Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2972954 A1 2016/07/21

(21) 2 972 954

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2016/01/14
(87) Date publication PCT/PCT Publication Date: 2016/07/21
(85) Entrée phase nationale/National Entry: 2017/07/04
(86) N° demande PCT/PCT Application No.: EP 2016/050659
(87) N° publication PCT/PCT Publication No.: 2016/113346
(30) Priorité/Priority: 2015/01/15 (EP PCT/EP2015/050691)

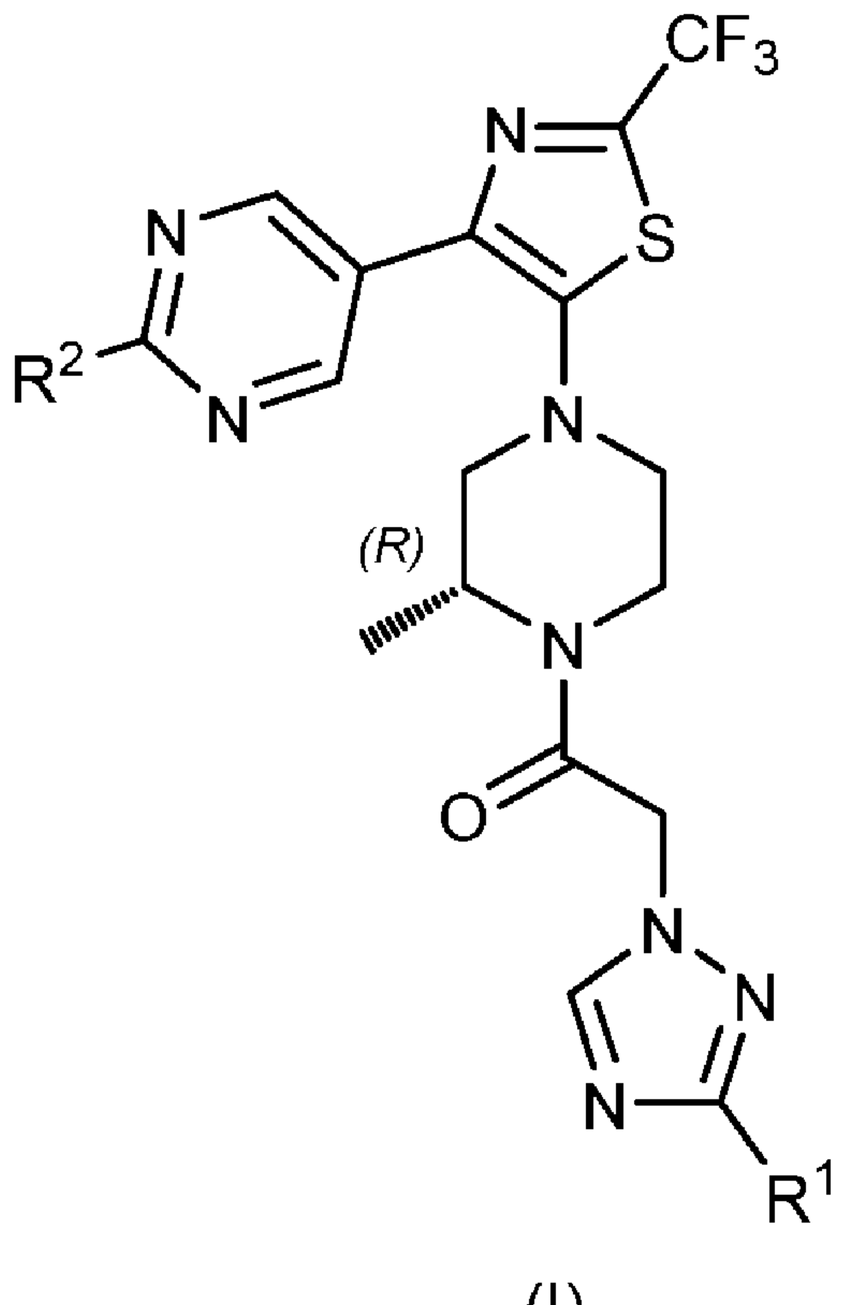
(51) Cl.Int./Int.Cl. *C07D 417/14* (2006.01), *A61K 31/427* (2006.01), *A61P 29/00* (2006.01)

(71) Demandeur/Applicant:
IDORSIA PHARMACEUTICALS LTD, CH

(72) Inventeurs/Inventors:
CAROFF, EVA, CH;
MEYER, EMMANUEL, CH

(74) Agent: GOWLING WLG (CANADA) LLP

(54) Titre : DERIVES DE LA (R)-2-METHYL PIPERAZINE UTILISES COMME MODULATEURS DU RECEPTEUR CXCR3
(54) Title: (R)-2-METHYL-PIPERAZINE DERIVATIVES AS CXCR3 RECEPTOR MODULATORS



(I)

(57) Abrégé/Abstract:
The invention relates to compounds of Formula (I), wherein R^1 and R^2 are as described in the description; to pharmaceutically acceptable salts thereof, and to the use of such compounds as medicaments, especially as modulators of the CXCR3 receptor.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 July 2016 (21.07.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/113346 A1

(51) **International Patent Classification**:
C07D 417/14 (2006.01) ***A61P 29/00*** (2006.01)
A61K 31/427 (2006.01)

(21) **International Application Number**:
PCT/EP2016/050659

(22) **International Filing Date**:
14 January 2016 (14.01.2016)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
PCT/EP2015/050691
15 January 2015 (15.01.2015) EP

(71) **Applicant**: **ACTELION PHARMACEUTICALS LTD** [CH/CH]; Gewerbestrasse 16, 4123 Allschwil (CH).

(72) **Inventors**: **CAROFF, Eva**; Actelion Pharmaceuticals Ltd, Gewerbestrasse 16, 4123 Allschwil (CH). **MEYER, Emmanuel**; Actelion Pharmaceuticals Ltd, Gewerbestrasse 16, 4123 Allschwil (CH).

(74) **Agent**: **KOBERSTEIN, Ralf**; Gewerbestrasse 16, 4123 Allschwil (CH).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

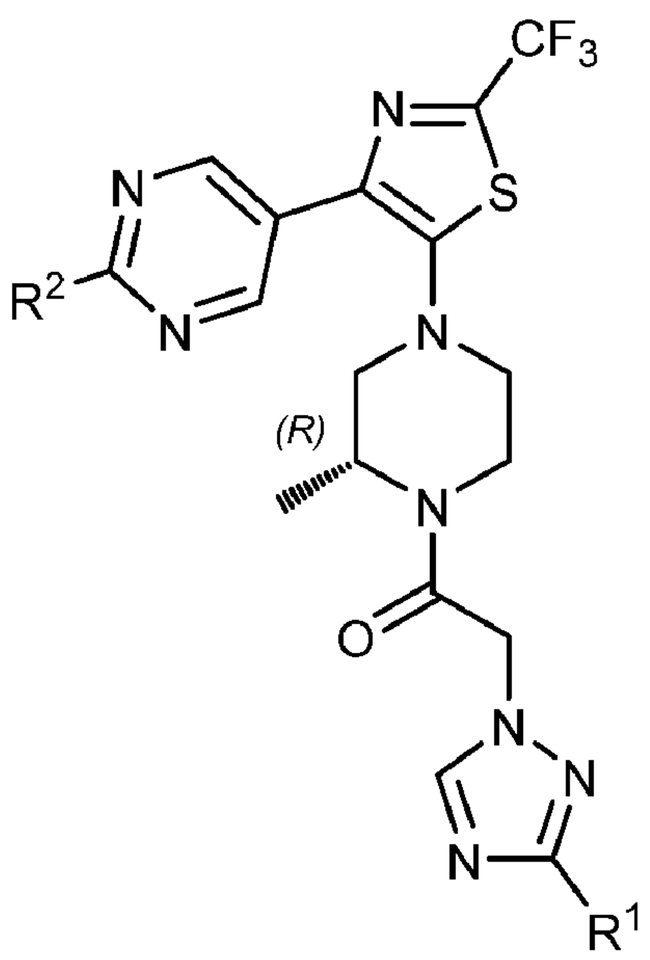
Declarations under Rule 4.17:

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

Published:

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

(54) Title: *(R)*-2-METHYL-PIPERAZINE DERIVATIVES AS CXCR3 RECEPTOR MODULATORS



(I)

(57) Abstract: The invention relates to compounds of Formula (I), wherein R^1 and R^2 are as described in the description; to pharmaceutically acceptable salts thereof, and to the use of such compounds as medicaments, especially as modulators of the CXCR3 receptor.

WO 2016/113346 A1

(R)-2-Methyl-piperazine Derivatives as CXCR3 Receptor Modulators

The present invention relates to novel *(R)*-2-methyl-piperazine derivatives of Formula (I), and their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of Formula (I), and 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 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 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 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 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 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.

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 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 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).

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 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 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 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 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 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 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).

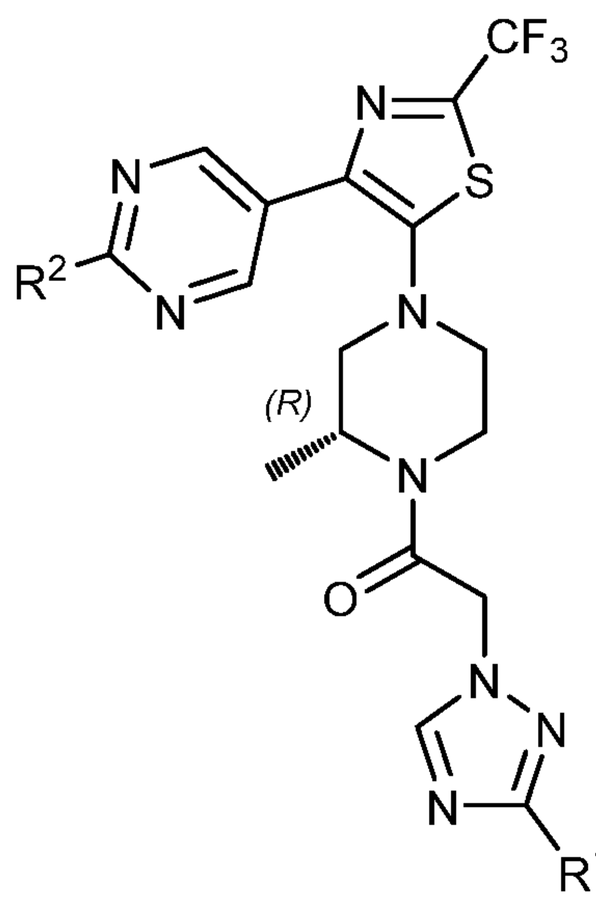
In the central nervous system, blocking the CXCR3 axis may have beneficial effects and prevent neurodegeneration. Increased expression of CXCL10 in the CNS has been demonstrated in ischemia, Alzheimer's disease, multiple sclerosis (MS), and human immunodeficiency virus (HIV)-encephalitis. For example, 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 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.)

4-Thiazolyl-piperidine derivatives as CXCR3 receptor modulators have been disclosed in WO 2007/064553 and WO 2007/070433.

Different 1-(Piperazin-1-yl)-2-heteroaryl-ethanone derivatives as CXCR3 receptor modulators have been disclosed in WO 2007/100610, WO 2010/126811, WO 2013/114332, WO 2015/011099, WO 2015/145322 and 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).

It has now been found that *(R)*-2-methyl-piperazine derivatives of Formula (I) are potent CXCR3 modulators with a surprisingly improved profile in a hERG Q-Patch assay indicating a reduced risk of QT prolongation. These derivatives 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

R^1 represents (C_{1-4})alkyl, (C_{1-2})alkoxy-(C_{1-2})alkyl, hydroxy-(C_{1-4})alkyl or $-C(O)NH_2$; and

R^2 represents (C_{3-6})cycloalkyl, (C_{1-4})alkoxy, (C_{3-6})cycloalkoxy or (C_{1-2})fluoroalkyl;

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

For the avoidance of any doubt, the compounds of Formula (I) are *(R)*-configurated at the asymmetric carbon atom of the piperazine ring.

Definitions provided herein are intended to apply uniformly to the compounds of Formula (I) as defined in any one of embodiments 1) to 23), and, *mutatis mutandis*, throughout the description and the claims unless an otherwise expressly set out definition provides a broader or narrower definition. It is well understood that a definition or preferred definition of a term defines and may replace the respective term independently of (and in combination with) any definition or preferred definition of any or all other terms as defined herein.

The compounds of Formula (I) as defined in any one of embodiments 1) to 23), 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.

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 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 "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 (C_{1-4})alkyl group contains from one to four carbon atoms. Examples of (C_{1-4})alkyl groups are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*.-butyl and *tert*.-butyl. Examples of (C_{1-2})alkyl groups are methyl and ethyl. In case $\mathbf{R^1}$ represents “(C_{1-4})alkyl” the term means methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*.-butyl and *tert*.-butyl; preferably methyl, ethyl, *n*-propyl, *iso*-propyl and *tert*.-butyl; and more preferably ethyl and *iso*-propyl.

The term "alkoxy", used alone or in combination, refers to an alkyl-O- group wherein the alkyl group is as defined before. The term "(C_{x-y})alkoxy" (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms. For example a (C_{1-4})alkoxy group means a group of the formula (C_{1-4})alkyl-O- in which the term "(C_{1-4})alkyl" has the previously given significance. Examples of (C_{1-4})alkoxy groups are methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *sec*.-butoxy and *tert*.-butoxy. Examples of (C_{1-2})alkoxy groups are methoxy and ethoxy. In case $\mathbf{R^2}$ represents “(C_{1-4})alkoxy" the term means methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *sec*.-butoxy and *tert*.-butoxy and preferably ethoxy.

The term “hydroxy-(C_{1-4})alkyl”, used alone or in combination, refers to an alkyl group as defined before containing from one to four carbon atoms in which one hydrogen atom has been replaced with hydroxy. Examples of said groups are hydroxy-methyl, 1-hydroxy-ethyl,

2-hydroxy-ethyl, 1-hydroxy-prop-1-yl, 2-hydroxy-prop-1-yl, 3-hydroxy-prop-1-yl, 1-hydroxy-prop-2-yl, 2-hydroxy-prop-2-yl, 1-hydroxy-but-1-yl, 2-hydroxy-but-1-yl, 3-hydroxy-but-1-yl, 4-hydroxy-but-1-yl, 1-hydroxy-but-2-yl, 2-hydroxy-but-2-yl, 3-hydroxy-but-2-yl, 4-hydroxy-but-2-yl, 1-hydroxy-2-methyl-prop-1-yl, 2-hydroxy-2-methyl-prop-1-yl, 3-hydroxy-2-methyl-prop-1-yl, and 2-hydroxy-1,1-dimethyl-eth-1-yl. In case "**R^1**" represents "hydroxy-(C_{1-4})alkyl" the term means hydroxy-methyl, 1-hydroxy-ethyl, 2-hydroxy-ethyl, 1-hydroxy-prop-1-yl, 2-hydroxy-prop-1-yl, 3-hydroxy-prop-1-yl, 1-hydroxy-prop-2-yl, 2-hydroxy-prop-2-yl, 1-hydroxy-but-1-yl, 2-hydroxy-but-1-yl, 3-hydroxy-but-1-yl, 4-hydroxy-but-1-yl, 1-hydroxy-but-2-yl, 2-hydroxy-but-2-yl, 3-hydroxy-but-2-yl, 4-hydroxy-but-2-yl, 1-hydroxy-2-methyl-prop-1-yl, 2-hydroxy-2-methyl-prop-1-yl, 3-hydroxy-2-methyl-prop-1-yl, and 2-hydroxy-1,1-dimethyl-eth-1-yl. Preferred are hydroxy-methyl, 1-hydroxy-ethyl and 2-hydroxy-prop-2-yl and more preferred is 1-hydroxy-ethyl.

The term "(C_{xa-ya})alkoxy-(C_{x-y})alkyl" (x, xa, y and ya each being an integer) refers to an alkyl 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 "(C_{1-2})alkoxy-(C_{1-2})alkyl group" refers to an (C_{1-2})alkyl group as defined before containing one or two carbon atoms wherein one hydrogen atom has been replaced with (C_{1-2})alkoxy as defined before containing one or two carbon atoms. Examples of (C_{1-2})alkoxy-(C_{1-2})alkyl groups are methoxy-methyl, 1-methoxy-ethyl, 2-methoxy-ethyl, ethoxy-methyl, 1-ethoxy-ethyl and 2-ethoxy-ethyl. In case "**R^1**" represents "(C_{1-2})alkoxy-(C_{1-2})alkyl" the term means methoxy-methyl, 1-methoxy-ethyl, 2-methoxy-ethyl, ethoxy-methyl, 1-ethoxy-ethyl and 2-ethoxy-ethyl and preferably methoxy-methyl.

The term "fluoroalkyl" refers to an alkyl group as defined before containing one or two carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. The term "(C_{x-y})fluoroalkyl" (x and y each being an integer) refers to a fluoroalkyl group as defined before containing x to y carbon atoms. For example a (C_{1-2})fluoroalkyl group contains one or two carbon atoms in which one to five hydrogen atoms have been replaced with fluorine. Representative examples of (C_{1-2})fluoroalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, and 2,2,2-trifluoroethyl. In case **R^2** represents "(C_{1-2})fluoroalkyl" the term means preferably fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, and 2,2,2-trifluoroethyl and more preferably trifluoromethyl.

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 (C_{3-6})cycloalkyl group contains from three to six carbon atoms. Examples of (C_{3-6})cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In case "**R^2**" represents "(C_{3-6})cycloalkyl" the term means cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl and 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 (C_{3-6})cycloalkoxy group means a group of the formula (C_{3-6})cycloalkyl-O- in which the term "(C_{3-6})cycloalkyl" has the previously given significance. Examples of (C_{3-6})cycloalkoxy groups are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy. In case **R^2** represents "(C_{3-6})cycloalkoxy" the term means cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy and preferably cyclobutyloxy.

2) A further embodiment of the invention relates to compounds of Formula (I) according to embodiment 1), wherein

R^1 represents (C_{1-4})alkyl, (C_{1-2})alkoxy-(C_{1-2})alkyl or hydroxy-(C_{1-4})alkyl; and

R^2 represents (C_{3-6})cycloalkyl, (C_{1-4})alkoxy or (C_{1-2})fluoroalkyl;

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 embodiment 1), wherein

R^1 represents (C_{1-4})alkyl; and

R^2 represents (C_{3-6})cycloalkyl, (C_{1-4})alkoxy or (C_{1-2})fluoroalkyl;

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 embodiment 1), wherein

R^1 represents methyl, ethyl, *n*-propyl, *iso*-propyl, *tert*.-butyl, methoxy-methyl, hydroxy-methyl, 1-hydroxy-ethyl, 2-hydroxy-prop-2-yl or $-C(O)NH_2$; and

R^2 represents cyclopropyl, ethoxy, cyclobutyloxy or trifluoromethyl;

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 embodiment 1), wherein

R^1 represents ethyl, *n*-propyl, *iso*-propyl, *tert*.-butyl, methoxy-methyl or 1-hydroxy-ethyl; and

R^2 represents cyclopropyl, ethoxy or trifluoromethyl;

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 embodiment 1), wherein

R^1 represents ethyl, *n*-propyl, *iso*-propyl or *tert*.-butyl; and

R^2 represents cyclopropyl, ethoxy or trifluoromethyl;

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 embodiment 1), wherein

R^1 represents (C_{1-4})alkyl or (C_{1-2})alkoxy-(C_{1-2})alkyl; and

R^2 represents (C_{3-6})cycloalkyl;

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 embodiment 1), wherein

R^1 represents ethyl, *iso*-propyl or *tert*.-butyl; and

R^2 represents cyclopropyl;

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

9) A further embodiment of the invention relates to compounds of Formula (I) according to embodiment 1), wherein

R^1 represents (C_{1-4})alkyl or (C_{1-2})alkoxy-(C_{1-2})alkyl; and

R^2 represents (C_{1-4})alkoxy;

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

10) A further embodiment of the invention relates to compounds of Formula (I) according to embodiment 1), wherein

R^1 represents ethyl, *iso*-propyl or *tert*.-butyl; and

R^2 represents ethoxy;

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

11) A further embodiment of the invention relates to compounds of Formula (I) according to embodiment 1), wherein

R^1 represents (C_{1-4})alkyl, (C_{1-2})alkoxy-(C_{1-2})alkyl, hydroxy-(C_{1-4})alkyl or –C(O)NH_2; and

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

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

12) A further embodiment of the invention relates to compounds of Formula (I) according to embodiment 1), wherein

R^1 represents methyl, ethyl, *n*-propyl, *iso*-propyl, *tert*.-butyl, methoxy-methyl, hydroxy-methyl, 1-hydroxy-ethyl, 2-hydroxy-prop-2-yl or –C(O)NH_2; and

R^2 represents trifluoromethyl;

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

13) A further embodiment of the invention relates to compounds of Formula (I) according to embodiment 1), wherein
R^1 represents ethyl, *n*-propyl, *iso*-propyl, *tert*.-butyl, methoxy-methyl or 1-hydroxy-ethyl; and
R^2 represents trifluoromethyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

14) A further embodiment of the invention relates to compounds of Formula (I) according to any one of embodiments 1), 2), 7), 9) or 11), wherein
R^1 represents (C_{1-4})alkyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

15) A further embodiment of the invention relates to compounds of Formula (I) according to any one of embodiments 1) to 5), 7), 9) or 11) to 13), wherein
R^1 represents ethyl, *n*-propyl, *iso*-propyl or *tert*.-butyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

16) A further embodiment of the invention relates to compounds of Formula (I) according to any one of embodiments 1), 2), 7), 9) or 11), wherein
R^1 represents (C_{1-2})alkoxy-(C_{1-2})alkyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

17) A further embodiment of the invention relates to compounds of Formula (I) according to any one of embodiments 1), 2) or 11), wherein
R^1 represents hydroxy-(C_{1-4})alkyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

18) A further embodiment of the invention relates to compounds of Formula (I) according to any one of embodiments 1), 2), 3) or 14) to 17), wherein
R^2 represents (C_{3-6})cycloalkyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

19) A further embodiment of the invention relates to compounds of Formula (I) according to any one of embodiments 1), 2), 3) or 14) to 17), wherein
R^2 represents (C_{1-4})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 (I) according to any one of embodiments 1) or 14) to 17), wherein
R^2 represents (C_{3-6})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 (I) according to any one of embodiments 1), 2), 3) or 14) to 17), wherein

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

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

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

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

2-(3-tert-Butyl-[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-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-methoxymethyl-[1,2,4]triazol-1-yl)-ethanone;

1-(2-{(R)-2-Methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl}-2-oxo-ethyl)-1H-[1,2,4]triazole-3-carboxylic acid amide;

2-(3-Ethyl-[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-Isopropyl-[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-tert-Butyl-[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-Methoxymethyl-[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-Hydroxymethyl-[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;

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

2-[3-(1-Hydroxy-ethyl)-[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)-[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;

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

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

1-{(R)-4-[4-(2-Cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-isopropyl-[1,2,4]triazol-1-yl)-ethanone;
2-(3-tert-Butyl-[1,2,4]triazol-1-yl)-1-{(R)-4-[4-(2-cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-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-methoxymethyl-[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-(3-methyl-[1,2,4]triazol-1-yl)-ethanone;
2-(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; and
1-{(R)-4-[4-(2-Cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-methyl-[1,2,4]triazol-1-yl)-ethanone;
or salts (in particular pharmaceutically acceptable salts) of such compounds.

23) The invention, thus, relates to compounds of the Formula (I) as defined in embodiment 1), and to such compounds further limited by the characteristics of any one of embodiments 2) to 22), 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 formula (I) are thus possible and intended and herewith specifically disclosed in individualized form:
1, 2+1, 3+1, 4+1, 5+1, 6+1, 7+1, 8+1, 9+1, 10+1, 11+1, 12+1, 13+1, 14+1, 14+2+1, 14+7+1, 14+9+1, 14+11+1, 15+1, 15+2+1, 15+3+1, 15+4+1, 15+5+1, 15+7+1, 15+9+1, 15+11+1, 15+12+1, 15+13+1, 16+1, 16+2+1, 16+7+1, 16+9+1, 16+11+1, 17+1, 17+2+1, 17+11+1, 18+1, 18+2+1, 18+3+1, 18+14+1, 18+14+2+1, 18+14+7+1, 18+14+9+1, 18+14+11+1, 18+15+1, 18+15+2+1, 18+15+3+1, 18+15+4+1, 18+15+5+1, 18+15+7+1, 18+15+9+1, 18+15+11+1, 18+15+12+1, 18+15+13+1, 18+16+1, 18+16+2+1, 18+16+7+1, 18+16+9+1, 18+16+11+1, 18+17+1, 18+17+2+1, 18+17+11+1, 19+1, 19+2+1, 19+3+1, 19+14+1, 19+14+2+1, 19+14+7+1, 19+14+9+1, 19+14+11+1, 19+15+1, 19+15+2+1, 19+15+3+1, 19+15+4+1, 19+15+5+1, 19+15+7+1, 19+15+9+1, 19+15+11+1, 19+15+12+1, 19+15+13+1, 19+16+1, 19+16+2+1, 19+16+7+1, 19+16+9+1, 19+16+11+1, 19+17+1, 19+17+2+1, 19+17+11+1, 20+1, 20+14+1, 20+14+2+1, 20+14+7+1, 20+14+9+1, 20+14+11+1, 20+15+1, 20+15+2+1, 20+15+3+1, 20+15+4+1, 20+15+5+1, 20+15+7+1, 20+15+9+1, 20+15+11+1, 20+15+12+1, 20+15+13+1, 20+16+1, 20+16+2+1, 20+16+7+1, 20+16+9+1, 20+16+11+1, 20+17+1, 20+17+2+1, 20+17+11+1, 21+1, 21+2+1, 21+3+1, 21+14+1, 21+14+2+1, 21+14+7+1, 21+14+9+1, 21+14+11+1, 21+15+1, 21+15+2+1,

21+15+3+1, 21+15+4+1, 21+15+5+1, 21+15+7+1, 21+15+9+1, 21+15+11+1, 21+15+12+1, 21+15+13+1, 21+16+1, 21+16+2+1, 21+16+7+1, 21+16+9+1, 21+16+11+1, 21+17+1, 21+17+2+1, 21+17+11+1, 22+1, and 23+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, "14+2+1" for example refers to embodiment 14) depending on embodiment 2), depending on embodiment 1), i.e. embodiment "14+2+1" corresponds to the compounds of embodiment 1) further limited by the features of the embodiments 2) and 14).

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, pharmaceutical composition, disease or the like.

Any reference to a compound of Formula (I) as defined in any one of embodiments 1) to 23) 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 ^{2}H (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 ^{2}H (deuterium) labelled compounds of Formula (I) and salts thereof are within the scope of the present invention. Substitution of hydrogen with the heavier isotope ^{2}H (deuterium) may lead to greater metabolic stability, resulting e.g. in increased *in-vivo* half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of Formula (I) 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 23) 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 (including topical application or inhalation) administration.

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 23).

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 below 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 23) or a pharmaceutically acceptable salt thereof.

The compounds according to Formula (I) as defined in any one of embodiments 1) to 23), or pharmaceutically acceptable salts thereof, 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.

Inflammatory diseases may be defined as comprising asthma; COPD; atherosclerosis; myocarditis; dry eye syndrome (comprising Sjögren’s dry eye syndrome); myopathies (comprising 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 threrefrom; 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; 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, narcolepsy, glossopharyngeal neuralgia, mild cognitive decline, cognitive decline, spinal muscular atrophy, and cerebral malaria.

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, esophagal 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 23), 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;

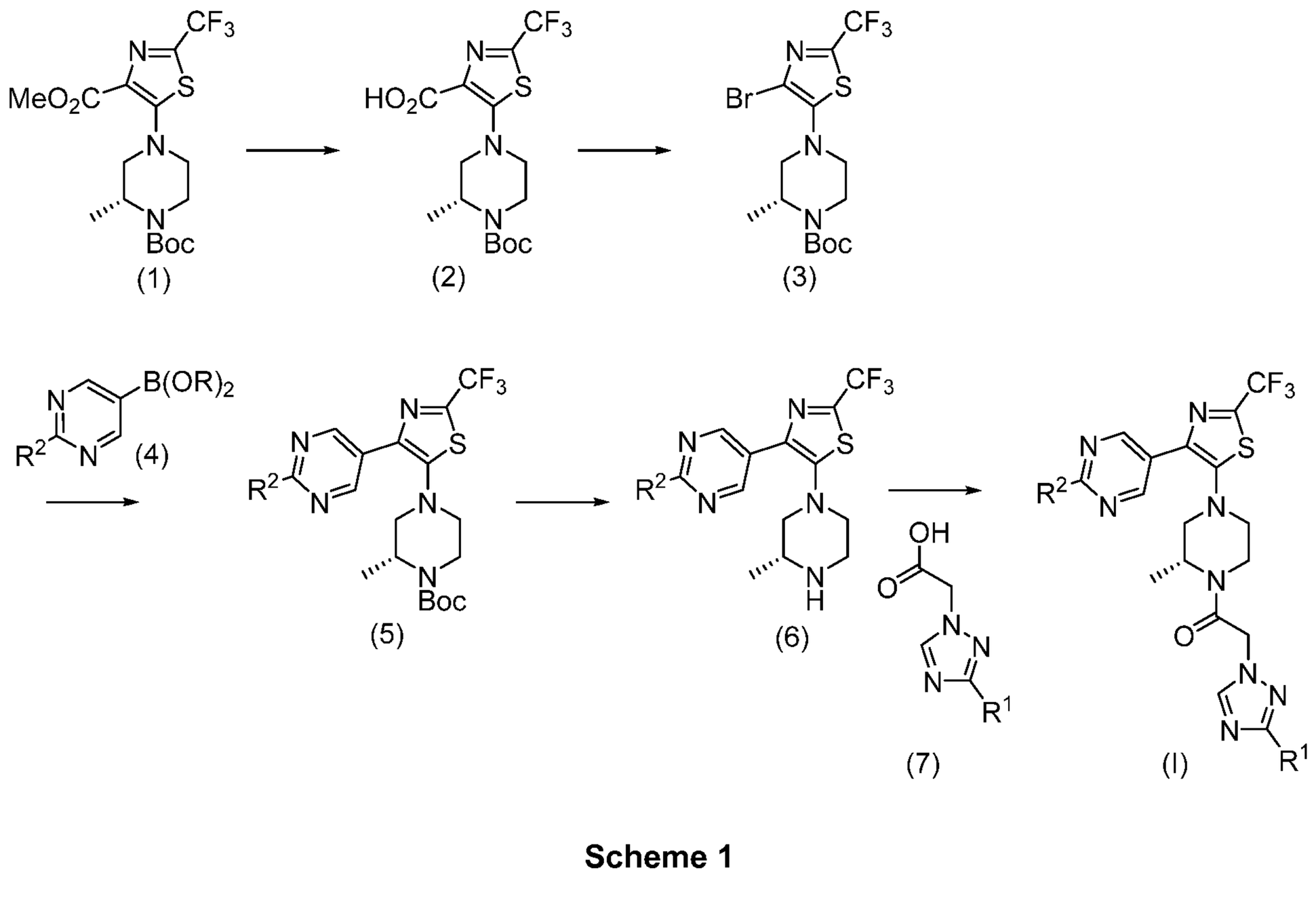
4) Fibrosis selected from liver cirrhosis (comprising primary biliary cirrhosis (PBC) and autoimmune hepatitis); and

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 in the experimental part; by analogous methods; or according to the general sequence of reactions outlined below, wherein R^1 and R^2 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 R^1 and R^2 might be incompatible with the assembly illustrated in the schemes below and so will require the use of protecting groups (PG). The use of protecting groups is well known in the art (see for example “Protective Groups in Organic Synthesis", T.W. Greene, P.G.M. Wuts, Wiley-Interscience, 1999). For the purposes of this discussion, it will be assumed that such protecting groups as necessary are in place. The compounds obtained may also be converted into salts, especially pharmaceutically acceptable salts thereof in a manner known *per se*.

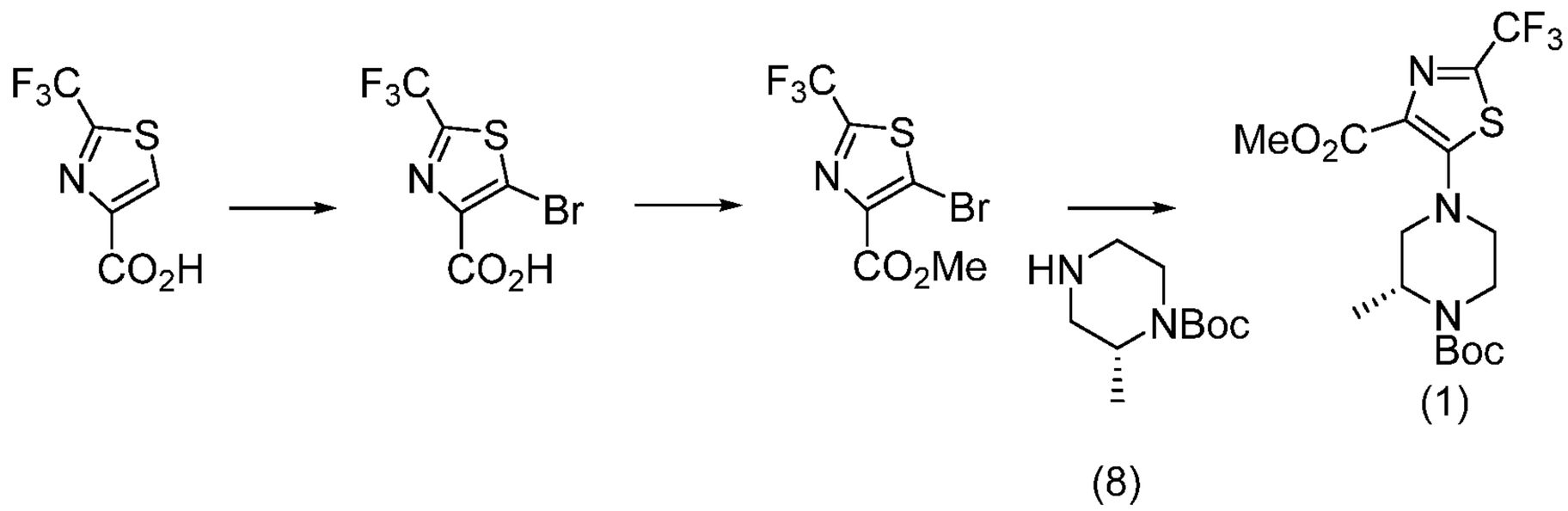
General preparation routes:



Scheme 1

Compounds of Formula (I) can be prepared starting from intermediate (1), which is saponified under standard conditions (e.g. aq. NaOH in MeOH) to give compounds of structure (2) (Scheme 1). The carboxylic acid group in the compound of structure (2) is

converted to the corresponding bromine (3) using (diacetoxyiodo)benzene and LiBr in THF at RT. Suzuki coupling can be performed using a coupling partner of structure (4), wherein R represents hydrogen or (C_{1-4})alkyl, using standard conditions for a Suzuki reaction, like using a suitable base such as aq. Na_2CO_3, a suitable palladium catalyst such as $Pd(PPh_3)_2Cl_2$, and a suitable solvent such as MeCN, preferably heating at a temperature around 80°C. The Boc protecting group of the obtained intermediate (5) can be subsequently cleaved under acidic conditions, preferably using HCl in a suitable solvent such as dioxane and at a temperature about RT to give the compound of structure (6). Compounds of Formula (I) can be obtained in a final step by an amide coupling with a carboxylic acid derivative (7) using standard peptide coupling methods such as HATU, in presence of a suitable base such as DIPEA or NEt_3 and in a suitable solvent such as DCM or DMF, preferably at a temperature about RT.

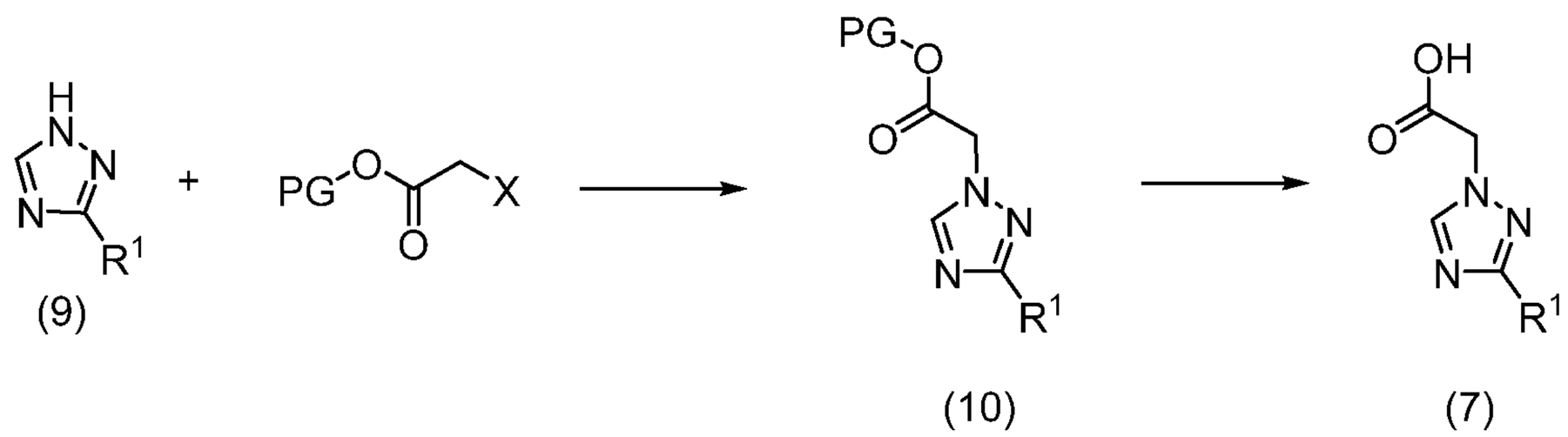


(8) (1)

Scheme 2

Compounds of structure (1) can be synthesized following the reaction sequence outlined in Scheme 2. Commercially available 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 concentrated sulphuric acid in MeOH and heating at a temperature around 70°C. Nucleophilic aromatic substitution using commercially available piperazine derivative (8), in presence of a suitable base such as DIPEA, in a suitable solvent such as MeCN, and at a temperature around 80°C provides compounds of structure (1).

The compounds of formula (7) are either commercially available, or can be synthesized following the route shown in Scheme 3.



Scheme 3

A triazole of structure (9) can be alkylated using an acetic acid derivative of formula X-CH_2-COO(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.

Deprotection of the intermediate (10), 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 (7). 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 (4) are either commercially available or can be prepared in analogy to methods known to one skilled in the art such as the reaction of the respective 5-bromo-pyrimidine derivative with triisopropyl borate and n-BuLi in THF and toluene at a temperature around -78°C.

Compounds of Formula (I) may be obtained from other compounds of Formula (I) or their analogues by interconversion of a substituent in R^1-position to another substituent R^1. For instance, an analogue of Formula (I) wherein R^1 represents bromine may be transferred to a compound of Formula (I) wherein R^1 represents (C_{2-4})alkyl by (i) Suzuki reaction using the respective (C_{2-4})alkenylboronic acid ester derivative (e.g. isopropenyboronic acid pinacol ester) in the presence of a palladium catalyst such as $Pd(PPh_3)_2Cl_2$ and (ii) hydrogenation using for instance hydrogen in the presence of Pd/C in a solvent such as MeOH. A compound of Formula (I) wherein R^1 represents $-C(O)NH_2$ may be prepared by hydrolysis of the respective nitrile using conc. H_2SO_4 in a solvent such as DCM. Further, a compound of Formula (I) wherein R^1 represents hydroxy-(C_{1-4})alkyl may be obtained from the respective compound wherein R^1 represents methoxy-(C_{1-4})alkyl by demethylation using BBr_3 in a solvent such as DCM or from the respective ketone wherein R^1 represents $-C(O)$-(C_{1-3})alkyl by reduction with $NaBH_4$.

Whenever the compounds of Formula (I) are obtained in the form of mixtures of enantiomers, the enantiomers can be separated using methods known to one skilled in the

art: *e.g.* by formation and separation of diastereomeric salts or by HPLC over a chiral stationary phase such as a Daicel ChiralPak IC (5 µm) column. Typical conditions of chiral HPLC are an isocratic mixture of eluent A (EtOH or *i*PrOH, in presence or absence of an amine such as NEt_3 or DEA) and eluent B (hexane or MeCN), at a flow rate of 0.8 to 16 mL/min.

Experimental section:

Abbrevations (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
CV	column volume
DCM	dichloromethane
DEA	diethylamine
DIPEA	*N*-ethyldiisopropylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EA	ethyl acetate
EDTA	ethylenediaminetetraacetic acid
EGTA	ethylene glycol tetraacetic acid
Et	ethyl
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*H*-xanthen-9-yl)phenyl](carboxymethyl)amino}acetic acid
G418	(2R,3S,4R,5R,6S)-5-amino-6-[(1R,2S,3S,4R,6S)-4,6-diamino-3-[(2R,3R,4R,5R)-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-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium
Hep	heptanes
HEPES	4-(2-hydroxyethyl)-piperazine-1-ethanesulfonic acid
HV	High vacuum

HPLC	high performance liquid chromatography
*i*Pr	*iso*-propyl
LC	liquid chromatography
m	multiplet
M	molarity [mol L^{-1}]
Me	methyl
MS	mass spectrometry
min	minute(s)
NMR	nuclear magnetic resonance spectroscopy
org.	organic
PBS	Phosphate buffered saline
Pd/C	palladium on carbon
PG	protecting group
Ph	phenyl
Prep	preparative
rpm	rotations per minute
RT	room temperature
s	singulet
sat.	Saturated
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin layer chromatography
t_R	retention time
UPLC	Ultra performance liquid chromatography

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 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:

I) LC-MS (A):

Zorbax SB-Aq, 3.5 μm, 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 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

II) LC-MS (B):

Acquity UPLC CSH C18 1.7 µm 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

Compound purity and identity was further confirmed by NMR spectroscopy (Bruker Avance II 400 MHz UltrashieldTM or Bruker AscendTM 500 equiped with a 5mm DCH cryoprobe), 1H (400 MHz or 500 MHz), 19F (376 MHz). The chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or trichlorofluoromethane, and multiplicities are given as s (singlet) or m (multiplet).

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

I) Preparative LC-MS (I):

A X-Bridge column (Waters C18, 10µm OBD, 30x75 mm) was used. The two elution solvents were as follows: solvent A = water + 0.5% NH_4OH (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):

X-Bridge column (Waters C18, 10µm OBD, 30x75 mm) was used. The two elution solvents were as follows: solvent A = water + 0.5% NH_4OH (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	3.5	6.0	6.2	6.6
Solvent A (%)	70	70	5	5	70	70
Solvent B (%)	30	30	95	95	30	30

III) Preparative LC-MS (III):

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):

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):

A X-Bridge column (Waters C18, 10µm OBD, 30x75 mm) was used. The two elution solvents were as follows: solvent A = water + 0.5% NH_4OH (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

Preparative chiral HPLC methods used:

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

I) Preparative chiral HPLC (I):

A ChiralPak IB column (5µm, 30x250mm) was used. The elution solvent was Hep/EtOH 60/40, run for 9min and at a flow rate of 40mL/min.

II) Preparative chiral HPLC (II):

A (R,R) Whelk-01 column (10µm, 50x250mm) was used. The elution solvent was Hep/EtOH 70/30, run for 16.3min and at a flow rate of 100mL/min.

III) Preparative chiral HPLC (III):

A ChiralPak IB column (5µm, 30x250mm) was used. The elution solvent was Hep/EtOH 50/50, run for 8min and at a flow rate of 34mL/min.

IV) Preparative chiral HPLC (IV):

A ChiralPak IB column (5µm, 20x250mm) was used. The elution solvent was Hep/EtOH 50/50, 0.1% DEA, run for 18.7min and at a flow rate of 16mL/min.

V) Preparative chiral HPLC (V):

A ChiralPak IB column (5µm, 30x250mm) was used. The elution solvent was Hep/EtOH 70/30, run for 11.8min and at a flow rate of 34mL/min.

VI) Preparative chiral HPLC (VI):

A ChiralPak OZ-H column (5µm, 20x250mm) was used. The elution solvent was Hep/EtOH 50/50, 0.1% DEA, run for 11min and at a flow rate of 19mL/min.

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

1.1. 5-Bromo-2-trifluoromethyl-thiazole-4-carboxylic acid

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 Br_2 (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 mixture was extracted with EA. The org. layers were washed with brine, dried ($MgSO_4$), filtered off and evaporated to dryness to afford 4.15g of brown solid, used without further purification. LC-MS (A): t_R = 0.67min. F-NMR (CD_3OD): -63.57ppm (s).

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

To a solution of intermediate 1.1 (12g), MeOH (130mL) was added H_2SO_4 (96%, 6.5mL) and the mixture was stirred at 70°C for 3h. After cooling down, the reaction mixture was quenched with sat. aq. Na_2CO_3 and the solvent partially evaporated off. The residue was diluted with DCM and washed with aq. sat. Na_2CO_3 (1x), water (1x) and brine (1x), and the aq. phases were extracted with DCM (2x). The combined org. layers were dried over $MgSO_4$, filtrated off, evaporated and dried under HV to afford 12g of brown resin. LC-MS (A): t_R = 0.83min. F-NMR (CD_3OD): -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 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 (A): t_R = 0.97min; $[M+H]^+$: 410.0.

1.4. (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 was 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 Na_2SO_4 and concentrated to dryness to afford 4.1g as orange solid. LC-MS (A): t_R = 0.88min; $[M+H]^+$: 395.9.

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

To a solution of intermediate 1.4 (10.17g) in THF (210mL) were added LiBr (2.26g) and (diacetoxyiodo)benzene (8.45g) at RT. The resulting suspension was stirred at RT for 1h30. 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 340g cartridge, solvent A: Hep; solvent B: EA; gradient in %B: 5 for 5CV, 5 to 10 over 3CV) to afford 9.63g as yellow solid. LC-MS (A): t_R = 1.04min; $[M+H]^+$: 429.2.

1.6. (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 1.5 (1.63g), 2-ethoxypyrimidine-5-boronic acid (778mg), $Pd(PPh_3)_2Cl_2$ (152mg), 1M Na_2CO_3 (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 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 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 (A): t_R = 1.04min; $[M+H]^+$: 473.9.

1.7. 2-Ethoxy-5-[5-((R)-3-methyl-piperazin-1-yl)-2-trifluoromethyl-thiazol-4-yl]-pyrimidine

To solution of intermediate 1.6 (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 $MgSO_4$, filtrated off, evaporated and dried at HV to afford 1.01g as beige solid. LC-MS (A): t_R = 0.64min; $[M+H]^+$: 374.0.

1.8. (3-Bromo-[1,2,4]triazol-1-yl)-acetate, lithium salt

To a solution of ethyl (3-bromo-1H-1,2,4-triazole-1-yl)acetate (200mg) in THF (0.75mL) and EtOH (0.75mL) was added H_2O (0.5mL) followed by 2M LiOH (0.47mL). The reaction mixture was stirred at RT overnight, was evaporated off and the residue dried at HV to afford 201mg as white solid. LC-MS (A): t_R = 0.29min; $[M+H]^+$: 205.9.

1.9. 2-(3-Bromo-[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 1.7 (120mg), intermediate 1.8 (76mg), HATU (159mg), and DIPEA (82µL) in DCM (4mL) and DMF (1mL) was stirred at RT overnight. DCM was removed by evaporation and the crude purified by Prep LC-MS (IV) to afford 102mg as white solid. LC-MS (A): t_R = 0.9min; $[M+H]^+$: 561.0.

1.10. 1-{(R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-isopropenyl-[1,2,4]triazol-1-yl)-ethanone

A mixture of intermediate 1.9 (40mg), isopropenylboronic acid pinacol ester (15.1mg), $Pd(PPh_3)_2Cl_2$ (2.8mg), 1M Na_2CO_3 (1mL) in MeCN (1mL) was vigorously stirred at 80°C under argon for 2h. The reaction mixture was allowed to cool down to RT and evaporated to dryness. The crude was purified by Prep LC-MS (I). LC-MS (A): t_R = 0.9min; $[M+H]^+$: 523.2.

1.11. 1-{(R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-isopropyl-[1,2,4]triazol-1-yl)-ethanone

A flask containing intermediate 1.10 (g), Pd/C (1.5mg) in MeOH (1mL) was evacuated and backfilled with argon (3x), afterwards evacuated and backfilled with H_2 (3x) and the reaction mixture was stirred at RT overnight. The reaction mixture was filtered over a syringe filter and the filtrate was evaporated to dryness. The crude was purified by Prep LC-MS (IV) to afford 7mg as white solid. LC-MS (B): t_R = 1.11min; $[M+H]^+$: 525.2.

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

2.1. (3-Ethyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester

To a solution of 3-ethyl-1H-1,2,4-triazole (2g) in MeCN (125mL) was added Cs_2CO_3 (6.37g) followed by benzyl bromoacetate (3.23mL). The reaction mixture was stirred at RT overnight and evaporated to dryness. The residue was taken up in EA and washed with water. The aq. layers were extracted with EA (2x) and the combined org. layers were dried over Na_2SO_4, filtered off and evaporated to dryness. The residue was purified by CC (Biotage, SNAP 100g cartridge, solvent A: DCM; solvent B: DCM/MeOH 8:2; gradient in %B: 15 for 4CV, 15 to 100 over 4CV, 100 for 1CV) to afford 3.89g as first eluting fraction (mixture of two triazole regioisomers) and 309mg as second eluting fraction ((3-ethyl-[1,2,4]triazol-4-yl)-acetic acid benzyl ester). The mixture of regioisomers was purified by preparative chiral HPLC (I). First eluting fraction: (5-ethyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester: 1.39g yellow oil. LC-MS (A): t_R = 0.72min; $[M+H]^+$: 246.2. Roesy signal seen between CH_2CH_3 at 2.72ppm and CH_2CO_2 at 4.93ppm.

Second eluting fraction: (3-ethyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester: 2.08g yellow solid. LC-MS (A): t_R = 0.71min; $[M+H]^+$: 246.2. Roesy signal seen between CH at 8.08 ppm (triazole) and CH_2CO_2 at 4.96ppm.

2.2. (3-Ethyl-[1,2,4]triazol-1-yl)-acetic acid

A flask containing (3-ethyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester from step 2.1 (2.06g), Pd/C (445mg) in EtOH (20mL) was evacuated and backfilled with argon (3x), afterwards evacuated and backfilled with H_2 (3x) and the reaction mixture was stirred at RT for 9h. The reaction mixture was filtered over a celite plug and the filtrate was evaporated to dryness to afford 1.27g as white solid. LC-MS (A): t_R = 0.25min; $[M+H]^+$: 156.2.

2.3. 1-{(R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-ethyl-[1,2,4]triazol-1-yl)-ethanone

A mixture of intermediate 1.7 (50mg), intermediate 2.2 (21mg), HATU (66mg), and NEt_3 (28µL) in DCM (1.5mL) was stirred at RT overnight. The reaction mixture was evaporated to

dryness and the crude purified by Prep LC-MS (I) to afford 15mg as white solid. LC-MS (B): t_R = 1.05 min; $[M+H]^+$: 511.2.

Example 3: 2-(3-tert-Butyl-[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

3.1. (3-tert-Butyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester

This compound was prepared using a method analogous to that of Example 2, step 2.1, 3-tert-butyl-1H-1,2,4-triazole replacing 3-ethyl-1H-1,2,4-triazole. The desired compound was obtained after CC as single regioisomer. LC-MS (A): t_R = 0.73min; $[M+H]^+$: 274.1.

3.2. (3-tert-Butyl-[1,2,4]triazol-1-yl)-acetic acid

This compound was prepared using a method analogous to that of Example 2, step 2.2, intermediate 3.1 replacing (3-ethyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester. LC-MS (A): t_R = 0.36min; $[M+H]^+$: 184.3.

3.3. 2-(3-tert-Butyl-[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

This compound was prepared using a method analogous to that of Example 2 step 2.3, intermediate 3.2 replacing intermediates 2.2. The desired compound was purified by Prep LC-MS (IV). LC-MS (A): t_R = 0.84min; $[M+H]^+$: 539.1.

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

4.1. (3-Methoxymethyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester

This compound was prepared using a method analogous to that of Example 2, step 2.1, 3-(methoxymethyl)-1H-1,2,4-triazol replacing 3-ethyl-1H-1,2,4-triazole. The crude was purified by two CC (1. Biotage, SNAP 10g cartridge, solvent A: DCM; solvent B: DCM/MeOH 8:2; gradient in %B: 5 for 7CV, 5 to 15 over 3CV, 15 for 3CV. 2. Biotage, SNAP 10g cartridge, solvent A: DCM; solvent B: DCM/MeOH 8:2; gradient in %B: 5 for 5CV, 5 to 10 over 3CV, 10 for 3CV, 10 to 15 for 3 CV) to yield two regiosiomers:

First eluting fraction: (5-methoxymethyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester: colourless oil. LC-MS (A): t_R = 0.71min; $[M+H]^+$: 262.2.

Second eluting fraction: (3-methoxymethyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester: colourless oil. LC-MS (A): t_R = 0.67min; $[M+H]^+$: 262.1. Roesy signal seen between CH (triazole) at 8.17ppm and NCH_2CO_2 at 5.01ppm.

4.2. (3-Methoxymethyl-[1,2,4]triazol-1-yl)-acetic acid

This compound was prepared using a method analogous to that of Example 2, step 2.2, (3-methoxymethyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester from step 4.1 replacing (3-ethyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester. LC-MS (A): t_R = 0.24min; $[M+H]^+$: 172.0.

4.3. 1-{(R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-methoxymethyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 2, step 2.3, intermediate 4.2 replacing intermediate 2.2. The desired compound was purified by Prep LC-MS (IV). LC-MS (B): t_R = 1.02 min; $[M+H]^+$: 527.2.

Example 5: 1-(2-{(R)-2-Methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl}-2-oxo-ethyl)-1H-[1,2,4]triazole-3-carboxylic acid amide

5.1. (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 1, step 1.6, 2-(trifluoromethyl)pyrimidine-5-yl-boronic acid replacing 2-ethoxypyrimidine-5-boronic acid. LC-MS (A): t_R = 1.06min; $[M+H]^+$: 497.9.

5.2. 5-[5-((R)-3-Methyl-piperazin-1-yl)-2-trifluoromethyl-thiazol-4-yl]-2-trifluoromethyl-pyrimidine, as hydrochloride salt

A mixture of intermediate 5.1 (2.3g) in HCl (10.2mL, 4M in dioxane) was stirred at RT for 3h. The white suspension was filtrated, the filtrate washed with Et_2O and dried under HV to give 1.6g as white solid. LC-MS (A): t_R = 0.72min; $[M+H^+ + CH_3CN]^+$: 438.9.

5.3. 1-(2-{(R)-2-Methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl}-2-oxo-ethyl)-1H-[1,2,4]triazole-3-carbonitrile

This compound was prepared using a method analogous to that of Example 2, step 2.3, 2-(3-cyano-1H-1,2,4-triazol-1-yl)acetic acid replacing intermediate 2.2 and intermediate 5.2 replacing intermediate 1.7. The desired compound was purified by Prep LC-MS (IV). LC-MS (B): t_R = 1.19min; $[M+H]^+$: 532.1.

5.4. 1-(2-{(R)-2-Methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl}-2-oxo-ethyl)-1H-[1,2,4]triazole-3-carboxylic acid amide

To a solution of intermediate 5.3 (18mg) in DCM (0.1mL) was added conc. H_2SO_4 (0.1mL), and the resulting emulsion was vigorously stirred for 4h15. The reaction mixture was added portionwise to a mixture of NH_4OH (25%) and ice, and the aq. layer was extracted with DCM (5x). The combined org. layers were washed with brine, dried over $MgSO_4$, evaporated and dried at HV. Purification by Prep. TLC (DCM/MeOH 95:5) afforded 9mg as white solid. LC-MS (A): t_R = 0.82min; $[M+H]^+$: 550.0.

Example 6: 2-(3-Ethyl-[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 2, step 2.3, intermediate 5.2 replacing intermediate 1.7. The desired compound was purified by Prep LC-MS (IV). LC-MS (A): t_R = 0.89min; $[M+H]^+$: 535.0.

Example 7: 2-(3-Isopropyl-[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

7.1. (3-Isopropyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester and *(5-Isopropyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester*

These compounds were prepared using a method analogous to that of Example 3, step 3.1, 3-isopropyl-1H-1,2,4-triazole replacing 3-ethyl-1H-1,2,4-triazole. The mixture of regioisomers was purified by preparative chiral HPLC (II). First eluting fraction: (3-isopropyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester. LC-MS (A): t_R = 0.76min; $[M+H]^+$: 260.2. Roesy signal seen between CH_2 at 4.96ppm and CH (triazole) at 8.08ppm.

Second eluting fraction: (5-isopropyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester. LC-MS (A): t_R = 0.76min; $[M+H]^+$: 260.2. Roesy signal seen between CH_2 at 4.96ppm and CH (isopropyl) at 2.97ppm.

7.2. (3-Isopropyl-[1,2,4]triazol-1-yl)-acetic acid and *(5-Isopropyl-[1,2,4]triazol-1-yl)-acetic acid*

(3-Isopropyl-[1,2,4]triazol-1-yl)-acetic acid was prepared using a method analogous to that of Example 2, step 2.2, (3-isopropyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester of step 7.1 replacing intermediate 2.1. LC-MS (A): t_R = 0.30min; $[M+H]^+$: 170.2.

Alternatively, the mixture of regioisomers from step 7.1 was used to give a mixture of (3-isopropyl-[1,2,4]triazol-1-yl)-acetic acid and (5-isopropyl-[1,2,4]triazol-1-yl)-acetic acid.

7.3. 2-(3-Isopropyl-[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 2, step 2.3, intermediate 5.2 replacing intermediate 1.7 and the mixture of regioisomers in step 7.2 replacing intermediate 2.2. The desired compound was purified by Prep LC-MS (IV) followed by preparative chiral HPLC (VI). First eluting fraction of preparative chiral HPLC: 2-(3-isopropyl-[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. LC-MS (B): t_R = 1.17min; $[M+H]^+$: 549.2.

Example 8: 2-(3-tert-Butyl-[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 2, step 2.3, intermediate 5.2 replacing intermediate 1.7 and intermediate 3.2 replacing intermediate 2.2.

The desired compound was purified by Prep LC-MS (II). LC-MS (B): t_R = 1.23 min; $[M+H]^+$: 563.2.

Example 9: 2-(3-Methoxymethyl-[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 2, step 2.3, intermediate 5.2 replacing intermediate 1.7 and intermediate 4.2 replacing intermediate 2.2. The desired compound was purified by Prep LC-MS (I). LC-MS (B): t_R = 1.09 min; $[M+H]^+$: 551.2.

Example 10: 2-(3-Hydroxymethyl-[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 solution of Example 9 (25mg) in DCM (1mL) was added at -30°C BBr_3 (58 µL; 1M in DCM) under argon and the resulting suspension was stirred at 0°C for 3h. The reaction mixture was quenched with H_2O, diluted with aq. sat. $NaHCO_3$ and extracted with EA (3x). The combined org. layers were washed with brine, dried over $MgSO_4$, filtrated off and evaporated to dryness. Prep LC-MS (IV) gave 5mg as white powder. LC-MS (A): t_R = 0.81min; $[M+H]^+$: 537.1.

Example 11: 1-{(R)-2-Methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl}-2-(3-propyl-[1,2,4]triazol-1-yl)-ethanone

11.1. (3-propyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester

These compounds were prepared using a method analogous to that of Example 2, step 2.1, 3-propyl-1H-1,2,4-triazole replacing 3-ethyl-1H-1,2,4-triazole. The mixture of regioisomers was purified by preparative chiral HPLC (III). First eluting fraction: (5-propyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester. LC-MS (A): t_R = 0.77min; $[M+H]^+$: 260.1. Roesy signal seen between CH_2CO_2 at 4.95ppm and $CH_2CH_2CH_3$ at 2.65ppm.

Second eluting fraction: (3-propyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester. LC-MS (A): t_R = 0.76min; $[M+H]^+$: 260.1. Roesy signal seen between CH_2CO_2 at 4.96ppm and CH (triazole) at 8.08ppm.

11.2. (3-Propyl-[1,2,4]triazol-1-yl)-acetic acid

These compounds were prepared using a method analogous to that of Example 2, step 2.2, (3-propyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester of step 11.1 replacing intermediate 2.1. LC-MS (A): t_R = 0.35min; $[M+H]^+$: 170.4.

11.3. 1-{(R)-2-Methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl}-2-(3-propyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 2, step 2.3, intermediate 5.2 replacing intermediate 1.7 and intermediate 11.2 replacing intermediate 2.2. The desired compound was purified by Prep LC-MS (I). LC-MS (B): t_R = 1.17 min; $[M+H]^+$: 548.9.

Example 12: 2-[3-(1-Hydroxy-ethyl)-[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

12.1. (3-Acetyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester

This compound was prepared using a method analogous to that of Example 2, step 2.1, 1-(1H-1,2,4-triazol-5-yl)ethanone replacing 3-ethyl-1H-1,2,4-triazole. The crude was purified by CC (Biotage, SNAP 10g cartridge, solvent A: Hep; solvent B: EA; gradient in %B: 30 for 4CV, 30 to 70 over 4CV, 70 for 2CV, 70 to 100 over 2CV, 100 for 2CV) to give the desired triazole regioisomer as second fraction. LC-MS (A): t_R = 0.7min; $[M+H]^+$: 260.1. Roesy signal seen between CH (triazole) at 8.28ppm and CH_2 at 5.1ppm.

12.2. (3-Acetyl-[1,2,4]triazol-1-yl)-acetic acid

This compound was prepared using a method analogous to that of Example 2, step 2.2, intermediate 12.1 replacing intermediate 2.1. LC-MS (A): t_R = 0.25min; $[M+H]^+$: 170.0.

12.3. 2-(3-Acetyl-[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 2, step 2.3, intermediate 5.2 replacing intermediate 1.7 and intermediate 12.2 replacing intermediate 2.2. The desired compound was purified by Prep LC-MS (I). LC-MS (A): t_R = 0.89min; $[M+H]^+$: 549.0.

12.4. 2-[3-(1-Hydroxy-ethyl)-[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 pale yellow solution of intermediate 12.3 (40mg) in THF (0.75mL) and EtOH (0.25mL) was added $NaBH_4$ (1.4mg) at 0°C under argon and the reaction mixture was stirred at 0°C for 1h30. Then a second batch of $NaBH_4$ (0.7mg) was added and the mixture further stirred for 2h20. The reaction mixture was evaporated to dryness, the residue was suspended in EA and aq. sat. NH_4Cl was added and stirring was allowed for 30min at RT. The layers were separated and the org. layer was washed with 1x brine. The aq. layers were re-extracted with EA (2x). The combined org. layers were dried over $MgSO_4$, filtrated off and evaporated to dryness. Purification by Prep TLC (DCM/MeOH 95/5) gave 10mg as white solid. LC-MS (A): t_R = 0.82min; $[M+H]^+$: 551.1.

Example 13: 2-[3-(1-Hydroxy-1-methyl-ethyl)-[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 suspension of intermediate 12.3 (40mg) in Et_2O (0.75mL) was added MeMgBr (48 µL; 3M in Et_2O) at -20°C and the resulting suspension was stirred at RT for 1h30. The reaction mixture was quenched by addition of aq. sat. NH_4Cl and the aq. layer was extracted with EA (3x). The combined org. layers were dried over $MgSO_4$, filtrated and evaporated to dryness. Purification by Prep LC-MS (IV) gave 7mg as white powder. LC-MS (A): t_R = 0.84min; $[M+H]^+$: 565.1.

Example 14: 1-{(R)-4-[4-(2-Cyclobutoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-isopropyl-[1,2,4]triazol-1-yl)-ethanone

14.1. (R)-4-[4-(2-Cyclobutoxy-pyrimidin-5-yl)-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 1.6, 2-(cyclobutoxy)pyrimidine-5-boronic replacing 2-ethoxypyrimidine-5-boronic acid. The crude was purified by Prep LC-MS (II) instead of CC. LC-MS (A): t_R = 1.08min; $[M+H]^+$: 500.1.

14.2. 2-Cyclobutoxy-5-[5-((R)-3-methyl-piperazin-1-yl)-2-trifluoromethyl-thiazol-4-yl]-pyrimidine, as hydrochloride salt

This compound was prepared using a method analogous to that of Example 5, step 5.2, intermediate 14.1 replacing intermediate 5.1. LC-MS (A): t_R = 0.71min; $[M+H]^+$: 400.1.

14.3. 1-{(R)-4-[4-(2-Cyclobutoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-isopropyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 2, step 2.3, intermediate 14.2 replacing intermediate 1.7 and the regioisomeric mixture in step 7.2 replacing intermediate 2.2. The crude was purified by CC (DCM/MeOH 97:3) followed by Prep LC-MS (I) and Preparative chiral HPLC (IV).

Second eluting fraction (preparative chiral HPLC): 1-{(R)-4-[4-(2-cyclobutoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-isopropyl-[1,2,4]triazol-1-yl)-ethanone: LC-MS (B): t_R = 1.21min; $[M+H]^+$: 551.3. Roesy signal seen between CH_2 at 5.14-5.37ppm and CH (triazole) at 8.36ppm.

Example 15: 1-{(R)-4-[4-(2-Cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-ethyl-[1,2,4]triazol-1-yl)-ethanone

15.1. (R)-4-[4-(2-Cyclopropyl-pyrimidin-5-yl)-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 1.6, 2-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine replacing 2-ethoxypyrimidine-5-boronic acid. LC-MS (A): t_R = 1.06min; $[M+H]^+$: 470.3.

15.2. 2-Cyclopropyl-5-[5-((R)-3-methyl-piperazin-1-yl)-2-trifluoromethyl-thiazol-4-yl]-pyrimidine, as hydrochloride salt

This compound was prepared using a method analogous to that of Example 5, step 5.2, intermediate 15.1 replacing intermediate 5.1. LC-MS (A): t_R = 0.6min; $[M+H]^+$: 370.1.

15.3. 1-{(R)-4-[4-(2-Cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-ethyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 2, step 2.3, intermediate 15.2 replacing intermediate 1.7. The crude was purified by Prep LC-MS (IV). LC-MS (B): t_R = 1.07min; $[M+H]^+$: 507.2.

Example 16: 1-{(R)-4-[4-(2-Cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-isopropyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 2, step 2.3, intermediate 15.2 replacing intermediate 1.7 and (3-isopropyl-[1,2,4]triazol-1-yl)-acetic acid from step 7.2 replacing intermediate 2.2. The crude was purified by Prep LC-MS (IV). LC-MS (A): t_R = 0.8min; $[M+H]^+$: 521.2.

Example 17: 2-(3-tert-Butyl-[1,2,4]triazol-1-yl)-1-{(R)-4-[4-(2-cyclopropyl-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 2, step 2.3, intermediate 15.2 replacing intermediate 1.7 and intermediate 3.2 replacing intermediate 2.2. The crude was purified by Prep LC-MS (IV). LC-MS (B): t_R = 1.18min; $[M+H]^+$: 535.2.

Example 18: 1-{(R)-4-[4-(2-Cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-methoxymethyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 2, step 2.3, intermediate 15.2 replacing intermediate 1.7 and intermediate 4.2 replacing intermediate 2.2. The crude was purified by Prep LC-MS (IV). LC-MS (A): t_R = 0.75min; $[M+H]^+$: 523.2.

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

19.1. (3-Methyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester

This compound was prepared using a method analogous to that of Example 2, step 2.1, 3-methyl-1H-1,2,4-triazole replacing 3-ethyl-1H-1,2,4-triazole. The mixture of regioisomers was purified by preparative chiral HPLC (V). First eluting fraction: (5-methyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester. LC-MS (A): t_R = 0.68min; $[M+H]^+$: 232.16. ^{1}H-NMR ($CDCl_3$): 7.83

(s, 1H); 7.40-7.33 (m, 5H); 5.23 (s, 2H); 4.93 (s, 2H); 2.43 (s, 3H). Roesy signal seen between CH_2CO_2 at 4.93ppm and CH_3 at 2.43ppm.

Second eluting fraction: (3-methyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester. LC-MS (A): t_R = 0.67min; $[M+H]^+$: 232.16. ^{1}H-NMR ($CDCl_3$): 8.05 (s, 1H); 7.40-7.30 (m, 5H); 5.23 (s, 0.95H, CH_2); 4.93-4.88 (3s, 2H); 2.42 (s, 3H). Roesy signal seen between CH (triazole) at 8.05ppm and CH_2CO_2 at 4.93-4.88ppm.

19.2. (3-Methyl-[1,2,4]triazol-1-yl)-acetic acid

This compound was prepared using a method analogous to that of Example 2, step 2.2, (3-methyl-[1,2,4]triazol-1-yl)-acetic acid benzyl ester from step 19.1 replacing intermediate 2.1. LC-MS (A): t_R = 0.18min; $[M+H]^+$: 142.22.

19.3. 1-{(R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-methyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 2, step 2.3, intermediate 19.2 replacing intermediate 2.2. The crude was purified by Prep LC-MS (V). LC-MS (A): t_R = 0.81min; $[M+H]^+$: 497.1.

Example 20: 2-(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 2, step 2.3, intermediate 5.2 replacing intermediate 1.7 and intermediate 19.2 replacing intermediate 2.2. DIPEA was used instead of NEt_3. The crude was purified by Prep LC-MS (III). LC-MS (A): t_R = 0.87min; $[M+H]^+$: 521.0.

Example 21: 1-{(R)-4-[4-(2-Cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-methyl-[1,2,4]triazol-1-yl)-ethanone

This compound was prepared using a method analogous to that of Example 2, step 2.3, intermediate 15.2 replacing intermediate 1.7 and intermediate 19.2 replacing intermediate 2.2. The crude was purified by Prep LC-MS (V). LC-MS (A): t_R = 0.81min; $[M+H]^+$: 493.1.

II. BIOLOGICAL ASSAYS

A) <u>FLIPR assay:</u> 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 (Galpha(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

(0.038%), containing 5 mM probenecid. This buffer, but lacking the dye and containing probenecid at a concentration of 2.5 mM, 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.

B) Receptor internalization assay (RIA): Stock solutions of test compounds are made up at a concentration of 10 mM in DMSO, and serially diluted in PBS containing 0,5% BSA to concentrations required for inhibition dose response curves. Diluted compounds are then mixed with an equal volume of CXCL10 (Peprotech) diluted in PBS. Anticoagulated venous human whole blood is added to the mixture, which is then incubated in a CO_2 incubator at 37°C to allow for ligand mediated receptor internalization (final CXCL10 concentration is 9 nM). After 30 min, the blood is mixed with fluorescently labeled CXCR3 and CD4 specific antibodies (Becton Dickinson) and incubated on ice for 10 minutes. Samples are then mixed with BD FACS Lysing Solution (Becton Dickinson) in order to eliminate red blood cells. After washing the cells with PBS containing 0,5% BSA, the samples are then analyzed in a flow cytometer (FACS Canto II, Becton Dickinson). For data analysis using FACSDiva software (Becton Dickinson), the mean fluorescence corresponding to CXCR3 cell surface expression was determined on CD4 positive cells.

The calculated IC_{50} 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 IC_{50} values have been determined several times for the same compound, mean values are given. Data for the FLIPR assay are shown in Table 1 and for the receptor internalization assay (RIA) in Table 2.

Table 1

Example No	FLIPR: IC_{50} (nM)	Example No	FLIPR: IC_{50} (nM)
1	2.3	**12**	0.9
2	1.6	**13**	3.2
3	1.0	**14**	1.2

4	13	**15**	2.5
5	12	**16**	0.7
6	2.0	**17**	4.6
7	1.3	**18**	3.1
8	1.6	**19**	1.8
9	2.7	**20**	1.6
10	5.2	**21**	5.2
11	4.4		

Table 2

Example No	RIA: IC_{50} (nM)	Example No	RIA: IC_{50} (nM)
1	299	**12**	564
2	235	**13**	830
3	552	**14**	459
4	950	**15**	190
5	1710	**16**	524
6	148	**17**	679
7	174	**18**	1390
8	349	**19**	211
9	606	**20**	189
10	809	**21**	462
11	221		

C) 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% CO_2, 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

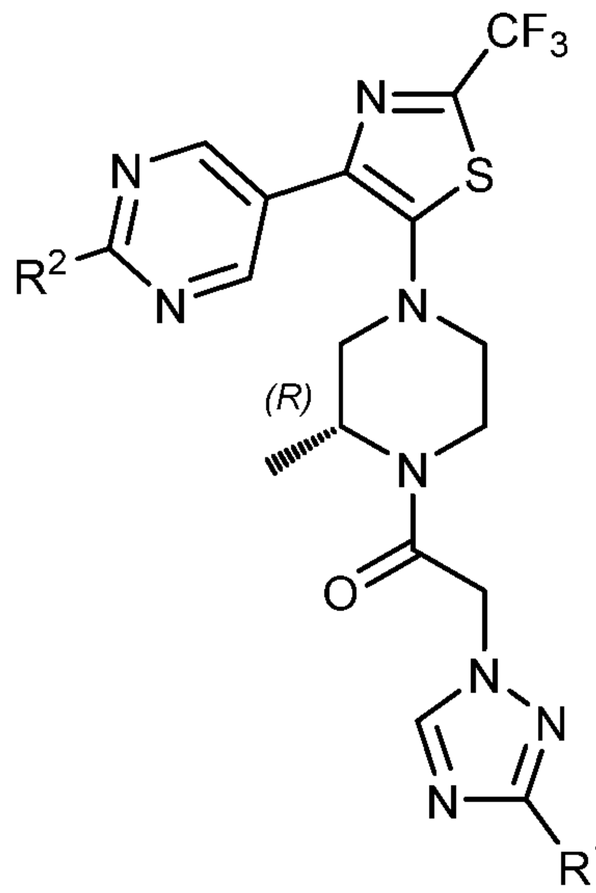
32-35°C in the QPatch robot until use, at which time aliquots are transferred to the extracellular solution (in mM: NaCl 150; KCl 4; $CaCl_2$ 1.2; $MgCl_2$ 1; HEPES 10; pH 7.4 with NaOH) containing 0.3 %v/v DMSO and applied to the test plates. K^+ currents are measured with the patch-voltage-clamp technique in the whole-cell configuration with the internal solution (in mM: KCl, 140; NaCl, 10; $MgCl_2$, 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	6	3000	20
2	300	-2	3000	4
3	300	10	3000	20
4	300	5	3000	10
5	300	1	3000	5
6	300	5	3000	22
7	300	5	3000	24
8	300	4	3000	23
9	300	2	3000	11
10	300	6	3000	17
11	300	5	3000	30
12	300	0	3000	4
13	300	10	3000	21
14	300	4	3000	27

15	300	3	3000	27
16	300	1	3000	25
17	300	0	3000	23
18	300	10	3000	22
19	300	9	3000	14
20	300	2	3000	18
21	300	3	3000	17

Claims

1. A compound of Formula (I)



Formula (I)

wherein

R^{1} represents (C_{1-4})alkyl, (C_{1-2})alkoxy-(C_{1-2})alkyl, hydroxy-(C_{1-4})alkyl or –C(O)NH_2; and

R^{2} represents (C_{3-6})cycloalkyl, (C_{1-4})alkoxy, (C_{3-6})cycloalkoxy or (C_{1-2})fluoroalkyl;

or a salt thereof.

2. A compound according to claim 1, wherein

R^{1} represents (C_{1-4})alkyl, (C_{1-2})alkoxy-(C_{1-2})alkyl or hydroxy-(C_{1-4})alkyl; and

R^{2} represents (C_{3-6})cycloalkyl, (C_{1-4})alkoxy or (C_{1-2})fluoroalkyl;

or a salt thereof.

3. A compound according to claim 1, wherein

R^{1} represents ethyl, *n*-propyl, *iso*-propyl, *tert*.-butyl, methoxy-methyl or 1-hydroxy-ethyl; and

R^{2} represents cyclopropyl, ethoxy or trifluoromethyl;

or a salt thereof.

4. A compound according to claim 1, wherein

R^{1} represents (C_{1-4})alkyl, (C_{1-2})alkoxy-(C_{1-2})alkyl, hydroxy-(C_{1-4})alkyl or –C(O)NH_2; and

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

or a salt thereof.

5. A compound according to any one of claims 1, 2 or 4, wherein

R^{1} represents (C_{1-4})alkyl;

or a salt thereof.

6. A compound according to any one of claims 1 to 4, wherein

R^{1} represents ethyl, *n*-propyl, *iso*-propyl or *tert*.-butyl;

or a salt thereof.

7. A compound according to any one of claims 1, 2, 5 or 6, wherein
R² represents (C_{3-6})cycloalkyl;
or a salt thereof.

8. A compound according to any one of claims 1, 2, 5 or 6, wherein
R² represents (C_{1-4})alkoxy;
or a salt thereof.

9. A compound according to any one of claims 1, 2, 5 or 6, wherein
R² represents (C_{1-2})fluoroalkyl;
or a salt thereof.

10. A compound according to claim 1 selected from the group consisting of:
1-{(R)-4-[4-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-isopropyl-[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-(3-ethyl-[1,2,4]triazol-1-yl)-ethanone;
2-(3-tert-Butyl-[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-(2-Ethoxy-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-piperazin-1-yl}-2-(3-methoxymethyl-[1,2,4]triazol-1-yl)-ethanone;
1-(2-{(R)-2-Methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl}-2-oxo-ethyl)-1H-[1,2,4]triazole-3-carboxylic acid amide;
2-(3-Ethyl-[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-Isopropyl-[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-tert-Butyl-[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-Methoxymethyl-[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-Hydroxymethyl-[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;
1-{(R)-2-Methyl-4-[2-trifluoromethyl-4-(2-trifluoromethyl-pyrimidin-5-yl)-thiazol-5-yl]-piperazin-1-yl}-2-(3-propyl-[1,2,4]triazol-1-yl)-ethanone;
2-[3-(1-Hydroxy-ethyl)-[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)-[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;

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

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

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

2-(3-tert-Butyl-[1,2,4]triazol-1-yl)-1-{(R)-4-[4-(2-cyclopropyl-pyrimidin-5-yl)-2-trifluoromethyl-thiazol-5-yl]-2-methyl-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-methoxymethyl-[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-(3-methyl-[1,2,4]triazol-1-yl)-ethanone;

2-(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; and

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

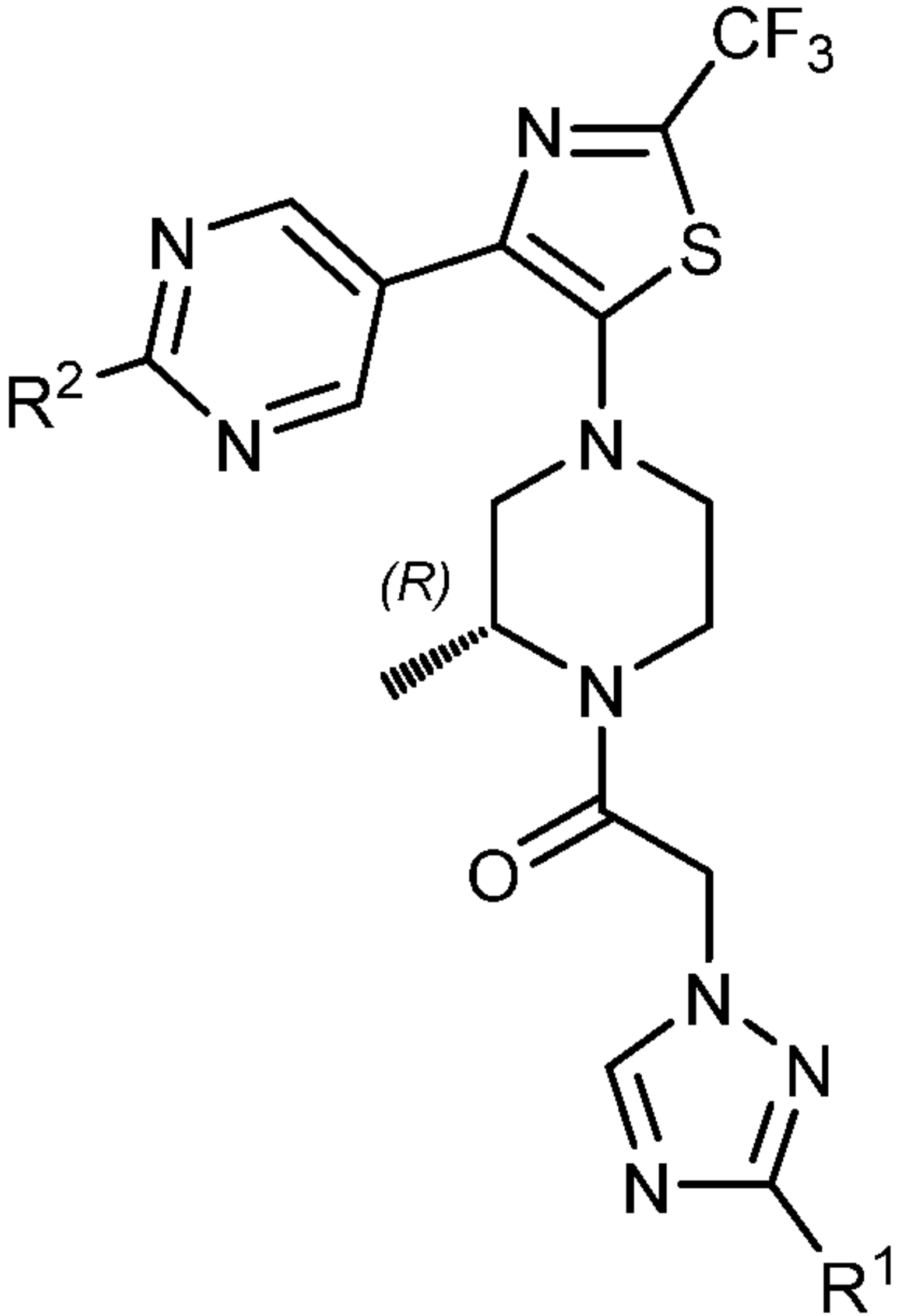
or a salt thereof.

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 prevention or treatment of a disease selected from the group consisting of autoimmune disorders, inflammatory diseases, infectious diseases, transplant rejection, fibrosis, neurodegenerative disorders and cancer.

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 prevention or treatment of a disease selected from the group consisting of autoimmune disorders, inflammatory diseases, infectious diseases, transplant rejection, fibrosis, neurodegenerative disorders and cancer.



(I)