41+39+36+33+1, 43+41+39+36+34+33+1, 43+41+39+

37+33+1, 43+41+39+37+34+33+1, and 44+1; in the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the dependency from another embodiment. The different individualized embodiments are separated by commas. In other words, "20+13+1P+1" for example refers to embodiment 20) depending on embodiment 13), depending on embodiment 1P), depending on embodiment 1), i.e. embodiment "20+13+1P+1" corresponds to the compounds of embodiment 1) further limited by the features of the embodiments 1P), 13) and 20).

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

Any reference to a compound of Formula (I) as defined in any one of embodiments 1) to 45) 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.

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 or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of Formula (I) 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.

Whenever the word "between" is used to describe a numerical range, it is to be understood that the end points of the indicated range are explicitly included in the range. For example: if

a temperature range is described to be between 40 °C and 80 °C, this means that the end points 40 °C and 80 °C are included in the range; or if a variable is defined as being an integer between 1 and 4, this means that the variable is the integer 1, 2, 3, or 4.

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

The compounds of formula (I) as defined in any one of embodiments 1) to 45) 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, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds of Formula (I) or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

The present invention also relates to a method for the prevention or treatment of a disease or disorder mentioned herein comprising administering to a subject a pharmaceutically active amount of a compound of Formula (I) as defined in any one of embodiments 1) to 45).

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.

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 treatment of said diseases.

Another aspect of the invention concerns a method for the prevention or the treatment of a disease or disorder as mentioned above in a patient comprising the administration to said

patient of a pharmaceutically active amount of a compound of Formula (I) as defined in any one of embodiments 1) to 45) or a pharmaceutically acceptable salt thereof.

The compounds according to Formula (I) as defined in any one of embodiments 1) to 45) are useful for the prevention or treatment of disorders relating to a dysfunction of the CXCR3 receptor or dysfunction of ligands signalling through CXCR3.

Such disorders relating to a dysfunction of the CXCR3 receptor or its ligands are diseases or disorders where a modulator of a human CXCR3 receptor is required. The above mentioned disorders may in particular be defined as comprising autoimmune disorders, inflammatory diseases, infectious diseases, transplant rejection, fibrosis, neurodegenerative disorders and cancer.

Autoimmune disorders may be defined as comprising rheumatoid arthritis (RA); multiple sclerosis (MS); inflammatory bowel disease (IBD; comprising Crohn's disease and ulcerative colitis); systemic lupus erythematosus (SLE); psoriasis; psoriatic arthritis; lupus nephritis; interstitial cystitis; celiac disease; antiphospholipid syndrome; thyroiditis such as Hashimoto's thyroiditis; lymphocytic thyroiditis; myasthenia gravis; type I diabetes; uveitis; episcleritis; scleritis; Kawasaki's disease, uveo-retinitis; posterior uveitis; uveitis associated with Behcet's disease; uveomeningitis syndrome; allergic encephalomyelitis; atopic diseases such as rhinitis, conjunctivitis, dermatitis; and post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis. In a sub-embodiment, autoimmune disorders include rheumatoid arthritis (RA); multiple sclerosis (MS); inflammatory bowel disease comprising Crohn's disease and ulcerative colitis; systemic lupus erythematosus (SLE); lupus nephritis; interstitial cystitis; celiac disease; and type I diabetes.

Inflammatory diseases may be defined as comprising asthma; COPD; atherosclerosis; myocarditis; dry eye disease (comprising Sjögren's dry eye syndrome); inflammatory myopathies; sarcoidosis; pulmonary arterial hypertension, especially associated with sarcoidosis; and obesity.

Infectious diseases may be defined as comprising diseases mediated by various infectious agents and complications resulting therefrom; such as malaria, cerebral malaria, leprosy, tuberculosis, influenza, toxoplasma gondii, dengue, hepatitis B and C, herpes simplex, leishmania, chlamydia trachomatis, lyme disease, west nile virus.

Transplant rejection may be defined as comprising rejection of transplanted organs such as kidney, liver, heart, lung, pancreas, cornea, and skin; graft-versus-host diseases brought about by stem cell transplantation; and chronic allograft vasculopathy.

Fibrosis may be defined as comprising liver cirrhosis (comprising primary biliary cirrhosis (PBC) and autoimmune hepatitis), idiopathic pulmonary fibrosis, renal fibrosis, endomyocardial fibrosis, systemic sclerosis, and arthrofibrosis.

Neurodegenerative disorders may be defined as comprising neurodegeneration and conditions involving neuronal death such as multiple sclerosis (including relapsing remitting multiple sclerosis and progressive multiple sclerosis), Alzheimer's disease, Parkinson's disease, Huntington's chorea, HIV associated dementia, prion mediated neurodegeneration, epilepsy, stroke, cerebral ischemia, cerebral palsy, neuromyelitis optica, clinically isolated syndrome, Alpers' disease, amyotrophic lateral sclerosis (ALS), senile dementia, dementia with Lewy bodies, Rett syndrome, spinal cord trauma, traumatic brain injury, trigeminal neuralgia, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, glossopharyngeal neuralgia, mild cognitive decline, cognitive decline, spinal muscular atrophy, and cerebral malaria. In another embodiment, neurodegenerative disorders may be defined as comprising in addition narcolepsy.

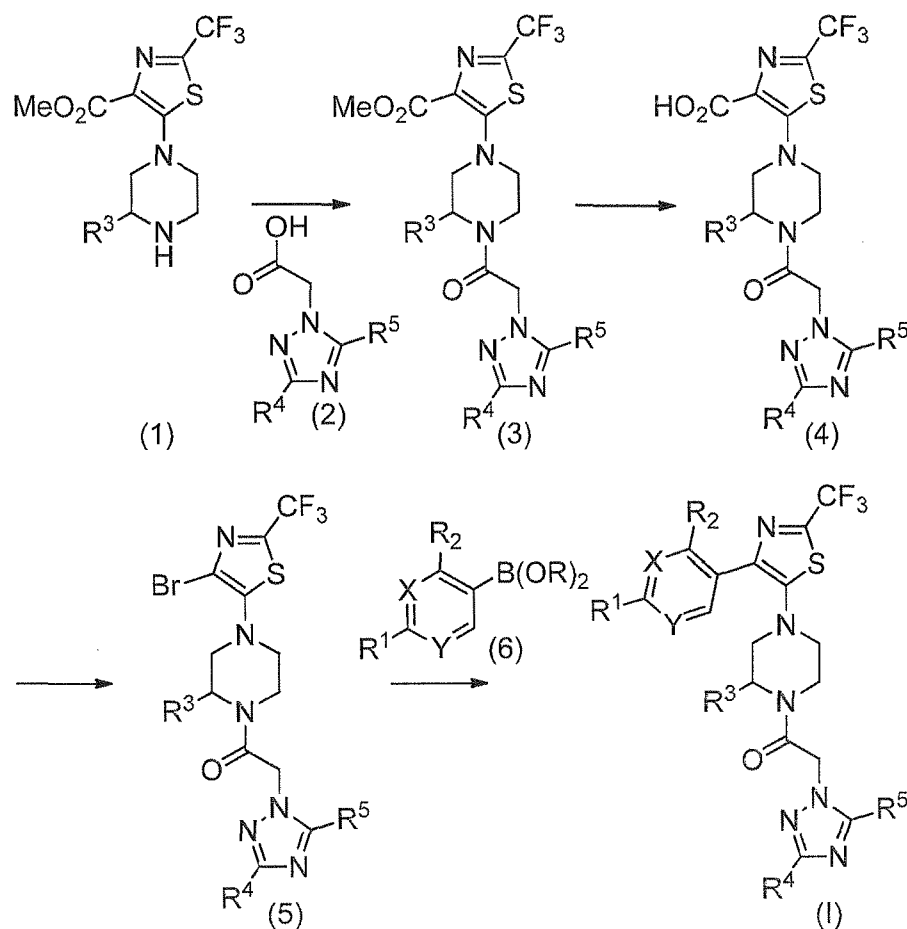
Cancer may be defined as comprising all sorts of cancers such as large intestine cancer, rectal cancer, breast cancer, lung cancer, non-small cell lung cancer, prostate cancer, esophageal cancer, stomach cancer, liver cancer, bile duct cancer, spleen cancer, kidney cancer, urinary bladder cancer, uterine cancer, ovarian cancer, cervical cancer, testicular cancer, thyroid cancer, pancreas cancer, brain tumor, blood tumor, basophil adenoma, prolactinoma, hyperprolactinemia, adenomas, endometrial cancer, colon cancer; chronic lymphocytic leukemia (CLL); and especially the metastatic spread of those cancers.

Especially, compounds of Formula (I) according to any one of embodiments 1) to 45), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of diseases selected from one, several or all of the following groups of diseases and disorders:

- 1) Autoimmune disorders selected from rheumatoid arthritis (RA); multiple sclerosis (MS); inflammatory bowel disease (IBD; comprising Crohn's disease and ulcerative colitis); systemic lupus erythematosus (SLE); psoriasis; lupus nephritis; and type I diabetes;
- 2) Inflammatory diseases selected from COPD; dry eye syndrome (comprising Sjögren's dry eye syndrome); myopathies (comprising inflammatory myopathies); and sarcoidosis;
- 3) Transplant rejection selected from graft-versus-host diseases;
- 4) Fibrosis selected from liver cirrhosis (comprising primary biliary cirrhosis (PBC) and autoimmune hepatitis); and
- 5) Neurodegenerative disorders selected from Guillain-Barré syndrome.

Preparation of compounds of Formula (I)

A further aspect of the invention is a process for the preparation of compounds of Formula (I). Compounds according to Formula (I) of the present invention can be prepared from commercially available or well known starting materials according to the methods described
5 in the experimental part; by analogous methods; or according to the general sequence of reactions outlined below, wherein X, Y, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as defined for Formula (I). Other abbreviations used herein are explicitly defined, or are as defined in the experimental section. In some instances the generic groups R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ might be incompatible with the assembly illustrated in the schemes below and so will
10 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. The compounds obtained may also be converted into salts, especially pharmaceutically acceptable salts thereof in a manner
15 known *per se*.

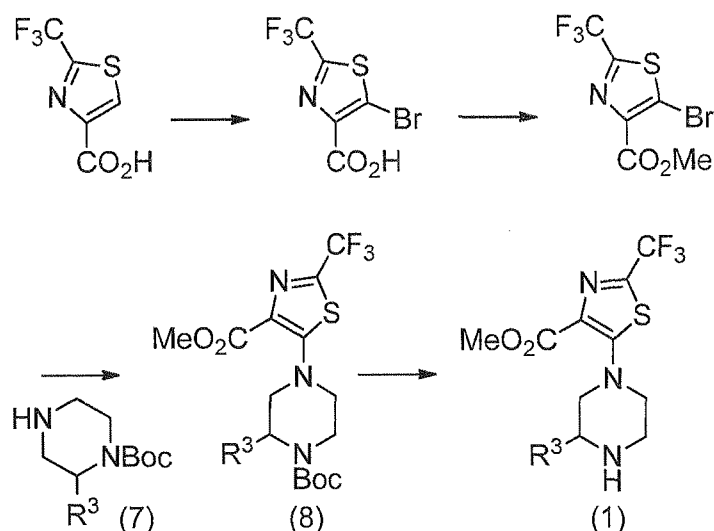
General preparation routes:

Scheme 1

Compounds of Formula (I) can be synthesized starting (Scheme 1) from a compound of structure (1) by, in a first step, amide coupling with a carboxylic acid derivative (2) using standard peptide coupling methods such as HATU in presence of a suitable base such as DIPEA and in a suitable solvent such as DCM, preferably at a temperature about RT. The obtained compound of structure (3) is saponified in basic medium using standard conditions (e.g. aq. NaOH in MeOH) and the carboxylic group in the compound of structure (4) is converted to the corresponding brominated thiazole (5) using (diacetoxyiodo)benzene and LiBr in THF at RT. Alternatively, NBS and lithium acetate in THF at RT may be employed.

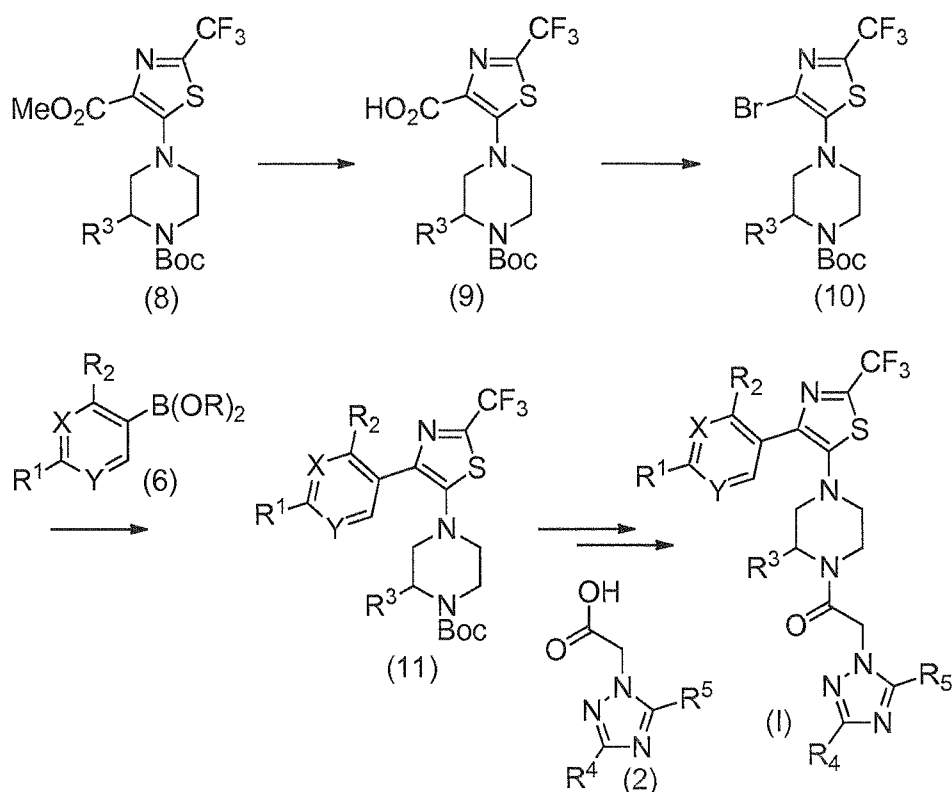
Suzuki coupling is performed using a coupling partner of structure (6), wherein R represents hydrogen or alkyl, using standard conditions for a Suzuki reaction, in presence of a suitable base such as aq. Na₂CO₃, K₂CO₃ or K₃PO₄, in presence of a suitable palladium catalyst such as Pd₂(dba)₃ with tricyclohexylphosphine as ligand, Pd(PPh₃)₄ or Pd(PPh₃)₂Cl₂, in a suitable solvent such as MeCN or dioxane, and preferably heating between 80°C and 100°C.

- 30 -

**Scheme 2**

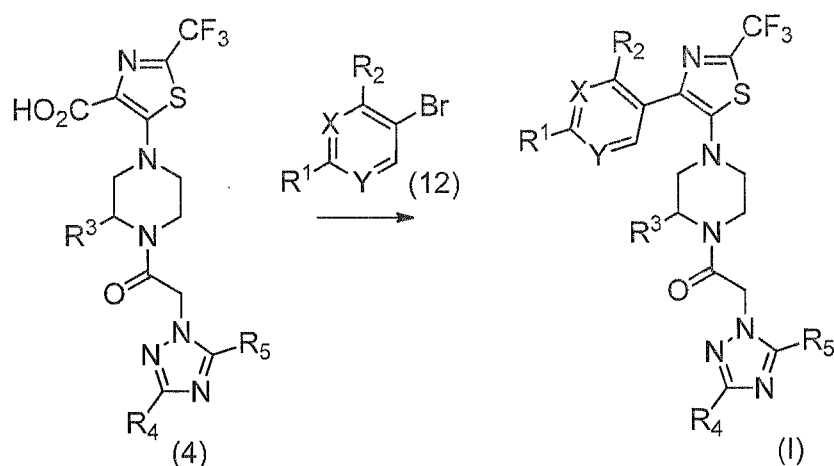
Compounds of structure (1) can be synthesized following the reaction sequence outlined in Scheme 2. 2-(Trifluoromethyl)thiazole-4-carboxylic acid is treated with n-butyl lithium and bromine in THF at a temperature around -78°C. The resulting brominated compound can be esterified using sulphuric acid in MeOH and heating at a temperature around 70°C. Nucleophilic aromatic substitution using commercially available piperazine derivatives (7), in presence of a suitable base such as DIPEA, in a suitable solvent such as MeCN, and at a temperature around 80°C provides compound of structure (8). The Boc protecting group of the intermediate (8) can be subsequently cleaved under standard acidic conditions, preferably using HCl in a suitable solvent such as EA, dioxane, Et₂O, EtOH or a mixture thereof, or using TFA in DCM, and at a temperature about RT to give the compound of structure (1).

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Scheme 3

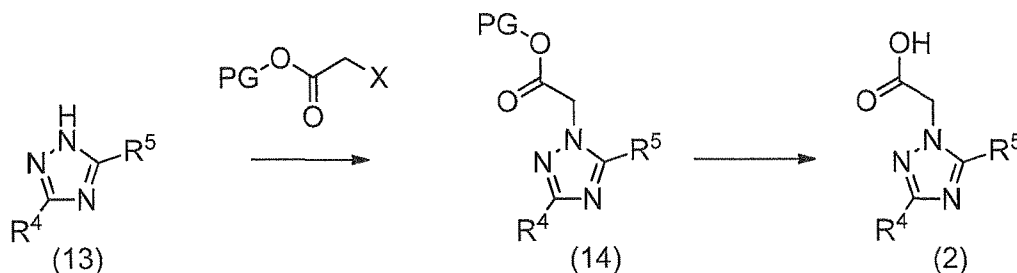
An alternative route to compounds of Formula (I) can be designed starting from intermediate (8), which is saponified under standard conditions (e.g. aq. NaOH in MeOH) to give compounds of structure (9) (Scheme 3). Conversion to the brominated thiazole (10) followed by Suzuki reaction to a compound of structure (11), Boc deprotection and final amide coupling provides the desired compounds of Formula (I) in synthetic steps already described in Scheme 1.



Scheme 4

A third route to compounds of Formula (I) is based on a decarboxylative arylation of intermediate (4) which can be coupled to the brominated derivative (12) using $\text{Pd}(\text{tBu}_3\text{P})_2$ as catalyst, Cs_2CO_3 as a base, TBACl and DMF as solvent, by heating the reaction mixture at 170°C in a microwave oven (Scheme 4).

5



Scheme 5

The compounds of structure (2) are either commercially available, or can be synthesized following the route shown in Scheme 5. A compound of structure (13) can be alkylated using an acetic acid derivative of formula $\text{X}-\text{CH}_2-\text{COO}(\text{PG})$, wherein X is a leaving group such as bromine and PG is a protecting group suitable for an acid function (e.g. benzyl), in presence of a base such as Cs_2CO_3 , in a suitable solvent such as MeCN, and at a temperature around RT. In case R^4 or R^5 represents (C_{1-4}) alkyl which is mono-substituted with hydroxy, the hydroxy group may be protected with a suitable protecting group such as TBS prior to alkylation with the acetic acid derivative of formula $\text{X}-\text{CH}_2-\text{COO}(\text{PG})$, which protecting group may be removed in the last step of the synthesis of compounds of formula (I) under conditions such as TBAF in THF at a temperature around RT.

Deprotection of the intermediate (14), such as benzyl deprotection under H_2 , using Pd/C as catalyst and EtOH as solvent at a temperature around RT, leads to the compound of structure (2). Other suitable acid function protecting groups and protection and deprotection methods are well known to one skilled in the art (see notably "Protective groups in organic synthesis", Greene T. W. and Wuts P. G. M., Wiley-Interscience, 1999).

The compounds of structure (6), (12) and (13) are either commercially available or can be prepared in analogy to methods described in the experimental part. For instance, compounds of structure (6) may be prepared from compounds of structure (12) using triisopropyl borate and n-BuLi in THF and toluene at a temperature around -78°C .

Experimental section:

Abbreviations (as used herein and in the description above):

aq. aqueous
Boc *tert.*-butyloxycarbonyl

	BSA	Bovine serum albumine
	Bu	butyl
	CC	column chromatography on silica gel
	CHO	Chinese hamster ovary
5	CV	column volume
	d	doublet
	dba	dibenzylideneacetone
	DCM	dichloromethane
	DEA	diethylamine
10	DIPEA	<i>N</i> -ethyl-diisopropylamine
	DMAP	4-Dimethylaminopyridine
	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
	Dppf	1,1'-bis(diphenylphosphanyl)ferrocene
15	EA	ethyl acetate
	EDTA	ethylenediaminetetraacetic acid
	EGTA	ethylene glycol tetraacetic acid
	Eq	equivalent
	Et	ethyl
20	FBS	fetal bovine serum
	FLIPR	Fluorescent imaging plate reader
	Fluo-4-AM	2-{[2-(2-{5-[bis(carboxymethyl)amino]-2-methylphenoxy}ethoxy)-4-(2,7-difluoro-6-hydroxy-3-oxo-3 <i>H</i> -xanthen-9-yl)phenyl](carboxymethyl)amino}acetic acid
25	G418	(2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i> ,5 <i>R</i> ,6 <i>S</i>)-5-amino-6-[(1 <i>R</i> ,2 <i>S</i> ,3 <i>S</i> ,4 <i>R</i> ,6 <i>S</i>)-4,6-diamino-3-[(2 <i>R</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i>)-3,5-dihydroxy-5-methyl-4-methylaminooxan-2-yl]oxy-2-hydroxycyclohexyl]oxy-2-(1-hydroxyethyl)oxane-3,4-diol
	h	hour(s)
	HATU	2-(7-Aza-1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethyluronium
30		hexafluorophosphate
	HBSS	Hank's balanced salt solution
	HEPES	4-(2-hydroxyethyl)-piperazine-1-ethanesulfonic acid
	Hep	heptanes
	HV	High vacuum
35	HPLC	high performance liquid chromatography
	LC	liquid chromatography
	M	molarity [mol L ⁻¹]

	Me	methyl
	MS	mass spectroscopy
	min	minute(s)
	N	normality
5	NBS	N-Bromosuccinimide
	org.	organic
	Pd/C	palladium on carbon
	PG	protecting group
	Ph	phenyl
10	rpm	rotations per minute
	RT	room temperature
	S	singlet
	sat.	Saturated
	sc	subcutaneous
15	sec	second(s)
	TBACl	Tetrabutylammonium chloride
	TBAF	Tetra-n-butylammonium fluoride
	TBS	tert-Butyldimethylsilyl
	TFA	trifluoroacetic acid
20	THF	tetrahydrofuran
	TLC	Thin layer chromatography
	t _R	retention time
	UPLC	Ultra performance liquid chromatography

25 I. Chemistry

The following examples illustrate the preparation of biologically active compounds of the invention but do not at all limit the scope thereof.

General: All temperatures are stated in degrees Celsius (°C). Unless otherwise indicated, the reactions take place at RT under an argon atmosphere and are run in a flame dried
 30 round-bottomed flask equipped with a magnetic stir bar.

Characterization methods used:

The LC-MS retention times have been obtained using the following elution conditions:

A) LC-MS (A):

Acquity UPLC BEH C18 1.7 µm 2.1x50 mm ID column from Waters, thermostated in the
 35 Acquity UPLC Column Manager (60°C) was used. The two elution solvents were as follows:
 solvent A = water + 0.05% formic acid; solvent B = MeCN + 0.045% formic acid. The eluent

flow rate was 1.0mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the table below (a linear gradient being used between two consecutive time points):

t (min)	0	1.4	1.8	1.9	2.0
Solvent A (%)	98	5	2	2	98
Solvent B (%)	2	95	98	98	2

5 B) LC-MS (B):

Zorbax SB-Aq, 3.5 μ m, 4.6x50mm column thermostated at 40°C. The two elution solvents were as follows: solvent A= water + 0.04%TFA; solvent B = MeCN. The eluent flow rate was 4.5 mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the table below (a linear gradient being used

10 between two consecutive time points):

t (min)	0	1.0	1.45	1.55
Solvent A (%)	95	5	5	95
Solvent B (%)	5	95	95	5

C) LC-MS (C):

Acquity UPLC HSS T3 C18 1.8 μ m 2.1x50 mm ID column from Waters, thermostated in the Acquity UPLC Column Manager (60°C) was used. The two elution solvents were as follows: solvent A = water + 0.05% formic acid; solvent B = MeCN + 0.045% formic acid. The eluent flow rate was 1mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the table below (a linear gradient being used between two consecutive time points):

t (min)	0	1.4	1.8	1.9	2.0
Solvent A (%)	98	5	2	2	98
Solvent B (%)	2	95	98	98	2

20 D) LC-MS (D):

Acquity UPLC HSS T3 C18 1.8 μ m 2.1x50 mm ID column from Waters, thermostated in the Acquity UPLC Column Manager (60°C) was used. The two elution solvents were as follows: solvent A = water + 0.05% TFA; solvent B = MeCN +0.045% TFA. The eluent flow rate was 1mL/min and the characteristics of the eluting mixture proportion in function of the time t

from start of the elution are summarized in the table below (a linear gradient being used between two consecutive time points):

t (min)	0	1.4	1.8	1.9	2.0
Solvent A (%)	98	5	2	2	98
Solvent B (%)	2	95	98	98	2

E) LC-MS (E):

- 5 Acquity UPLC CSH C18 1.7 μ m 2.1x50 mm ID column from Waters, thermostated in the Acquity UPLC Column Manager (60°C) was used. The two elution solvents were as follows: solvent A = water + 0.05% formic acid; solvent B = MeCN +0.045% formic acid. The eluent flow rate was 1mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the table below (a linear gradient being used between two consecutive time points):

t (min)	0	1.4	1.8	1.9	2.0
Solvent A (%)	98	5	2	2	98
Solvent B (%)	2	95	98	98	2

Preparative LC-MS methods used:

The purifications by preparative LC-MS have been performed using the conditions described hereafter.

15 I) Preparative LC-MS (I):

A X-Bridge column (Waters C18, 10 μ m OBD, 30x75 mm) was used. The two elution solvents were as follows: solvent A = water + 0.5% NH₄OH (25%); solvent B = MeCN. The eluent flow rate was 75 mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the tables below (a linear gradient being used between two consecutive time points):

t (min)	0	0.01	4.0	6.0	6.2	6.6
Solvent A (%)	80	80	5	5	80	80
Solvent B (%)	20	20	95	95	20	20

II) Preparative LC-MS (II):

A X-Bridge column (Waters C18, 10 μ m OBD, 30x75 mm) was used. The two elution solvents were as follows: solvent A = water + 0.5% NH₄OH (25%); solvent B = MeCN. The eluent flow rate was 75 mL/min and the characteristics of the eluting mixture proportion in

function of the time t from start of the elution are summarized in the tables below (a linear gradient being used between two consecutive time points):

t (min)	0	0.01	4.0	6.0	6.2	6.6
Solvent A (%)	90	90	5	5	90	90
Solvent B (%)	10	10	95	95	10	10

III) Preparative LC-MS (III):

- 5 A X-Bridge column (Waters C18, 10µm OBD, 30x75 mm) was used. The two elution solvents were as follows: solvent A = water + 0.5% formic acid; solvent B = MeCN. The eluent flow rate was 75 mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the tables below (a linear gradient being used between two consecutive time points):

t (min)	0	0.01	4.0	6.0	6.2	6.6
Solvent A (%)	80	80	5	5	80	80
Solvent B (%)	20	20	95	95	20	20

IV) Preparative LC-MS (IV):

- 15 An Atlantis column (Waters T3, 10µm OBD, 30x75 mm) was used. The two elution solvents were as follows: solvent A = water + 0.5% formic acid; solvent B = MeCN. The eluent flow rate was 75 mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the tables below (a linear gradient being used between two consecutive time points):

t (min)	0	0.01	4.0	6.0	6.2	6.6
Solvent A (%)	80	80	5	5	80	80
Solvent B (%)	20	20	95	95	20	20

V) Preparative LC-MS (V):

- 20 An Atlantis column (Waters T3, 10µm OBD, 30x75 mm) was used. The two elution solvents were as follows: solvent A = water + 0.5% formic acid; solvent B = MeCN. The eluent flow rate was 75 mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the tables below (a linear gradient being used between two consecutive time points):

t (min)	0	0.01	4.0	6.0	6.2	6.6
Solvent A (%)	90	90	5	5	90	90
Solvent B (%)	10	10	95	95	10	10

VI) Preparative LC-MS (VI):

A X-Bridge column (Waters C18, 5 μ m OBD, 19x50 mm) was used. The two elution solvents were as follows: solvent A = water + 0.1% NH₄OH (25%); solvent B = MeCN + 0.1% NH₄OH (25%). The eluent flow rate was 40 mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the tables below (a linear gradient being used between two consecutive time points):

Gradient 1:

t (min)	0	0.2	0.3	4.4	4.5	5.6	5.7
Solvent A (%)	75	75	65	35	5	5	95
Solvent B (%)	25	25	35	65	95	95	5

Gradient 2:

t (min)	0	0.2	0.3	4.4	4.5	5.6	5.7
Solvent A (%)	60	60	50	20	5	5	95
Solvent B (%)	40	40	50	80	95	95	5

VII) Preparative LC-MS (VII):

A X-Bridge column (Waters C18, 10 μ m OBD, 30x75 mm) was used. The two elution solvents were as follows: solvent A = water + 0.5% NH₄OH (25%); solvent B = MeCN. The eluent flow rate was 75 mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the tables below (a linear gradient being used between two consecutive time points):

t (min)	0	0.01	4.0	6.0	6.2	6.6
Solvent A (%)	70	70	5	5	70	70
Solvent B (%)	30	30	95	95	30	30

VIII) Preparative LC-MS (VIII):

A Gemini column (Phenomenex NX 10 μ m, 30x100mm) was used. The two elution solvents were as follows: solvent A = water + 0.5% NH₄OH; solvent B = acetonitrile. The eluent flow rate was 100 mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the tables below (a linear gradient being used between two consecutive time points):

t (min)	0	0.6	7.8	9.2	9.5	10
Solvent A (%)	90	90	5	5	90	90
Solvent B (%)	10	10	95	95	10	10

Preparative chiral HPLC methods used:

The purifications by preparative chiral HPLC have been performed using the conditions described hereafter.

5 I) Preparative chiral HPLC (I):

A ChiralCel OD-H column (5µm, 20x250mm) was used. The elution solvent was Hep/EtOH/DEA 70/30/0.1, run for 15min and at a flow rate of 16 mL/min.

II) Preparative chiral HPLC (II):

10 A ChiralPak IB column (5µm, 20x250mm) was used. The elution solvent was Hep/EtOH/DEA 70/30/0.1, run for 11min and at a flow rate of 19 mL/min.

Example 1: 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(4-methoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone*1.1. 5-Bromo-2-trifluoromethyl-thiazole-4-carboxylic acid*

15 To a solution of 2-(trifluoromethyl)thiazole-4-carboxylic acid (3.2g) in anhydrous THF (60mL) under argon cooled down to -78°C was added n-BuLi (1.6M in hexane, 21.3mL) dropwise over 15min so that the internal temperature did not rise above -60°C. A solution of Br₂ (0.92mL) in cyclohexane (8mL) was then added dropwise to keep the internal temperature below -60°C. The resulting mixture was stirred at -78°C for 2h and carefully quenched by addition of water (50mL). Citric acid (10%) was added until pH=2 and the
20 mixture was extracted with EA. The org. layers were washed with brine, dried (MgSO₄), filtered off and evaporated to dryness to afford 4.15g of brown solid, used without further purification. LC-MS (B): t_R = 0.67min. F-NMR (CD₃OD): -63.57ppm (s).

1.2. 5-Bromo-2-trifluoromethyl-thiazole-4-carboxylic acid methyl ester

25 To a solution of intermediate 1.1 (12g), MeOH (130mL) was added H₂SO₄ (6.5mL) and the mixture stirred at 70°C for 3h. After cooling down, the reaction mixture was quenched with sat. aq. Na₂CO₃ and the solvent partially evaporated off. The residue was diluted with DCM and washed with aq. sat. Na₂CO₃ (1x), water (1x) and brine (1x), and the aq. phases were extracted with DCM (2x). The combined org. layers were dried over MgSO₄, filtrated off, evaporated and dried under HV to afford 12g of brown resin. LC-MS (B): t_R = 0.83min. F-
30 NMR (CD₃OD): -63.59ppm (s).

1.3. (R)-4-(4-Methoxycarbonyl-2-trifluoromethyl-thiazol-5-yl)-2-methyl-piperazine-1-carboxylic acid tert-butyl ester

To a solution of intermediate 1.2 (10g) in MeCN (250mL) were added (R)-1-N-Boc-2-methylpiperazine (7.19g) and DIPEA (8.85mL) at RT. The reaction mixture was stirred at
35 80°C for 43h. After cooling down, the reaction mixture was diluted with EA and washed with

water and brine. The aq. layers were extracted with EA. The combined org. layers were dried over MgSO_4 , filtrated off and evaporated to dryness. The crude was purified by CC (Biotage, SNAP 340g, solvent A: Hep; solvent B: EA; gradient in %B: 10 over 5CV, 10 to 30 over 5CV, 30 over 5CV) to afford 9.14g of yellow resin. LC-MS (B): $t_R = 0.97\text{min}$; $[\text{M}+\text{H}]^+$: 410.0.

1.4. 5-((R)-3-Methyl-piperazin-1-yl)-2-trifluoromethyl-thiazole-4-carboxylic acid methyl ester, hydrochloride salt

A solution of intermediate 1.3 (4.5g) in 4M HCl in dioxane (30mL) was stirred at RT for 2h. The solvent was removed under reduced pressure to afford 3.66g of beige solid. LC-MS (B): $t_R = 0.54\text{min}$; $[\text{M}+\text{H}]^+$: 310.0.

1.5. (R)-methyl 5-(4-(2-(3,5-dimethyl-1H-1,2,4-triazol-1-yl)acetyl)-3-methylpiperazin-1-yl)-2-(trifluoromethyl)thiazole-4-carboxylate

To a suspension of (3,5-dimethyl-[1,2,4]triazol-1-yl)-acetic acid (2.25g) and intermediate 1.4 (3.4g) in DCM (100mL) were added HATU (6.06g) and DIPEA (5.62g) and the reaction mixture was stirred at RT for 2h. The mixture was diluted with DCM, washed with aq. sat. NaHCO_3 (2x) and the aq. layers extracted with DCM (3x). The combined org. layers were dried over Na_2SO_4 and concentrated to dryness. The crude was purified by CC (Biotage, SNAP 340g cartridge, solvent A: DCM; solvent B: DCM/MeOH 8:2; gradient in %B: 0 over 1CV, 0 to 15 over 3CV, 15 for 5CV, 15 to 30 over 5CV) to afford 5.02g as white foam. LC-MS (B): $t_R = 0.68\text{min}$; $[\text{M}+\text{H}]^+$: 446.8.

1.6. (R)-5-(4-(2-(3,5-dimethyl-1H-1,2,4-triazol-1-yl)acetyl)-3-methylpiperazin-1-yl)-2-(trifluoromethyl)thiazole-4-carboxylic acid

To a solution of intermediate 1.5 (2.5g) in MeOH (25 mL) was added aq. NaOH (1M, 25 mL) and the reaction mixture stirred for 2h at RT. The mixture was concentrated to dryness, and citric acid (10%) was added until pH=2-3. The mixture was extracted with DCM (3x) and the combined org. layers were dried over Na_2SO_4 , filtrated off and evaporated to afford 1.73g as white solid. LC-MS (B): $t_R = 0.60\text{min}$; $[\text{M}+\text{H}]^+$: 432.8.

1.7. (R)-1-(4-(4-bromo-2-(trifluoromethyl)thiazol-5-yl)-2-methylpiperazin-1-yl)-2-(3,5-dimethyl-1H-1,2,4-triazol-1-yl)ethanone

To a solution of intermediate 1.6 (1g) in THF (20mL) were added LiBr (203mg) and (diacetoxyiodo)benzene (760mg) at RT. The resulting suspension was stirred at RT for 15h30. The reaction mixture was diluted with H_2O and extracted with DCM (3x). The combined org. layers were dried over MgSO_4 , filtrated off and evaporated to dryness. The crude was purified by CC (Biotage, SNAP 100g cartridge, solvent A: DCM; solvent B: DCM/MeOH 8:2; gradient in %B: 0 for 1CV, 0 to 10 over 3CV, 10 over 5CV, 10 to 2 over

3CV, 20 over 5CV, 20 to 30% over 3CV) to afford 0.96g as white foam. LC-MS (B): t_R = 0.76min; $[M+H]^+$: 466.8.

1.8. 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(4-methoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone

- 5 To a vial containing 4-methoxyphenylboronic acid (20mg), $Pd_2(dba)_3$ (4.0mg) and tricyclohexylphosphine (3.0mg) were added a degased solution of intermediate 1.7 (41mg) in dioxane (0.6mL) and a degased 1M aq. K_3PO_4 solution (0.15mL). The reaction mixture was stirred at 90°C for 2h under argon. MeOH was added and the reaction mixture filtered through a neutral alumina cartridge previously conditioned with MeOH. Purification by Prep LC-MS (VI, gradient 1) afforded 28mg of the desired compound. LC-MS (A): t_R = 1.08min; $[M+H]^+$: 495.4.

Example 2 to Example 16 were synthesized using the appropriate boronic acid derivative and following the procedure described in Example 1, step 1.8. LC-MS data of Example 2 to Example 16 are listed in the table below. The LC-MS conditions used were LC-MS (A). All examples were purified by Prep LC-MS (VI, gradient 1) except examples 2, 7 and 9 which were purified by Prep LC-MS (VI, gradient 2).

Example N°	Name	t_R	$[M+H]^+$
2	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(4-isopropoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone	1.2	523.4
3	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[4-(4-trifluoromethoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone	1.23	549.4
4	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[4-(4-(2,2,2-trifluoro-ethoxy)-phenyl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone	1.17	563.4
5	4-(5-((R)-4-[2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-acetyl]-3-methyl-piperazin-1-yl)-2-trifluoromethyl-thiazol-4-yl)-benzonitrile	1.05	490.4
6	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(4-fluoro-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone	1.11	483.4

7	1-[(R)-4-[4-(4-Chloro-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone	1.18	499.4
8	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-(4-p-tolyl-2-trifluoromethyl-thiazol-5-yl)-piperazin-1-yl]-ethanone	1.15	479.4
9	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(4-ethyl-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone	1.21	493.4
10	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(3-fluoro-4-methoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone	1.09	513.4
11	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(2-fluoro-4-methoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone	1.05	513.4
12	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(4-methoxy-3-methyl-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone	1.16	509.4
13	1-[(R)-4-(4-Benzo[1,3]dioxol-5-yl-2-trifluoromethyl-thiazol-5-yl)-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone	1.06	509.4
14	1-[(R)-4-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone	1.06	523.4
15	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(6-ethoxy-pyridin-3-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone	1.09	510.4
16	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(6-methoxy-pyridin-3-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone	1.02	496.4

Example 17: 2-(3-Dimethylaminomethyl-5-methyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone

17.1. Methyl-(5-methyl-1H-[1,2,4]triazol-3-ylmethyl)-carbamic acid tert-butyl ester

To a suspension of ethyl acetimidate hydrochloride (492mg) in MeCN (10mL) was added Amberlyst A21 (1.12g). The suspension was stirred at RT for 15min, filtered off and tert-butyl(2-hydrazino-2-oxoethyl)methylcarbamate (0.761mL) was added to the filtrate. The reaction mixture was stirred at 50°C for 92h and at 100°C for 8h and was then evaporated to dryness. The residue was purified by CC (EA/MeOH 1/0, then 9/1) to afford 520mg as yellow oil. LC-MS (B): t_R = 0.54min; $[M+H]^+$: 227.1.

17.2. *Benzyl 2-(3-(((tert-butoxycarbonyl)(methyl)amino)methyl)-5-methyl-1H-1,2,4-triazol-1-yl)acetate*

To a solution of intermediate 17.1 (470mg) in MeCN (20mL) was added Cs_2CO_3 (677mg) followed by benzyl bromoacetate (0.343mL). The reaction mixture was stirred at RT overnight and evaporated to dryness. The residue was taken up in DCM and washed with water. The aq. layers were extracted with DCM, the combined org. layers were dried over Na_2SO_4 , filtered off and evaporated to dryness. The residue was purified by CC (Hep/EA 1/1 then DCM/MeOH 9/1) to afford 290mg as yellow oil. LC-MS (B): t_R = 0.83min; $[M+H]^+$: 375.1. ^1H -NMR (CD_3OD): 7.39-7.35 (m, 5H); 5.24 (s, 2H); 5.09 (s, 2H); 4.43 (m, 2H); 2.89 (m, 3H); 2.41 (s, 3H); 1.44 (d, 9H). Roesy signal seen between CH_2 at 5.09ppm and CH_3 at 2.41ppm.

17.3. *(5-methyl-3-methylaminomethyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester*

The Boc protecting group of intermediate 17.2 was cleaved using a method analogous to that of Example 1 step 1.4, intermediate 17.2 replacing intermediate 1.3. LC-MS (B): t_R = 0.53min; $[M+H]^+$: 275.1.

17.4. *(3-Dimethylaminomethyl-5-methyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester*

A solution of intermediate 17.3 (250mg) and formaldehyde (36.5% in water, 27.4mg) in DCM (8mL) was stirred at RT overnight. $NaBH(OAc)_3$ (272mg) was added and the reaction mixture was stirred at RT for 1h, diluted with DCM and washed with water. The aq. phase was extracted with DCM and evaporated to dryness to afford 150mg as colourless oil. LC-MS (B): t_R = 0.54min; $[M+H]^+$: 289.1.

17.5. *(3-Dimethylaminomethyl-5-methyl-[1,2,4]triazol-1-yl)-acetic acid*

A flask containing intermediate 17.4 (150mg), Pd/C (28mg) in EtOH (10mL) was evacuated and backfilled with argon (3x), afterwards evacuated and backfilled with H_2 (3x) and the reaction mixture stirred at RT for 2h. The reaction mixture was filtered over a celite plug and the filtrate evaporated to dryness to afford 77mg as white solid. LC-MS (B): t_R = 0.15min; $[M+H]^+$: 199.2.

17.6. *(R)-4-(4-Carboxy-2-trifluoromethyl-thiazol-5-yl)-2-methyl-piperazine-1-carboxylic acid tert-butyl ester*

To a solution of intermediate 1.3 (4.25g) in EtOH (40mL) was added 1M NaOH (40mL) at RT and the reaction mixture stirred for 1h20. The solvent was evaporated off and the residue acidified to pH 2 by the addition of aq. citric acid (10%). The aq. layer was extracted with DCM (3x) and the combined org. layers were dried over Na₂SO₄ and concentrated to dryness to afford 4.1g as orange solid. LC-MS (B): t_R = 0.88min; [M+H]⁺: 395.9.

17.7. (R)-4-(4-Bromo-2-trifluoromethyl-thiazol-5-yl)-2-methyl-piperazine-1-carboxylic acid tert-butyl ester

This compound was prepared using a method analogous to that of Example 1 step 1.7, intermediate 17.6 replacing intermediate 1.6. LC-MS (B): t_R = 1.04min; [M+H]⁺: 429.2.

17.8. (R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazine-1-carboxylic acid tert-butyl ester

A mixture of intermediate 17.7 (1.63g), 2-ethoxypyrimidine-5-boronic acid (778mg), Pd(PPh₃)₂Cl₂ (152mg), 1M Na₂CO₃ (12mL) in MeCN (12mL) was vigorously stirred at 80°C under argon overnight. The reaction mixture was allowed to cool down to RT, diluted with H₂O and extracted with DCM (3x). The combined org. layers were dried over MgSO₄, filtrated off and evaporated to dryness. The crude was purified by CC (Biotage, SNAP 50g cartridge, solvent A: Hep; solvent B: EA; gradient in %B: 10 for 5CV, 10 to 30 over 5CV, 30 for 3CV) to afford 1.35g as pale yellow resin. LC-MS (B): t_R = 1.04min; [M+H]⁺: 473.9.

17.9. 2-Ethoxy-5-[5-((R)-3-methyl-piperazin-1-yl)-2-trifluoromethyl-thiazol-4-yl]-pyrimidine

To solution of intermediate 17.8 (1.32g) in DCM (45mL) was added TFA (4.28mL) at RT. The resulting mixture was stirred at RT overnight. The reaction mixture was treated with 1M NaOH to pH=14 and extracted with DCM (3x). The combined org. layers were dried over MgSO₄, filtrated off, evaporated and dried at HV to afford 1.01g as beige solid. LC-MS (B): t_R = 0.64min; [M+H]⁺: 374.0.

17.10. 2-(3-Dimethylaminomethyl-5-methyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone

A mixture of intermediate 17.5 (26mg), intermediate 17.9 (50mg), HATU (66mg), and DIPEA (34μL) in DCM (1.5mL) was stirred for 1h40 at RT. The reaction mixture was evaporated to dryness and the crude purified by Prep LC-MS (I) to afford 38mg as white solid. LC-MS (D): t_R = 1.23min; [M+H]⁺: 554.5.

Example 18 and Example 19: 1-((R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3-ethyl-5-methyl-[1,2,4]triazol-1-yl)-ethanone and 1-((R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(5-ethyl-3-methyl-[1,2,4]triazol-1-yl)-ethanone

Acid precursors for Example 18 and 19:

Step 18.1. To ethylacetimidate hydrochloride (500mg) in MeCN (6mL) was added Amberlyst A21 (1.14g) and the suspension stirred at RT for 15min. Then the mixture was filtrated and the resin washed with MeCN (1mL). Propanoic acid hydrazide (353mg) was added to the filtrate and the resulting white suspension stirred at 50°C under argon for 4d and at 80°C overnight. The reaction mixture was evaporated. Purification by CC (Biotage, SNAP 10g cartridge, solvent A: DCM; solvent B: MeOH; gradient in %B: 10 for 6CV, 10 to 20 over 3CV, 20 for 6CV) followed by a second CC (Biotage, SNAP 10g cartridge, solvent A: DCM; solvent B: DCM/MeOH 8:2; gradient in %B: 25 for 7CV, 25 to 50 over 3CV, 50 for 5CV) afforded 3-ethyl-5-methyl-1H-[1,2,4]triazole (125mg as yellow oil). LC-MS (B): t_R = 0.21min; $[M+H]^+$: 112.4.

Step 18.2: A method analogous to that of Example 17 step 17.2 was followed, 3-ethyl-5-methyl-1H-[1,2,4]triazole from step 18.1 replacing intermediate 17.1. A mixture of regioisomers was obtained: (3-Ethyl-5-methyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester and (5-ethyl-3-methyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester.

Step 18.3: A method analogous to that of Example 17 step 17.5 was followed, intermediates from step 18.2 replacing intermediate 17.4. A mixture of regioisomers (45:55) was obtained: (3-Ethyl-5-methyl-[1,2,4]triazol-1-yl)-acetic acid and (5-ethyl-3-methyl-[1,2,4]triazol-1-yl)-acetic acid.

To a suspension of the acid precursor mixture described in step 18.3 (85mg) in DCM (6mL) were added intermediate 17.9 (199mg), DIPEA (129 μ L) and HATU (249mg) and the reaction mixture was stirred at RT for 1h30. The mixture was evaporated and purified by Prep LC-MS (IV) followed by preparative chiral HPLC (I). Both fractions were taken up in DCM and washed with water (2x) and the aq. layers extracted with DCM (1x). The combined org. layers were dried over MgSO₄, filtrated off, evaporated and dried at HV.

First eluting fraction (Example 18): 1-{(R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-ethyl-5-methyl-[1,2,4]triazol-1-yl)-ethanone: 102mg yellow resin. LC-MS (A): t_R = 1.02min; $[M+H]^+$: 525.4.

Second eluting fraction (Example 19): 1-{(R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(5-ethyl-3-methyl-[1,2,4]triazol-1-yl)-ethanone. 75mg yellow resin. LC-MS (A): t_R = 1.02min; $[M+H]^+$: 525.4.

Example 20: 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-{(R)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-ethanone

A mixture of intermediate 1.6 (30mg), 5-bromo-2-ethoxypyrimidine (14mg), TBACl (19mg), Cs₂CO₃ (34mg), [Pd(tBu₃P)₂] (1.8mg) and DMF (1.5mL) was stirred at 170°C for 20min under argon in the microwave. The crude mixture was purified by Prep LC-MS (I) followed by Prep LC-MS (IV) to afford 18mg as white solid. LC-MS (A): t_R = 0.98min; $[M+H]^+$: 511.4.

Example 21 to Example 33 were synthesized following the procedure described in Example 20, the appropriate bromoaryl precursor replacing 5-bromo-2-ethoxypyrimidine:

LC-MS data and purification methods are listed for these examples in the table below.

Bromoaryl precursor for Example 25: 5-Bromo-2-(2-methoxy-ethoxy)-pyrimidine

- 5 NaH (60% in oil, 122mg) was added to a solution of 2-methoxy-ethanol (0.3mL) in THF (25mL) under argon at 0°C and the reaction mixture stirred for 45min at 0°C. Then, 5-bromo-2-chloropyrimidine (500mg) was added and the reaction mixture allowed reaching RT. After 3.5h, the reaction was quenched by the addition of aq. sat. NH₄Cl and THF was evaporated off. The aq. layer was extracted with DCM (2x) and the combined org. layers
- 10 were dried over Na₂SO₄ and concentrated to dryness. Purification by CC (Hep/EA 7:3) afforded 5-bromo-2-(2-methoxy-ethoxy)-pyrimidine (0.37g as yellow oil). LC-MS (B): t_R = 0.64min; [M+H]⁺: 233.0.

Bromoaryl precursor for Example 26: [2-(5-Bromo-pyrimidin-2-yloxy)-ethyl]-dimethyl-amine

- 15 NaH (60% in oil, 122mg) was added to a solution of dimethylethanolamine (0.38mL) in THF (25mL) under argon at 0°C and the reaction mixture stirred for 45 min at 0°C. Then, 5-bromo-2-chloropyrimidine (500mg) was added and the reaction mixture allowed reaching RT. After 1.5h at RT, the reaction was quenched by the addition of aq. sat. NH₄Cl and THF was evaporated off. The aq. layer was extracted with DCM (2x) and the combined org.
- 20 layers were dried over Na₂SO₄ and concentrated to dryness. Purification by CC (Hep/EA 7:3, then DCM/MeOH 9:1 +1% Et₃N) afforded [2-(5-bromo-pyrimidin-2-yloxy)-ethyl]-dimethyl-amine (0.43g as yellow oil). LC-MS (B): t_R = 0.39min; [M+H]⁺: 246.1.

Example N°	Name	Purification	t _R	[M+H] ⁺	LC-MS Method
21	1-[(R)-4-(4-Chroman-6-yl-2-trifluoromethyl-thiazol-5-yl)-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone	Prep LC-MS (IV, VII)	1.13	521.4	A

22	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[4-(2-propyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl]-ethanone	Prep LC-MS (III, I) + PrepTLC (DCM/MeOH 95:5)	0.77	509.0	B
23	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[4-(2-methyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl]-ethanone	Prep LC-MS (III, I)	1.22	481.4	C
24	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone	Prep LC-MS (III)	1.06	535.4	A
25	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-[2-(2-methoxyethoxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone	Prep LC-MS (III), PrepTLC (DCM/MeOH 95:5)	0.92	541.4	A
26	1-[(R)-4-[4-[2-(2-Dimethylaminoethoxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone	Prep LC-MS (I), PrepTLC (DCM/MeOH 95:5)	1.04	554.5	D
27	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(2-isopropoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone	Prep LC-MS (IV)	1.05	525.4	A

28	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-{4-[2-(2,2,2-trifluoro-ethoxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl}-piperazin-1-yl)-ethanone	CC (DCM/MeOH 97:3 to 8:2), Prep LC-MS (IV)	1.07	565.4	A
29	1-((R)-4-[4-(2,4-Diethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone	CC (DCM/MeOH 97:3), Prep LC-MS (IV)	1.03	555.5	A
30	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-{4-[2-(oxetan-3-yloxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl}-piperazin-1-yl)-ethanone	CC (DCM/MeOH 97:3)	1.25	539.4	C
31	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(4-ethoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone	Prep LC-MS (VII)	1.15	509.4	A
32	2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-methoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone	Prep LC (III) + PrepTLC (DCM/MeOH 95:5)	0.91	497.4	A
33	1-((R)-4-[4-(2-Cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone	Prep LC-MS (III, I)	0.99	507.4	A

Example 34: 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((S)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone

34.1. 5-((S)-4-[2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-acetyl]-3-methyl-piperazin-1-yl)-2-trifluoromethyl-thiazole-4-carboxylic acid

This compound was prepared using a method analogous to that of Example 1 (step 1.3 to step 1.6), (S)-1-N-Boc-2-methylpiperazine replacing (R)-1-N-Boc-2-methylpiperazine in step 1.3. LC-MS (B): $t_R = 0.61\text{min}$; $[M+H]^+$: 432.9.

34.2. 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(S)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone

This compound was prepared using a method analogous to that of Example 20, intermediate 34.1 replacing intermediate 1.6. The desired compound was purified by Prep LC-MS (IV). LC-MS (A): $t_R = 0.98\text{min}$; $[M+H]^+$: 511.4.

Example 35: 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone

35.1. 4-(4-Methoxycarbonyl-2-trifluoromethyl-thiazol-5-yl)-piperazine-1-carboxylic acid tert-butyl ester

This compound was prepared using a method analogous to that of Example 1 step 1.3, 1-Boc-piperazine replacing (R)-1-N-Boc-2-methylpiperazine. LC-MS (B): $t_R = 0.94\text{min}$; $[M+H]^+$: 339.9.

35.2. 2-Ethoxy-5-(5-piperazin-1-yl-2-trifluoromethyl-thiazol-4-yl)-pyrimidine

This compound was prepared using a method analogous to that of Example 17, step 17.6 to step 17.9, intermediate 35.1 replacing intermediate 1.3 in step 1.4. LC-MS (B): $t_R = 0.65\text{min}$; $[M+H]^+$: 360.0.

35.3. 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 1, step 1.5, intermediate 35.2 replacing intermediate 1.4. The desired compound was purified by Prep LC-MS (IV). LC-MS (A): $t_R = 0.96\text{min}$; $[M+H]^+$: 497.4.

Example 36: 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[4-(2-pyrrolidin-1-yl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl]-ethanone

This compound was prepared using a method analogous to that of Example 17 step 17.8, intermediate 1.7 replacing intermediate 17.7 and 2-pyrrolidinopyrimidine-5-boronic acid replacing 2-ethoxypyrimidine-5-boronic acid. The desired compound was purified by Prep LC-MS (I). LC-MS (A): $t_R = 1.02\text{min}$; $[M+H]^+$: 536.5.

Example 37: 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl]-ethanone

This compound was prepared using a method analogous to that of Example 36, 2-(4-methylpiperazino)pyrimidine-5-boronic acid replacing 2-pyrrolidinopyrimidine-5-boronic acid.

The desired compound was purified by Prep LC-MS (I). LC-MS (D): t_R = 1.08min; $[M+H]^+$: 565.5.

Example 38: 1-((R)-4-[4-(2-Cyclobutoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone

5 38.1. 5-Bromo-2-cyclobutoxy-pyrimidine

To a solution of cyclobutanol (0.2mL) in THF (25mL) was added at 0°C NaH (122mg, 60% in oil) and the mixture was stirred for 45min under argon. Then, 5-bromo-2-chloropyrimidine (500mg) was added and the mixture allowed to warm up to RT overnight. The reaction mixture was quenched by the addition of sat. NH_4Cl and extracted with DCM (2x). The combined org. layers were dried over Na_2SO_4 and concentrated to dryness. Purification by Prep LC-MS (II) afforded 0.38g as white solid. LC-MS (B): t_R = 0.82min. ^1H NMR (400 MHz, MeOD) δ : 1.67-1.78 (m, 1 H), 1.84-1.93 (m, 1 H), 2.13-2.24 (m, 2 H), 2.44-2.53 (m, 2 H), 5.14-5.22 (m, 1 H), 8.59-8.69 (m, 2 H)

38.2. (2-Cyclobutoxypyrimidin-5-yl)boronic acid

15 To a solution of intermediate 38.1 (350mg) and triisopropyl borate (0.43mL) in THF (1.1mL) and toluene (4.4mL) was added at -78°C n-BuLi (1.83mL, 1.6M) dropwise and the resulting suspension was stirred at -78°C for 1h. The reaction mixture was allowed to warm up to RT, acidified by addition of HCl (1M) to pH=1, diluted with H_2O and extracted with EA (3x). The combined org. layers were dried over Na_2SO_4 and concentrated to dryness. The residue was purified by Prep LC-MS (V) to afford 35mg as white solid. LC-MS (B): t_R = 0.56min; $[M+H]^+$: 195.2.

38.3. 1-((R)-4-[4-(2-Cyclobutoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 36, intermediate 38.2 replacing 2-pyrrolidinopyrimidine-5-boronic acid. The desired compound was purified by Prep LC-MS (I). LC-MS (A): t_R = 1.09min; $[M+H]^+$: 537.4.

Example 39: 1-((R)-4-[4-(3,4-Dihydro-2H-pyrano[2,3-b]pyridin-6-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone

A mixture of intermediate 1.7 (30mg), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-pyrano[2,3-b]pyridine (16.8mg), $Pd(PPh_3)_4$ (3.8mg), sat. aq. K_2CO_3 (0.3mL) in dioxane (0.6mL) at RT was vigorously stirred at 100°C under argon for 16h30. The solvent was evaporated off and the residue diluted with water and extracted with DCM (3x). The combined org. layers were dried over Na_2SO_4 and concentrated to dryness. Purification by Prep LC-MS (I) followed by Prep TLC (DCM/MeOH 97:3) afforded 5mg as colorless resin. LC-MS (A): t_R = 0.93min; $[M+H]^+$: 522.4.

Example 40: 1-((R)-4-[4-(2,3-Dihydro-benzofuran-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 39, 2,3-dihydro-1-benzofuran-5-ylboronic acid replacing 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-pyrano[2,3-b]pyridine. The desired compound was purified by Prep LC-MS (I). LC-MS (A): t_R = 1.08min; $[M+H]^+$: 507.4.

Example 41: 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2,2-dideuterium-ethanone

A solution of Example 20 (30mg) and DIPEA (5 μ L) in CD₃OD (0.5mL) was stirred at RT overnight. The reaction mixture was evaporated, diluted with DCM (1mL) and H₂O (1mL) and stirred for a few minutes. Then the phases were separated using a phase separator and the aq. layer was re-extracted with DCM. The combined org. layers were evaporated and dried at HV to give 24mg as white solid. LC-MS (A): t_R = 0.98min; $[M+H]^+$: 513.4.

Example 42: 1-((R)-4-[4-[2-(2-Dimethylamino-ethyl)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone**42.1. 5-Bromo-2-vinyl-pyrimidine**

To a solution of 5-bromo-2-iodopyrimidine (750mg) and Pd(PPh₃)₄ (46mg) in abs. THF (15mL) under argon was added vinylmagnesium bromide (5.27mL, as 1M THF solution) dropwise within 5min at RT. The resulting solution was stirred at reflux for 2h30 and the reaction mixture then allowed to cool to RT. The mixture was diluted with water and extracted with EA (3x). The combined org layers were washed with brine (2x), dried over MgSO₄, filtrated off and evaporated to dryness. Purification by CC (Biotage, SNAP 25g cartridge, solvent A: Hep; solvent B: EA; gradient in %B: 0 to 5 over 1CV, 5 for 5CV, 5 to 10 over 3CV, 10 for 3CV) afforded 186mg as yellow liquid. LC-MS (6): t_R = 0.67min. ¹H NMR (400 MHz, CDCl₃): 5.80 (dd, J = 10.5 Hz, 1 H), 6.65 (d, J = 17.3 Hz, 1 H), 6.85 (dd, J_1 = 10.5 Hz, J_2 = 17.3 Hz 1 H), 8.76 (s, 2 H).

42.2. (4-vinylphenyl)boronic acid

To a solution of intermediate 42.1 (181mg) in THF (1mL) and toluene (4mL) was added triisopropyl borate (0.28mL) at -78°C followed by dropwise addition over 5min of n-BuLi (0.73mL; 1.6M in hexanes) at -78°C under argon. The suspension was stirred at -78°C for 45min and then allowed to warm up to RT. The reaction mixture was quenched by addition of 1M HCl (2.5ml) to pH=1, diluted with H₂O and EA. The aq. layer was separated and extracted with EA (2x). The combined org. layers were dried over MgSO₄, filtrated off, evaporated and dried at HV to give 108mg as orange solid, which was used without further purification. LC-MS (B): t_R = 0.44min; $[M+H]^+$: 151.2.

42.3. *(R)*-2-Methyl-4-[2-trifluoromethyl-4-(2-vinyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazine-1-carboxylic acid *tert*-butyl ester

This compound was prepared using a method analogous to that of Example 17, step 17.8, intermediate 42.2 replacing 2-ethoxypyrimidine-5-boronic acid. LC-MS (B): t_R = 1.04min; [M+H]⁺: 456.2.

42.4. *(R)*-4-{4-[2-(2-Dimethylamino-ethyl)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl}-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

To a solution of intermediate 42.3 (23mg) in MeOH (0.5mL) was added dimethylamine (76μL, as 2M solution in MeOH) at RT and the reaction mixture stirred at RT for 1h. The mixture was evaporated to dryness, dried at HV to afford 30mg as yellow resin. LC-MS (B): t_R = 0.78min; [M+H]⁺: 501.3.

42.5. Dimethyl-(2-{5-[5-((*R*)-3-methyl-piperazin-1-yl)-2-trifluoromethyl-thiazol-4-yl]-pyrimidin-2-yl}-ethyl)-amine, as hydrochloride salt

This compound was prepared using a method analogous to that of Example 1, step 1.4, intermediate 42.4 replacing intermediate 1.3. LC-MS (B): t_R = 0.49min; [M+H]⁺: 401.3.

42.6. 1-((*R*)-4-{4-[2-(2-Dimethylamino-ethyl)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl}-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 17 step 17.10, intermediate 42.5 replacing intermediate 17.9 and (3,5-dimethyl-[1,2,4]triazol-1-yl)-acetic acid replacing intermediate 17.5. LC-MS (D): t_R = 1.03min; [M+H]⁺: 538.5.

Example 43: 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((*R*)-4-[4-(2-ethyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 20, 5-bromo-2-ethylpyrimidine replacing 5-bromo-2-ethoxypyrimidine. LC-MS (B): t_R = 0.75min; [M+H]⁺: 494.5.

Example 44: 2-(3-Hydroxymethyl-5-methyl-[1,2,4]triazol-1-yl)-1-((*R*)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl)-ethanone

44.1. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-methyl-1H-[1,2,4]triazole

To a solution of (5-methyl-1H-1,2,4-triazol-3-yl)methanol (500mg) in DMF (17.5mL) was added at 0°C Et₃N (1.08mL), DMAP (54mg) and *tert*-butyl(chloro)dimethylsilane (806mg) and the reaction mixture was allowed to reach RT. After stirring for 16h30, the reaction mixture was diluted with EA and washed with water (2x) and brine (1x). The aq. layers were re-extracted with EA (2x). The combined org. layers were dried over MgSO₄, filtrated off and

evaporated to dryness. Purification by CC (Hep/EA 3:7) afforded 0.88g as white solid. LC-MS (B): t_R = 0.71min; $[M+H]^+$: 228.2.

44.2A. *[3-(tert-butyl-dimethyl-silanyloxymethyl)-5-methyl-[1,2,4]triazol-1-yl]-acetic acid benzyl ester* and 42.2B. *[5-(tert-butyl-dimethyl-silanyloxymethyl)-3-methyl-[1,2,4]triazol-1-yl]-acetic acid benzyl ester*

To a solution of intermediate 44.1 (860mg) in DMF (15mL) was added at 0°C NaH (60% in oil, 182mg) and the reaction mixture was stirred for 30 min at 0°C. After dropwise addition of benzyl bromoacetate (0.72mL) at 0°C, the reaction mixture was allowed to reach RT overnight. The reaction was quenched by the addition of water and extracted with DCM (3x). The combined org. layers were washed with brine and water, dried over Na₂SO₄ and concentrated to dryness. The residue was dissolved in EA and washed with water (3x) and the org. layer dried over Na₂SO₄ and concentrated to dryness. Purification by CC (Hep/EA 7:3) gave as first eluting fraction 0.29g of the regioisomer 42.2B *[5-(tert-butyl-dimethyl-silanyloxymethyl)-3-methyl-[1,2,4]triazol-1-yl]-acetic acid benzyl ester*. LC-MS (B): t_R = 0.98min; $[M+H]^+$: 376.06. Roesy signal at 5.11ppm and 4.84ppm seen between CH₂CO₂Bn and CH₂OTBS. The second isolated fraction was purified again by CC (Biotage, SNAP 50g cartridge, solvent A: Hep; solvent B: EA; gradient in %B: 0 to 30 over 20CV, 30 for 10CV) to afford 0.31g of the other regioisomer 42.2A *[3-(tert-butyl-dimethyl-silanyloxymethyl)-5-methyl-[1,2,4]triazol-1-yl]-acetic acid benzyl ester*. LC-MS (B): t_R = 0.96min; $[M+H]^+$: 376.1. Roesy signal seen between CH₂CO₂Bn at 4.88ppm and CH₃ at 2.4ppm.

44.3. *[3-(tert-Butyl-dimethyl-silanyloxymethyl)-5-methyl-[1,2,4]triazol-1-yl]-acetic acid*

This compound was prepared using a method analogous to that of Example 17 step 17.5, intermediate 44.2A (*[3-(tert-butyl-dimethyl-silanyloxymethyl)-5-methyl-[1,2,4]triazol-1-yl]-acetic acid benzyl ester*) replacing intermediate 17.4. LC-MS (B): t_R = 0.73min; $[M+H]^+$: 286.1.

44.4. *(R)-2-Methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazine-1-carboxylic acid tert-butyl ester*

This compound was prepared using a method analogous to that of Example 17, step 17.8, 2-(trifluoromethyl)pyrimidine-5-yl-boronic acid replacing 2-ethoxypyrimidine-5-boronic acid. LC-MS (B): t_R = 1.06min; $[M+H]^+$: 441.8.

44.5. *5-[5-((R)-3-Methyl-piperazin-1-yl)-2-trifluoromethyl-thiazol-4-yl]-2-trifluoromethyl-pyrimidine, as hydrochloride salt*

This compound was prepared using a method analogous to that of Example 1, step 1.4, intermediate 44.4 replacing intermediate 1.3. LC-MS (B): t_R = 0.7min; $[M+H]^+$: 439.0.

44.6. 2-[3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-methyl-[1,2,4]triazol-1-yl]-1-[(*R*)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone

This compound was prepared using a method analogous to that of Example 17 step 17.10, intermediate 44.3 replacing intermediate 17.5 and intermediate 44.5 replacing intermediate 17.9. A Prep TLC (DCM/MeOH 97:3) was done instead of a Prep LC-MS. LC-MS (B): t_R = 1.03min; $[M+H]^+$: 664.9.

44.7. 2-(3-Hydroxymethyl-5-methyl-[1,2,4]triazol-1-yl)-1-[(*R*)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone

To a solution of intermediate 44.6 (22mg) in THF (1mL) was added TBAF (1M in THF; 39 μ L) and the reaction mixture was stirred at RT for 2h. The mixture was evaporated to dryness and the residue dissolved in DCM. The org. layer was washed with water and brine and the aq. layers were re-extracted with DCM (2x). The combined org. layers were dried over Na₂SO₄ and concentrated to dryness. Prep TLC (DCM/MeOH 95:5) gave 9mg as yellowish solid. LC-MS (E): t_R = 1.06min; $[M+H]^+$: 551.2.

Example 45: 2-(5-Hydroxymethyl-3-methyl-[1,2,4]triazol-1-yl)-1-[(*R*)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone

45.1. [5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-methyl-[1,2,4]triazol-1-yl]-acetic acid

This compound was prepared using a method analogous to that of Example 17 step 17.5, intermediate 44.2B ([5-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-methyl-[1,2,4]triazol-1-yl]-acetic acid benzyl ester) replacing intermediate 17.4. LC-MS (B): t_R = 0.75min; $[M+H]^+$: 286.1.

45.2. 2-[5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-methyl-[1,2,4]triazol-1-yl]-1-[(*R*)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone

This compound was prepared using a method analogous to that of Example 44 step 44.6, intermediate 45.1 replacing intermediate 44.3. LC-MS (B): t_R = 1.05min; $[M+H]^+$: 665.0.

45.3. 2-(5-Hydroxymethyl-3-methyl-[1,2,4]triazol-1-yl)-1-[(*R*)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone

This compound was prepared using a method analogous to that of Example 44 step 44.7, intermediate 45.2 replacing intermediate 44.6. LC-MS (E): t_R = 1.08min; $[M+H]^+$: 551.2.

Example 46 and Example 47: 2-(3-Ethyl-5-methyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl)-ethanone and 2-(5-Ethyl-3-methyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl)-ethanone

These compounds were prepared using a method analogous to that of Example 18 and Example 19, intermediate 44.5 replacing intermediate 17.9. A preparative chiral HPLC (II) was used to separate the regioisomers:

First eluting fraction (Example 46): 2-(3-Ethyl-5-methyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl)-ethanone: 33mg, white solid. LC-MS (E): t_R = 1.14min; $[M+H]^+$: 549.3. Roesy signal seen between triazol-CH₃ 2.47ppm and CH₂CO at 4.96ppm.

Second eluting fraction (Example 47): 2-(5-Ethyl-3-methyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl)-ethanone. 32mg, white solid. LC-MS (E): t_R = 1.13min; $[M+H]^+$: 549.3. Roesy signal seen between triazol-CH₂CH₃ 2.74ppm and CH₂CO at 4.94ppm.

Example 48: 2-[3-(1-Hydroxy-1-methyl-ethyl)-5-methyl-[1,2,4]triazol-1-yl]-1-((R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl)-ethanone

48.1. [3-(1-Hydroxy-1-methyl-ethyl)-5-methyl-[1,2,4]triazol-1-yl]-acetic acid benzyl ester

This compound was prepared using a method analogous to that of Example 17 step 17.2, 2-(5-methyl-1H-1,2,4-triazol-1-yl)propan-2-ol replacing intermediate 17.1. LC-MS (B): t_R = 0.63min; $[M+H]^+$: 290.3.

48.2. [3-(1-Hydroxy-1-methyl-ethyl)-5-methyl-[1,2,4]triazol-1-yl]-acetic acid

This compound was prepared using a method analogous to that of Example 17 step 17.5, intermediate 48.1 replacing intermediate 17.4. LC-MS (B): t_R = 0.18min; $[M+H]^+$: 200.6.

48.3. 2-[3-(1-Hydroxy-1-methyl-ethyl)-5-methyl-[1,2,4]triazol-1-yl]-1-((R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 17 step 17.10, intermediate 48.2 replacing intermediate 17.5 and intermediate 44.5 replacing intermediate 17.9. LC-MS (E): t_R = 1.1min; $[M+H]^+$: 579.3.

Example 49: 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[2-trifluoromethyl-4-(6-trifluoromethyl-pyridin-3-yl)-thiazol-5-yl]-piperazin-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 36, 2-trifluoromethylpyridine-5-boronic acid replacing 2-pyrrolidinopyrimidine-5-boronic acid. The

desired compound was purified by Prep LC-MS (IV). LC-MS (E): t_R = 1.13min; $[M+H]^+$: 534.3.

Example 50: 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(S)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone

5 50.1. 1-[(S)-4-(4-Bromo-2-trifluoromethyl-thiazol-5-yl)-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 1 step 1.7, intermediate 34.1 replacing intermediate 1.6. LC-MS (B): t_R = 0.76min; $[M+H]^+$: 468.8.

10 50.2. 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(S)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone

This compound was prepared using a method analogous to that of Example 1 step 1.8, 2-trifluoromethylpyrimidine-5-boronic acid replacing 4-methoxyphenylboronic acid and intermediate 50.1 replacing intermediate 1.7. The desired compound was purified by Prep LC-MS (I). LC-MS (E): t_R = 1.1min; $[M+H]^+$: 535.2

15 **Example 51: 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-ethyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone**

51.1. (R)-2-Ethyl-4-(4-methoxycarbonyl-2-trifluoromethyl-thiazol-5-yl)-piperazine-1-carboxylic acid tert-butyl ester

20 This compound was prepared using a method analogous to that of Example 1, step 1.3, (R)-1-Boc-2-ethyl-piperazine replacing (R)-1-N-Boc-2-methylpiperazine. LC-MS (B): t_R = 1.0min; $[M+H]^+$: 424.1.

51.2. (R)-5-(4-(tert-butoxycarbonyl)-3-ethylpiperazin-1-yl)-2-(trifluoromethyl)thiazole-4-carboxylic acid

25 This compound was prepared using a method analogous to that of Example 17, step 17.6, intermediate 51.1 replacing intermediate 1.3. LC-MS (B): t_R = 0.91min; $[M+H]^+$: 410.0.

51.3. (R)-4-(4-Bromo-2-trifluoromethyl-thiazol-5-yl)-2-ethyl-piperazine-1-carboxylic acid tert-butyl ester

30 To a suspension of lithium acetate (35mg) and NBS (945mg) in THF (3mL) was added dropwise over 10min a solution of intermediate 51.2 (1.25g) in THF (5mL). After 30min at RT, the reaction mixture was evaporated to dryness. The residue was taken up in EA and water, the phases were separated and the aq. layer was extracted with EA (1x). The combined org. layers were washed with brine, dried over Na_2SO_4 and evaporated to dryness to give 1.25g as orange oil. LC-MS (B): t_R = 1.07min; $[M+H]^+$: 384.9.

35 51.4. (R)-2-Ethyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazine-1-carboxylic acid tert-butyl ester

This compound was prepared using a method analogous to that of Example 17 step 17.8, intermediate 51.3 replacing intermediate 17.7 and 2-trifluoromethylpyrimidine-5-boronic acid replacing 2-ethoxypyrimidine-5-boronic acid. The crude was used after extraction without further purification. LC-MS (B): t_R = 1.08min; $[M+H]^+$: 512.1.

5 51.5. 5-[5-((R)-3-Ethyl-piperazin-1-yl)-2-trifluoromethyl-thiazol-4-yl]-2-trifluoromethyl-pyrimidine; as hydrochloride salt

This compound was prepared using a method analogous to that of Example 1 step 1.4, intermediate 51.4 replacing intermediate 1.3. LC-MS (B): t_R = 0.73min; $[M+H]^+$: 412.0.

10 51.6. 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-ethyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl)-ethanone

To a suspension of (3,5-dimethyl-[1,2,4]triazol-1-yl)-acetic acid (30.5mg) and intermediate 51.5 (80mg) in DCM (2.25mL) were added HATU (74.7mg) and NEt_3 (62 μ L) and the reaction mixture was stirred at RT for 3h. The mixture was diluted with DCM, washed with 1M $NaHSO_4$, aq. sat. $NaHCO_3$, and brine, and the aq. layers were extracted with DCM (2x).
15 The combined org. layers were dried over Na_2SO_4 and concentrated to dryness. The crude was purified by Prep LC-MS (VIII) to afford 38mg as white solid. LC-MS (E): t_R = 1.14min; $[M+H]^+$: 549.3.

Example 52: 1-((R)-4-{4-[2-(1,1-Difluoro-ethyl)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl}-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone

20 52.1. 5-Bromo-2-(1,1-difluoro-ethyl)-pyrimidine

To a solution of 1-(5-bromopyrimidin-2-yl)ethanone (500mg) in DCM (5mL) was added at RT bis(2-methoxyethyl)aminosulfur trifluoride (50% in toluene, 3.67mL) and the reaction mixture was heated to 40°C for 2h. The mixture was allowed to reach RT and was added dropwise to a mixture of 1M $NaOH$ and ice under vigorous stirring. The org. layer was
25 extracted with DCM (2x). The combined org. layers were washed with brine, dried over Na_2SO_4 and concentrated to dryness. Purification by CC (Biotage, SNAP 25g cartridge, solvent A: Hep; solvent B: EA; gradient in %B: 0 for 1CV, 0 to 10 over 10CV, 10 for 5CV) gave 284mg as bright-yellow liquid. LC-MS (B): t_R = 0.7 min; $[M+H]^+$: 264.02.

52.2. (2-(1,1-difluoroethyl)pyrimidin-5-yl)boronic acid

30 This compound was prepared using a method analogous to that of Example 38 step 38.2, intermediate 52.1 replacing intermediate 38.1. The crude was used without Prep LC-MS purification. LC-MS (B): t_R = 0.47min; $[M+H]^+$: 189.23.

52.3. 1-((R)-4-{4-[2-(1,1-Difluoro-ethyl)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl}-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 36, intermediate 52.2 replacing 2-pyrrolidinopyrimidine-5-boronic acid. The desired compound was purified by Prep LC-MS (I) followed by Prep TLC (DCM/MeOH 97:3). LC-MS (E): t_R = 1.03min; $[M+H]^+$: 531.3.

5

II. BIOLOGICAL ASSAYS

A) FLIPR assay: The bioactivity of compounds is tested in a fluorometric imaging plate reader (FLIPR: Molecular Devices) using engineered CHO-K1 cells expressing the human CXCR3A (GenBank: AY242128) coupled to a G protein (G α 16). Cells are plated the day prior to bioassay in F12 medium supplemented with 10% FBS and G418 and hygromycin antibiotics to maintain recombinant selection. At the day of bioassay, cells are washed and dye loaded for one hour with Fluo-4-AM (Invitrogen) in Hanks Balanced Salt Solution (Invitrogen), buffered with 20 mM Hepes at pH 7.4 and sodium bicarbonate (0.015%), containing 5 mM probenecid. This buffer, but lacking the dye and containing probenecid at a concentration of 2.5 nM, is also used for washing steps (wash buffer); or lacking both dye and probenecid but supplemented with 0.1% BSA for compound dilution steps (dilution buffer). Cells are washed free of excess dye and 60 microliter of wash buffer is added. Stock solutions of test compounds are made up at a concentration of 10 mM in DMSO, and serially diluted in dilution buffer to concentrations required for inhibition dose response curves. After a 10 minute incubation period at 37°C, 10 microliters of each compound dilution are transferred from a compound plate to the plate containing the recombinant cells in the FLIPR instrument according to the manufacturer's instructions. Following basal readings, 10 microliter CXCL10 agonist at a concentration of 20 nM (from Peprotech) is added, again using the FLIPR instrument. Changes in fluorescence are monitored before and after addition of the test compounds. Emission peak values above base level after CXCL10 addition are exported after base line subtraction. The program XLfit is used to fit the data to a single site dose response curve and to calculate IC₅₀ values. The calculated IC₅₀ values may fluctuate depending on the daily assay performance. Fluctuations of this kind are known to those skilled in the art. In the case where IC₅₀ values have been determined several times for the same compound, mean values are given. Data are shown in Table 1.

Table 1

Example No	FLIPR: IC ₅₀ (nM)	Example No	FLIPR: IC ₅₀ (nM)
1	111	27	3.5
2	16	28	2.8
3	9.8	29	4.5

4	12	30	22
5	24	31	10
6	64	32	27
7	9.3	33	2.9
8	28	34	5.7
9	36	35	4.6
10	20	36	1.6
11	45	37	4.8
12	25	38	2.3
13	76	39	31
14	31	40	22
15	9.2	41	5.6
16	14	42	91
17	20	43	14
18	3.1	44	5.1
19	8.5	45	15
20	5.7	46	1.6
21	4.7	47	3.5
22	2.9	48	4.7
23	24	49	3.6
24	2.7	50	2.6
25	6.8	51	0.6
26	41	52	4.5

B) hERG Q-Patch assay: Compounds are evaluated for block of the hERG K channel using CHO cells stably expressing the hERG gene (accession number U04270, bSys, Witterswil, Switzerland) and the QPatch robotic platform (Sophion, Ballerup, Denmark) in single-cell mode at room temperature. Cells are grown in culture flasks at 37°C in 5% CO₂, in culture medium (Ham's F-12 Nutrient Mixture, Invitrogen 21765-029) supplemented with 9% (v/v) fetal calf serum, 0.9% Penicillin/Streptomycin (10,000 U/mL, Invitrogen 15140148), 100 µg/mL Hygromycin B (Invitrogen 10687010). When the cells are ~80% confluent (every 2-3 days), they are either split for further culture or used for electrophysiology. For further culture, cells are detached with 0.25% Trypsin EDTA solution (Invitrogen 25200-056) and a fraction of the cells (10-30%) is reseeded in culture medium. For electrophysiology, on the experimental day, cells are detached with 0.25% Trypsin EDTA solution and all cells are suspended in suspension medium (293 SFM II, Invitrogen 11686-029) supplemented with

20 mM HEPES and 0.04 mg/mL Trypsin inhibitor. Cells are kept in suspension medium at 32-35°C in the QPatch robot until use, at which time aliquots are transferred to the extracellular solution (in mM: NaCl 150; KCl 4; CaCl₂ 1.2; MgCl₂ 1; HEPES 10; pH 7.4 with NaOH) containing 0.3 %v/v DMSO and applied to the test plates. K⁺ currents are measured with the patch-voltage-clamp technique in the whole-cell configuration with the internal solution (in mM: KCl, 140; NaCl, 10; MgCl₂, 1; HEPES, 10; EGTA, 5; pH = 7.2 with KOH). Currents are low-pass filtered using the internal Bessel filter of the QPatch robot with a cut-off frequency of 2 kHz and are digitized at 10 kHz. K⁺ tail currents are produced from a holding voltage of -80 mV by a 500-ms depolarization to +20 mV followed by a 500-ms repolarization to -40 mV; tail current amplitudes are measured at the end of the repolarization to -40 mV. The pulse pattern is repeated every 10 sec during the experiment, baseline K⁺ current is measured after 3 min in extracellular solution, test-solution containing compound is then applied, and K⁺ current in presence of compound is measured 3 minutes after application to the cells. The respective test-solution is prepared by (1) dissolving the test-compound in pure DMSO, (2) diluting this DMSO solution in extracellular solution, and (3) adding further DMSO, such that the final test-solution has a concentration of either 300 nM or 3000 nM of the test-compound and contains 0.3 %v/v DMSO. Compound effects are quantified as % block by dividing the current in presence of compound by the baseline current; two or three experiments are performed for each compound and the final value represents the mean of the results of each experiment.

Example No	concentration [nM]	% block	concentration [nM]	% block
1	300	4	3000	13
2	300	7	3000	38
3	300	19	3000	60
4	300	25	3000	54
5	300	nd	3000	nd
6	300	11	3000	51
7	300	34	3000	88
8	300	22	3000	61
9	300	12	3000	44
10	300	7	3000	20
11	300	10	3000	19
12	300	6	3000	27
13	300	9	3000	39

14	300	5	3000	14
15	300	1	3000	13
16	300	4	3000	14
17	300	13	3000	26
18	300	3	3000	13
19	300	4	3000	12
20	300	9	3000	20
21	300	1	3000	12
22	300	1	3000	7
23	300	-1	3000	-2
24	300	6	3000	18
25	300	-1	3000	1
26	300	-1	3000	-8
27	300	2	3000	6
28	300	0	3000	6
29	300	-2	3000	0
30	300	1	3000	6
31	300	6	3000	14
32	300	-6	3000	-5
33	300	4	3000	17
34	300	3	3000	4
35	300	2	3000	4
36	300	7	3000	15
37	300	2	3000	4
38	300	5	3000	11
39	300	3	3000	15
40	300	1	3000	25
41	300	nd	3000	nd
42	300	-3	3000	0
43	300	4	3000	8
44	300	-3	3000	-6
45	300	0	3000	1
46	300	13	3000	29
47	300	5	3000	18
48	300	1	3000	2
49	300	nd	3000	nd

50	300	6	3000	15
51	300	6	3000	18
52	300	2	3000	6

nd: not determined

C) Human Liver Microsome Assay:

Incubation with human liver microsomes was performed to assess metabolic stability at a single compound concentration of 1 μM . A 1 μL -aliquot of the compounds stock solutions in DMSO were added to 899 μL of 100 mM phosphate buffer (pH 7.4) containing the liver microsomes at a concentration of 0.5 mg/mL and the mixture was incubated at 37 °C in an Eppendorf thermomixer at 450 rpm. The reaction was initiated by addition of 100 μL of NADPH-regenerating system containing the glucose-6-phosphate dehydrogenase and at the pre-defined time points, 0, 1.5, 2.5, 5, 10, and 15 min, 100 μL of the incubation was transferred in 100 μL of ice-cold methanol to stop the reaction. Samples were centrifuged at 3220 g for 20 min at 4 °C and the supernatants were submitted to LC/MS-MS analysis. Calculation of intrinsic clearance CL_{int} :

Natural logarithm of remaining amount of compound was plotted as function of time and the slope of the line determined.

Elimination rate constant (k) = - slope

Half-life ($t_{1/2}$) = 0.693/k

V = volume of incubation/amount of protein

Intrinsic clearance (CL_{int}) = V x 0.693/ $t_{1/2}$

Example No	CL_{int}
7	7
15	66
18	60
20	8
22	78
24	0
27	13
33	7
36	338
38	51
45	14

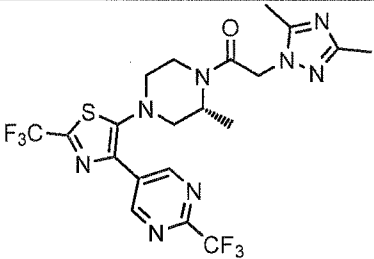
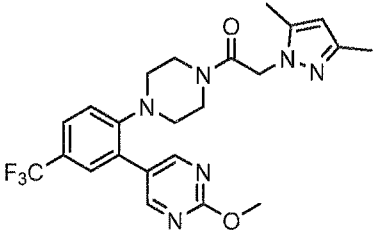
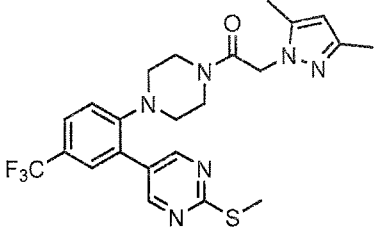
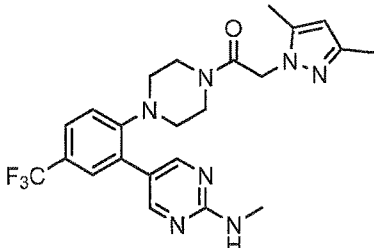
49	4
50	11
51	1
52	0

D) Determination of pharmacokinetic parameters:

Male Wistar rats (RccHan:WIST) were obtained from Harlan (Venray, The Netherlands) and used for pharmacokinetic experiments after an acclimatization period of at least 7 days. The body weight of the rats was about 250 g at the day of the experiment. Two days prior to dosing, rats were anesthetized for surgery via inhalation of isoflurane (4–5% for induction and 1.5–3% for maintenance) in oxygen. Buprenorphine was dosed as analgesic at 0.03 mg/kg sc half an hour before surgery. Under aseptic conditions, catheters were implanted into jugular vein for dosing and carotid artery to allow for multiple serial blood sampling. Animals foreseen for oral dosing did not undergo surgery, but blood samples were taken sublingually under light anesthesia with isoflurane. Compounds were administered intravenously via a 5-minute infusion at doses of 0.5 or 1 mg/kg body weight formulated as solutions in water prepared by pH adjustment or as an aqueous mixed micellar vehicle based on phospholipids and bile acids (mixed micelles). Oral administration at doses of 2 or 10 mg/kg was performed by gavage. Oral formulations were solutions in water prepared by pH adjustment or dispersions prepared by addition of a DMSO stock solution of the compounds to methylcellulose (0.5% w/v) in water. Blood samples were generally taken 0.5, 1, 2, 3, 4, 6, 8, and 24 hours after oral dosing and 2, 10, 20, 30 min and 1, 2, 3, 4, 6, 8, and 24 hours after end of infusion. Blood samples were centrifuged at 3000 g (10 minutes, 4 °C) and plasma was submitted to LC-MS/MS analysis.

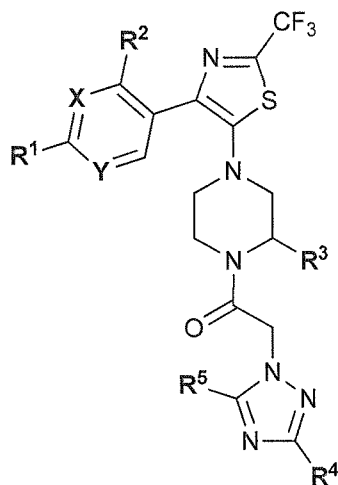
Example 24 has a surprisingly high plasma concentration after oral administration if compared to reference compounds disclosed in WO 2010/126811. The reference compounds may be prepared according to the procedures disclosed in WO 2010/126811.

Compound	Oral dose [mg/kg]	Formulation	AUC [ng*h]/mL
example 24: 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl]-ethanone	2	Solution in purified water, pH modification for solubilization, pH 2.1	14000

			
<p>reference compound 1: 2-(3,5-Dimethyl-pyrazol-1-yl)-1-{4-[2-(2-methoxy-pyrimidin-5-yl)-4-trifluoromethyl-phenyl]-piperazin-1-yl}-ethanone</p> 	2	Suspension in methylcellulose (0.5% w/v) in water	273
<p>reference compound 2: 2-(3,5-Dimethyl-pyrazol-1-yl)-1-{4-[2-(2-methylsulfanyl-pyrimidin-5-yl)-4-trifluoromethyl-phenyl]-piperazin-1-yl}-ethanone</p> 	2	Suspension in methylcellulose (0.5% w/v) in water	202
<p>reference compound 3: 2-(3,5-Dimethyl-pyrazol-1-yl)-1-{4-[2-(2-methylamino-pyrimidin-5-yl)-4-trifluoromethyl-phenyl]-piperazin-1-yl}-ethanone</p> 	2	Solution in purified water, pH modification for solubilization, pH 3.03	271

Claims

1. A compound of Formula (I_P)

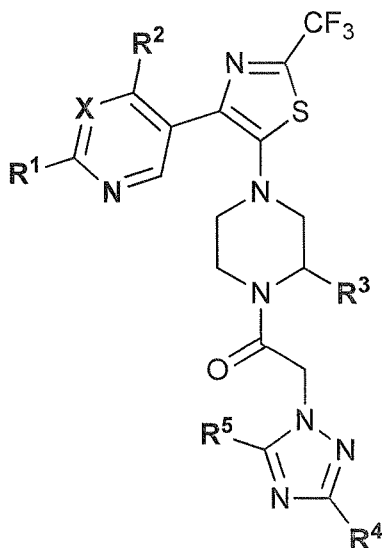


Formula (I_P)

- 5 wherein
- X** represents N or CH;
- Y** represents N or CR⁶;
- R¹** represents (C₁₋₄)alkyl; (C₃₋₆)cycloalkyl; (C₁₋₄)alkoxy; (C₃₋₆)cycloalkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; cyano; (C₁₋₂)alkoxy-(C₂₋₃)alkoxy; (C₁₋₃)alkyl which is mono-
- 10 substituted with -NR⁷R⁸; (C₂₋₃)alkoxy which is mono-substituted with -NR⁷R⁸; heterocyclyl, wherein the heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one or two heteroatoms independently selected from nitrogen and oxygen and wherein said heterocyclyl is unsubstituted or mono-substituted with (C₁₋₂)alkyl; or heterocycloxy, wherein the heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one
- 15 oxygen atom;
- R²** represents hydrogen, (C₁₋₄)alkoxy or fluoro;
- R³** represents hydrogen or methyl;
- R⁴** represents (C₁₋₄)alkyl, or (C₁₋₂)alkyl which is mono-substituted with -NR⁷R⁸;
- R⁵** represents (C₁₋₄)alkyl;
- 20 **R⁶** represents hydrogen, (C₁₋₄)alkyl or fluoro; or **R¹** and **R⁶** form, together with the carbon atoms to which they are attached, a 5- or 6-membered heterocyclic ring, wherein the moiety needed to complete said heterocyclic ring is selected from -OCH₂CH₂-, -OCH₂O-, -OCH₂CH₂CH₂-, and -OCH₂CH₂O-, wherein the asterisks indicate the bond which is linked to the **R⁶** bearing carbon atom;
- 25 **R⁷** represents (C₁₋₂)alkyl; and
- R⁸** represents (C₁₋₂)alkyl;
- or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 represents ethyl; *n*-propyl; cyclopropyl; ethoxy; *iso*-propoxy; cyclobutyloxy; trifluoromethyl; trifluoromethoxy; or 2,2,2-trifluoroethoxy; or a pharmaceutically acceptable salt thereof.

5 3. A compound according to claim 1, which is also a compound of Formula (II)



Formula (II)

wherein

X represents N or CH;

10 R^1 represents (C₁₋₄)alkyl; (C₃₋₆)cycloalkyl; (C₁₋₄)alkoxy; (C₃₋₆)cycloalkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; (C₁₋₂)alkoxy-(C₂₋₃)alkoxy; (C₁₋₃)alkyl which is mono-substituted with -NR⁷R⁸; (C₂₋₃)alkoxy which is mono-substituted with -NR⁷R⁸; heterocyclyl, wherein the heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one or two heteroatoms independently selected from nitrogen and oxygen and wherein said
15 heterocyclyl is unsubstituted or mono-substituted with (C₁₋₂)alkyl; or heterocycloxy, wherein the heterocyclyl is a 4- to 6-membered mono-cyclic saturated ring containing one oxygen atom;

R^2 represents hydrogen or (C₁₋₄)alkoxy;

R^3 represents hydrogen or methyl;

20 R^4 represents (C₁₋₄)alkyl, or (C₁₋₂)alkyl which is mono-substituted with -NR⁷R⁸;

R^5 represents (C₁₋₄)alkyl;

R^7 represents (C₁₋₂)alkyl; and

R^8 represents (C₁₋₂)alkyl;

or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 3, wherein

X represents N or CH;

R¹ represents (C₁₋₄)alkyl; (C₃₋₆)cycloalkyl; (C₁₋₄)alkoxy; (C₃₋₆)cycloalkoxy; (C₁₋₂)fluoroalkyl; or (C₁₋₂)fluoroalkoxy;

5 **R**² represents hydrogen or ethoxy;

R³ represents hydrogen or methyl;

R⁴ represents methyl or ethyl; and

R⁵ represents methyl or ethyl;

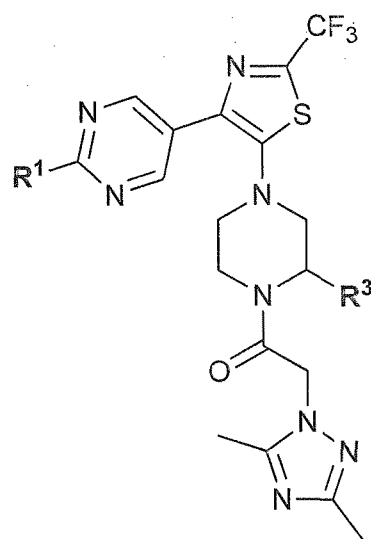
or a pharmaceutically acceptable salt thereof.

10 5. A compound according to any one of claims 3 or 4, wherein

X represents N;

or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 1, which is also a compound of Formula (III)



Formula (III)

wherein

R¹ represents (C₁₋₄)alkyl; (C₃₋₆)cycloalkyl; (C₁₋₄)alkoxy; (C₃₋₆)cycloalkoxy; (C₁₋₂)fluoroalkyl; or (C₁₋₂)fluoroalkoxy; and

R³ represents hydrogen or methyl;

20 or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 6, wherein

R¹ represents ethyl; *n*-propyl; cyclopropyl; ethoxy; *iso*-propoxy; cyclobutyloxy; trifluoromethyl; or 2,2,2-trifluoroethoxy;

or a pharmaceutically acceptable salt thereof.

25 8. A compound according to claim 6, wherein

R¹ represents (C₁₋₄)alkoxy; or (C₁₋₂)fluoroalkyl;
or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 6 to 8, wherein

R³ represents methyl;

5 or a pharmaceutically acceptable salt thereof.

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

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(4-methoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(4-isopropoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[4-(4-trifluoromethoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-[4-(2,2,2-trifluoro-ethoxy)-phenyl]-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl]-ethanone;

15 4-(5-[(R)-4-[2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-acetyl]-3-methyl-piperazin-1-yl]-2-trifluoromethyl-thiazol-4-yl)-benzonitrile;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(4-fluoro-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

1-[(R)-4-[4-(4-Chloro-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-2-methyl-4-(4-p-tolyl-2-trifluoromethyl-thiazol-5-yl)-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(4-ethyl-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

25 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(3-fluoro-4-methoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(2-fluoro-4-methoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(4-methoxy-3-methyl-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

1-[(R)-4-(4-Benzo[1,3]dioxol-5-yl-2-trifluoromethyl-thiazol-5-yl)-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

1-[(R)-4-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

35 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-[(R)-4-[4-(6-ethoxy-pyridin-3-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl]-ethanone;

- 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(6-methoxy-pyridin-3-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;
- 2-(3-Dimethylaminomethyl-5-methyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;
- 5 1-((R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3-ethyl-5-methyl-[1,2,4]triazol-1-yl)-ethanone;
- 1-((R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(5-ethyl-3-methyl-[1,2,4]triazol-1-yl)-ethanone;
- 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;
- 10 1-[(R)-4-(4-Chroman-6-yl-2-trifluoromethyl-thiazol-5-yl)-2-methyl-piperazin-1-yl]-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;
- 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[4-(2-propyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone;
- 15 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[4-(2-methyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone;
- 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl)-ethanone;
- 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-[2-(2-methoxy-ethoxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;
- 20 1-((R)-4-[4-[2-(2-Dimethylamino-ethoxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;
- 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-isopropoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;
- 25 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[4-[2-(2,2,2-trifluoro-ethoxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone;
- 1-((R)-4-[4-(2,4-Diethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;
- 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[4-[2-(oxetan-3-yloxy)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone;
- 30 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(4-ethoxy-phenyl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;
- 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-methoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;
- 35 1-((R)-4-[4-(2-Cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((S)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-{4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl}-ethanone;

5 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-[4-(2-pyrrolidin-1-yl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-piperazin-1-yl)-ethanone;

2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-2-methyl-4-{4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl}-piperazin-1-yl)-ethanone;

10 1-((R)-4-[4-(2-Cyclobutoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

1-((R)-4-[4-(3,4-Dihydro-2H-pyrano[2,3-b]pyridin-6-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

1-((R)-4-[4-(2,3-Dihydro-benzofuran-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone;

15 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-2,2-dideuterium-ethanone;

1-((R)-4-{4-[2-(2-Dimethylamino-ethyl)-pyrimidin-5-yl]-2-trifluoromethyl-thiazol-5-yl}-2-methyl-piperazin-1-yl)-2-(3,5-dimethyl-[1,2,4]triazol-1-yl)-ethanone; and

20 2-(3,5-Dimethyl-[1,2,4]triazol-1-yl)-1-((R)-4-[4-(2-ethyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl)-ethanone;

or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising, as active principle, a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

12. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use as a medicament.

13. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease selected from the group consisting of autoimmune rheumatoid arthritis, multiple sclerosis, neuromyelitis optica, inflammatory bowel disease, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, psoriasis, psoriatic arthritis, lupus nephritis, interstitial cystitis, celiac disease, myasthenia gravis, type I diabetes, uveitis, asthma, chronic obstructive pulmonary disorder, atherosclerosis, myocarditis, inflammatory myopathies, dry eye disease, sarcoidosis, influenza, cerebral malaria, transplant rejection, liver cirrhosis, systemic sclerosis, pulmonary arterial hypertension, neurodegeneration, Alzheimer's disease, HIV associated dementia, Huntington's chorea, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, brain tumor, colon cancer, breast cancer, or metastatic spread of those cancers.

14. Use of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a disease selected from the group consisting of Crohn's disease, ulcerative colitis, systemic lupus erythematosus, psoriasis, psoriatic arthritis, lupus nephritis, interstitial cystitis, celiac disease, myasthenia gravis, type I diabetes, uveitis, asthma, chronic obstructive pulmonary disorder, atherosclerosis, myocarditis, inflammatory myopathies, dry eye disease, sarcoidosis, influenza, cerebral malaria, transplant rejection, liver cirrhosis, systemic sclerosis, pulmonary arterial hypertension, neurodegeneration, Alzheimer's disease, HIV associated dementia, Huntington's chorea, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, brain tumor, colon cancer, breast cancer, or metastatic spread of those cancers.