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Inventor(s)	NOVAK; Andrew et al.

Compounds

Abstract

Compounds of formula (I):
##STR00001##
and related aspects.

Inventors: NOVAK; Andrew (Nottingham, GB), JONES; Geraint (Nottingham, GB),
WRIGGLESWORTH; Joseph (Nottingham, GB), DUFFY; Loma (Nottingham,
GB), BIRCH; Louise (Nottingham, GB), George; Pascal (Paris, FR)

Applicant: Step Pharma S.A.A. (Paris, FR)

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Background/Summary

FIELD OF THE INVENTION

[0001] The invention relates to novel benzamide compounds, processes for the manufacture of such compounds, related intermediates, compositions comprising such compounds and the use of such compounds as cytidine triphosphate synthase 1 inhibitors, particularly in the treatment or prophylaxis of disorders associated with cell proliferation.

BACKGROUND OF THE INVENTION

[0002] Nucleotides are a key building block for cellular metabolic processes such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis. There are two classes of nucleotides, that contain either purine or pyrimidine bases, both of which are important for metabolic processes. Based on this, many therapies have been developed to target different aspects of nucleotide synthesis, with some inhibiting generation of purine nucleotides and some pyrimidine nucleotides or both.

[0003] The pyrimidine nucleotide cytidine 5' triphosphate (CTP) is a precursor required not just for the metabolism of DNA and RNA but also phospholipids and sialylation of proteins. CTP originates from two sources: a salvage pathway and a de novo synthesis pathway that depends on two enzymes, the CTP synthases (or synthetases) 1 and 2 (CTPS1 and CTPS2) (Evans and Guy 2004; Higgins, et al. 2007; Ostrander, et al. 1998).

[0004] CTPS1 and CTPS2 catalyse the conversion of uridine triphosphate (UTP) and glutamine into cytidine triphosphate (CTP) and L-glutamate:

##STR00002##

[0005] Both enzymes have two domains, an N-terminal synthetase domain and a C-terminal glutaminase domain (Kursula, et al. 2006). The synthetase domain transfers a phosphate from adenosine triphosphate (ATP) to the 4-position of UTP to create an activated intermediate, 4-phospho-UTP. The glutaminase domain generates ammonia from glutamine, via a covalent thioester intermediate with a conserved active site cysteine, generating glutamate. This ammonium is transferred from the glutaminase domain to the synthetase domain via a tunnel or can be derived from external ammonium. This ammonium is then used by the synthetase domain to generate CTP from the 4-phospho-UTP (Lieberman, 1956).

[0006] Although CTPS exists as two isozymes in humans and other eukaryotic organisms, CTPS1 and CTPS2, functional differences between the two isozymes are not yet fully elucidated (van Kuilenburg, et al. 2000).

[0007] The immune system provides protection from infections and has therefore evolved to rapidly respond to the wide variety of pathogens that the individual may be exposed to. This response can take many forms, but the expansion and differentiation of immune populations is a critical element and is hence closely linked to rapid cell proliferation. Within this, CTP synthase activity appears to play an important role in DNA synthesis and the rapid expansion of lymphocytes following activation (Fairbanks, et al. 1995; van den Berg, et al. 1995).

[0008] Strong clinical validation that CTPS1 is the critical enzyme in human lymphocyte proliferation came with the identification of a loss-of-function homozygous mutation (rs145092287) in this enzyme that causes a distinct and life-threatening immunodeficiency,

characterized by an impaired capacity of activated T- and B-cells to proliferate in response to antigen receptor-mediated activation. Activated CTPS1-deficient cells were shown to have decreased levels of CTP. Normal T-cell proliferation was restored in CTPS1-deficient cells by expressing wild-type CTPS1 or by addition of exogenous CTP or its nucleoside precursor, cytidine. CTPS1 expression was found to be low in resting lymphocytes, but rapidly upregulated following activation of these cells. Expression of CTPS1 in other tissues was generally low. CTPS2 seems to be ubiquitously expressed in a range of cells and tissues but at low levels, and the failure of CTPS2, which is still intact in the patients, to compensate for the mutated CTPS1, supports CTPS1 being the critical enzyme for the immune populations affected in the patients (Martin, et al. 2014).

[0009] Overall, these findings suggest that CTPS1 is a critical enzyme necessary to meet the demands for the supply of CTP required by several important immune cell populations.

[0010] Normally the immune response is tightly regulated to ensure protection from infection, whilst controlling any response targeting host tissues. In certain situations, the control of this process is not effective, leading to immune-mediated pathology. A wide range of human diseases are thought to be due to such inappropriate responses mediated by different elements of the immune system.

[0011] Given the role that cell populations, such as T and B lymphocytes, are thought to play in a wide range of autoimmune and other diseases, CTPS1 represents a target for a new class of immunosuppressive agents. Inhibition of CTPS1 therefore provides a novel approach to the inhibition of activated lymphocytes and selected other immune cell populations such as Natural Killer cells, Mucosal-Associated Invariant T (MAIT) and Invariant Natural Killer T cells, highlighted by the phenotype of the human mutation patients (Martin, et al. 2014).

[0012] Cancer can affect multiple cell types and tissues but the underlying cause is a breakdown in the control of cell division. This process is highly complex, requiring careful coordination of multiple pathways, many of which remain to be fully characterised. Cell division requires the effective replication of the cell's DNA and other constituents. Interfering with a cell's ability to replicate by targeting nucleic acid synthesis has been a core approach in cancer therapy for many years. Examples of therapies acting in this way are 6-thioguanine, 6-mecaptopurine, 5-fluorouracil, cytarabine, gemcitabine and pemetrexed.

[0013] As indicated above, pathways involved in providing the key building blocks for nucleic acid replication are the purine and pyrimidine synthesis pathways, and pyrimidine biosynthesis has been observed to be up-regulated in tumors and neoplastic cells.

[0014] CTPS activity is upregulated in a range of tumour types of both haematological and non-haematological origin, although heterogeneity is observed among patients. Linkages have also been made between high enzyme levels and resistance to chemotherapeutic agents.

[0015] Currently, the precise role that CTPS1 and CTPS2 may play in cancer is not completely clear. Several non-selective CTPS inhibitors have been developed for oncology indications up to phase I/II clinical trials, but were stopped due to toxicity and efficacy issues.

[0016] Most of the developed inhibitors are nucleoside-analogue prodrugs (3-deazauridine, CPEC, carbodine), which are converted to the active triphosphorylated metabolite by the kinases involved in pyrimidine biosynthesis: uridine/cytidine kinase, nucleoside monophosphate-kinase (NM P-kinase) and nucleoside diphosphatekinase (NDP-kinase). The remaining inhibitors (acivicin, DON) are reactive analogues of glutamine, which irreversibly inhibit the glutaminase domain of CTPS. Gemcitabine is also reported to have some inhibitory activity against CTPS (McClusky et al., 2016).

[0017] CTPS therefore appears to be an important target in the cancer field. The nature of all of the above compounds is such that effects on other pathways are likely to contribute to the efficacy they show in inhibiting tumours.

[0018] Selective CTPS inhibitors therefore offer an attractive alternative approach for the treatment of tumours. Compounds with different potencies against CTPS1 and CTPS2 may offer important

opportunities to target different tumours depending upon their relative dependence on these enzymes.

[0019] CTPS1 has also been suggested to play a role in vascular smooth muscle cell proliferation following vascular injury or surgery (Tang et al., 2013).

[0020] As far as is known to date, no selective CTPS1 inhibitors have been developed. Recently, the CTPS1 selective inhibitory peptide CT pep-3 has been identified. The inhibitory effects of CT pep-3 however, were seen in cell free assays but not in the cellular context. This was not unexpected though, since the peptide is unlikely to enter the cell and hence is not easily developable as a therapeutic (Sakamoto, et al. 2017).

[0021] In summary, the available information and data strongly suggest that inhibitors of CTPS1 will reduce the proliferation of a number of immune and cancer cell populations, with the potential for an effect on other selected cell types such as vascular smooth muscle cells as well. Inhibitors of CTPS1 may therefore be expected to have utility for treatment or prophylaxis in a wide range of indications where the pathology is driven by these populations.

[0022] CTPS1 inhibitors represent a novel approach for inhibiting selected components of the immune system in various tissues, and the related pathologies or pathological conditions such as, in general terms, rejection of transplanted cells and tissues, Graft-related diseases or disorders, allergies and autoimmune diseases. In addition, CTPS1 inhibitors offer therapeutic potential in a range of cancer indications and in enhancing recovery from vascular injury or surgery and reducing morbidity and mortality associated with neointima and restenosis.

SUMMARY OF THE INVENTION

[0023] The invention provides a compound of formula (I):

##STR00003##

wherein [0024] R.sub.1 is C.sub.1-5alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl which cycloalkyl is optionally substituted by CH.sub.3, C.sub.1-3alkyleneOC.sub.1-2alkyl, or CF.sub.3; [0025] R.sub.3 is H, CH.sub.3, halo, OC.sub.1-2alkyl or CF.sub.3; [0026] R.sub.4 and R.sub.5 are each independently H, C.sub.1-6alkyl, C.sub.0-2alkyleneC.sub.3-6cycloalkyl, C.sub.0-2alkyleneC.sub.3-6heterocycloalkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-6alkylOH or C.sub.1-6haloalkyl, [0027] or R.sub.4 and R.sub.5 together with the carbon atom to which they are attached form a C.sub.3-6cycloalkyl [0028] or C.sub.3-6heterocycloalkyl ring; [0029] R.sub.6 is H or C.sub.1-3alkyl; [0030] Ar₁ is a 6-membered aryl or heteroaryl; [0031] Ar₂ is a 6-membered aryl or heteroaryl and is attached to Ar₁ in the para position relative to the amide; [0032] R.sub.10 is H, halo, C.sub.1-3alkyl, OC.sub.1-2alkyl, C.sub.1-2haloalkyl, OC.sub.1-2haloalkyl or CN; [0033] R.sub.11 is H, F, Cl, CH.sub.3, ethyl, OCH.sub.3, CF.sub.3, OCF.sub.3 or CN; [0034] R.sub.12 is attached to Ar₂ in the meta or ortho position relative to Ar₁ and R.sub.12 is H, halo, C.sub.1-4alkyl, C.sub.2-4alkynyl, C(=O)C.sub.1-2alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl, OC.sub.1-4alkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-4 haloalkyl, OC.sub.1-4haloalkyl, CN, OC.sub.0-2alkyleneC.sub.3-5cycloalkyl, OCH.sub.2CH.sub.2N(CH.sub.3).sub.2, OH, C.sub.1-4alkylOH, NR.sub.23R.sub.24, SO.sub.2CH.sub.3, C(O)N(CH.sub.3).sub.2, NHC(O)C.sub.1-3alkyl, or a C.sub.3-6heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar₂, or R.sub.12 together with a nitrogen atom to which it is attached forms an N-oxide (N^{sup.+}—O^{sup.-}); [0035] R.sub.23 is H or C.sub.1-2alkyl; and [0036] R.sub.24 is H or C.sub.1-2alkyl.

[0037] Suitably, there is provided a compound of formula (I):

##STR00004## [0038] wherein [0039] R.sub.1 is C.sub.1-4alkyl, C.sub.1-2alkyleneOC.sub.1-2alkyl or C.sub.0-1alkyleneC.sub.3-4cycloalkyl which cycloalkyl is optionally substituted by CH.sub.3; [0040] R.sub.3 is H, CH.sub.3, F or Cl; [0041] R.sub.4 and R.sub.5 are each independently H, C.sub.1-4alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-4alkylOH or C.sub.1-4haloalkyl; [0042] R.sub.6 is H or C.sub.1-3alkyl; [0043] Ar₁ is a 6-membered aryl or heteroaryl; [0044] Ar₂ is a 6-membered aryl or heteroaryl and is attached to Ar₁ in the para position relative to the amide; [0045] R.sub.10 is H,

halo, C.sub.1-3alkyl, OC.sub.1-2alkyl, C.sub.1-2haloalkyl or CN; and [0046] R.sub.12 is attached to Ar₂ in the meta position relative to Ar₁ and R.sub.12 is H, halo, C.sub.1-4alkyl, C.sub.2alkynyl, C(=O)C.sub.1-2alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl, OC.sub.1-4alkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-4haloalkyl, OC.sub.1-4haloalkyl or CN.

[0047] A compound of formula (I) may be provided in the form of a salt and/or solvate thereof and/or derivative thereof. Suitably, the compound of formula (I) may be provided in the form of a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof. In particular, the compound of formula (I) may be provided in the form of a pharmaceutically acceptable salt and/or solvate, such as a pharmaceutically acceptable salt.

[0048] Also provided is a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, for use as a medicament, in particular for use in the inhibition of CTPS1 in a subject or the prophylaxis or treatment of associated diseases or disorders, such as those in which a reduction in T-cell and/or B-cell proliferation would be beneficial.

[0049] Further, there is provided a method for the inhibition of CTPS1 in a subject or the prophylaxis or treatment of associated diseases or disorders, such as those in which a reduction in T-cell and/or B-cell proliferation would be beneficial, by administering to a subject in need thereof a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof.

[0050] Additionally provided is the use of a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, in the manufacture of a medicament for the inhibition of CTPS1 in a subject or the prophylaxis or treatment of associated diseases or disorders, such as those in which a reduction in T-cell and/or B-cell proliferation would be beneficial.

[0051] Suitably the disease or disorder is selected from: inflammatory skin diseases such as psoriasis or lichen planus; acute and/or chronic GVHD such as steroid resistant acute GVHD; acute lymphoproliferative syndrome (ALPS); systemic lupus erythematosus, lupus nephritis or cutaneous lupus; and transplantation. In addition, the disease or disorder may be selected from myasthenia gravis, multiple sclerosis, and scleroderma/systemic sclerosis.

[0052] Also provided is a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, for use in the treatment of cancer.

[0053] Further, there is provided a method for treating cancer in a subject, by administering to a subject in need thereof a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof.

[0054] Additionally provided is the use of a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, in the manufacture of a medicament for the treatment of cancer in a subject.

[0055] Also provided is a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, for use in enhancing recovery from vascular injury or surgery and reducing morbidity and mortality associated with neointima and restenosis in a subject.

[0056] Further, there is provided a method for enhancing recovery from vascular injury or surgery and reducing morbidity and mortality associated with neointima and restenosis in a subject, by administering to a subject in need thereof a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof.

[0057] Additionally provided is the use of a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, in the manufacture of a medicament for enhancing recovery from vascular injury or surgery and reducing morbidity and mortality associated with neointima and restenosis in a subject.

[0058] Also provided are pharmaceutical compositions containing a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, and a pharmaceutically acceptable carrier or excipient.

[0059] Also provided are processes for preparing compounds of formula (I) and novel intermediates of use in the preparation of compounds of formula (I).

Description

DETAILED DESCRIPTION OF THE INVENTION

[0060] The invention provides a compound of formula (I):

##STR00005##

wherein [0061] R.sub.1 is C.sub.1-5alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl which cycloalkyl is optionally substituted by CH.sub.3, C.sub.1-3alkyleneOC.sub.1-2alkyl, or CF.sub.3; [0062] R.sub.3 is H, CH.sub.3, halo, OC.sub.1-2alkyl or CF.sub.3; [0063] R.sub.4 and R.sub.5 are each independently H, C.sub.1-6alkyl, C.sub.0-2alkyleneC.sub.3-6cycloalkyl, C.sub.0-2alkyleneC.sub.3-6heterocycloalkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-6alkylOH or C.sub.1-6haloalkyl, [0064] or R.sub.4 and R.sub.5 together with the carbon atom to which they are attached form a C.sub.3-6cycloalkyl [0065] or C.sub.3-6heterocycloalkyl ring; [0066] R.sub.6 is H or C.sub.1-3alkyl; [0067] Ar1 is a 6-membered aryl or heteroaryl; [0068] Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide; [0069] R.sub.10 is H, halo, C.sub.1-3alkyl, OC.sub.1-2alkyl, C.sub.1-2haloalkyl, OC.sub.1-2haloalkyl or CN; [0070] R.sub.11 is H, F, Cl, CH.sub.3, ethyl, OCH.sub.3, CF.sub.3, OCF.sub.3 or CN; [0071] R.sub.12 is attached to Ar2 in the meta or ortho position relative to Ar1 and R.sub.12 is H, halo, C.sub.1-4alkyl, C.sub.2-4alkynyl, C(=O)C.sub.1-2alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl, OC.sub.1-4alkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-4haloalkyl, OC.sub.1-4haloalkyl, CN, OC.sub.0-2alkyleneC.sub.3-5cycloalkyl, OCH.sub.2CH.sub.2N(CH.sub.3).sub.2, OH, C.sub.1-4alkylOH, NR.sub.23R.sub.24, SO.sub.2CH.sub.3, C(O)N(CH.sub.3).sub.2, NHC(O)C.sub.1-3alkyl, or a C.sub.3-6heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R.sub.12 together with a nitrogen atom to which it is attached forms an N-oxide (N.sup.+—O.sup.—); [0072] R.sub.23 is H or C.sub.1-2alkyl; and [0073] R.sub.24 is H or C.sub.1-2alkyl; [0074] or a salt and/or solvate thereof and/or derivative thereof.

[0075] Suitably, the invention provides a compound of formula (I):

##STR00006##

wherein [0076] R.sub.1 is C.sub.1-4alkyl, C.sub.1-2alkyleneOC.sub.1-2alkyl or C.sub.0-1alkyleneC.sub.3-4cycloalkyl which cycloalkyl is optionally substituted by CH.sub.3; [0077] R.sub.3 is H, CH.sub.3, F or Cl; [0078] R.sub.4 and R.sub.5 are each independently H, C.sub.1-4alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-4alkylOH or C.sub.1-4haloalkyl; [0079] R.sub.6 is H or C.sub.1-3alkyl; [0080] Ar1 is a 6-membered aryl or heteroaryl; [0081] Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide; [0082] R.sub.10 is H, halo, C.sub.1-3alkyl, OC.sub.1-2alkyl, C.sub.1-2haloalkyl, OC.sub.1-2haloalkyl or CN; and [0083] R.sub.12 is attached to Ar2 in the meta position relative to Ar1 and R.sub.12 is H, halo, C.sub.1-4alkyl, C.sub.2alkynyl, C(=O)C.sub.1-2alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl, OC.sub.1-4alkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-4haloalkyl, OC.sub.1-4haloalkyl or CN; [0084] or a salt and/or solvate thereof and/or derivative thereof.

[0085] Suitably, the invention provides a compound of formula (I):

##STR00007##

wherein [0086] R.sub.1 is C.sub.0-1alkyleneC.sub.3-4cycloalkyl; [0087] R.sub.3 is H, CH.sub.3 or Cl; [0088] R.sub.4 and R.sub.5 are each independently H, C.sub.1-4alkyl or C.sub.1-3alkyleneOC.sub.1-3alkyl; [0089] or R.sub.4 together with R.sub.5 form a C.sub.3-6cycloalkyl ring [0090] R.sub.6 is H or C.sub.1-3alkyl; [0091] Ar1 is a 6-membered aryl or heteroaryl; [0092] Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the

amide; [0093] R.sub.10 is H, halo, C.sub.1-3alkyl, OC.sub.1-2alkyl or C.sub.1-2haloalkyl; and [0094] R.sub.12 is attached to Ar₂ in the meta position relative to Ar₁ and R.sub.12 is H, halo, C.sub.1-4alkyl, C(=O)C.sub.1-2alkyl, OC.sub.1-4alkyl, C.sub.1-4haloalkyl, OC.sub.1-4haloalkyl or CN; [0095] or a salt and/or solvate thereof and/or derivative thereof.

[0096] The term 'alkyl' as used herein, such as in C.sub.1-2alkyl, C.sub.1-3alkyl or C.sub.1-4alkyl, whether alone or forming part of a larger group such as an Oalkyl group (e.g. OC.sub.1-2alkyl, OC.sub.1-3alkyl or OC.sub.1-4alkyl), is a straight or a branched fully saturated hydrocarbon chain containing the specified number of carbon atoms. Examples of alkyl groups include the C.sub.1-4alkyl groups methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl, in particular the C.sub.1-3alkyl groups methyl, ethyl, n-propyl and iso-propyl such as C.sub.1-2alkyl groups methyl and ethyl. Reference to "propyl" includes n-propyl and iso-propyl, and reference to "butyl" includes n-butyl, isobutyl, sec-butyl and tert-butyl. Examples of Oalkyl groups include the OC.sub.1-4alkyl groups methoxy, ethoxy, propoxy (which includes n-propoxy and iso-propoxy) and butoxy (which includes n-butoxy, iso-butoxy, sec-butoxy and tert-butoxy). C.sub.5alkyl groups as used herein, whether alone or forming part of a larger group such as an OC.sub.5alkyl group is a straight or a branched fully saturated hydrocarbon chain containing five carbon atoms. Examples of C.sub.5alkyl groups include n-pentyl, sec-pentyl, 3-pentyl, sec-isopentyl and active pentyl.

C.sub.6alkyl groups as used herein, whether alone or forming part of a larger group such as an OC.sub.6alkyl group is a straight or a branched fully saturated hydrocarbon chain containing six carbon atoms. Examples of C.sub.6alkyl groups include n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl and 2,3-dimethylbutyl.

[0097] The term 'alkylene' as used herein, such as in C.sub.0-2alkyleneC.sub.3-5cycloalkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-2alkyleneOC.sub.1-2alkyl or C.sub.0-1alkyleneC.sub.3-4cycloalkyl is a bifunctional straight or a branched fully saturated hydrocarbon chain containing the specified number of carbon atoms. Examples of C.sub.0-2alkylene groups are where the group is absent (i.e. C.sub.0), methylene (C.sub.1) and ethylene (C.sub.2). Examples of C.sub.1-3alkylene groups are where the group is methylene (C.sub.1), ethylene (C.sub.2) and propylene (C.sub.3). Examples of C.sub.1-2alkylene groups are where the group is methylene (C.sub.1) and ethylene (C.sub.2). Examples of C.sub.0-1alkylene groups are where the group is absent (C.sub.0) and methylene (C.sub.1).

[0098] The term 'cycloalkyl' as used herein, such as in C.sub.3-6cycloalkyl, such as C.sub.3-5cycloalkyl or C.sub.3-4cycloalkyl, whether alone or forming part of a larger group such as C.sub.0-2alkyleneC.sub.3-6cycloalkyl such as C.sub.0-2alkyleneC.sub.3-5cycloalkyl or C.sub.0-1alkyleneC.sub.3-4cycloalkyl is a fully saturated hydrocarbon ring containing the specified number of carbon atoms. Examples of cycloalkyl groups include the C.sub.3-5cycloalkyl groups cyclopropyl, cyclobutyl and cyclopentyl. Examples of cycloalkyl groups also include the C.sub.6cycloalkyl group cyclohexyl.

Example 'Cycloalkyl' Groups are as Follows

##STR00008##

[0099] The term 'heterocycloalkyl' as used herein, such as in C.sub.3-6heterocycloalkyl or C.sub.0-2alkyleneC.sub.3-6heterocycloalkyl is a fully saturated hydrocarbon ring containing the specified number of ring atoms and includes the ring atom through which the heterocycloalkyl group is attached, wherein at least one of the atoms in the ring is a heteroatom such as O, N or S. As required by valency, the nitrogen atom(s) may be connected to a hydrogen atom to form an NH group. Alternatively the nitrogen atom(s) may be substituted (such as one nitrogen atom is substituted), for example by C.sub.1-4alkyl, C(O)H, C(O)C.sub.1-4alkyl, C(O)OC.sub.1-4alkyl, C(O)OC.sub.1-4alkylaryl such as C(O)OBz, C(O)NHC.sub.1-4alkyl, C(O)NHC.sub.1-4alkylaryl such as C(O)NHBz, an F moc group, C(O)C.sub.1-4haloalkyl, C(O)OC.sub.1-4haloalkyl or C(O)NHC.sub.1-4haloalkyl such as C(O)OtBu. Wherein a ring heteroatom is S, the term 'heterocycloalkyl' includes wherein the S atom(s) is substituted (such as one S atom is substituted)

by one or two oxygen atoms (i.e. S(O) or S(O).sub.2). Alternatively, any sulphur atom(s) in the C.sub.3-6heterocycloalkyl ring is not substituted.

[0100] Examples of C.sub.3-6heterocycloalkyl groups include those comprising one heteroatom such as containing one heteroatom (e.g. one oxygen atom or one nitrogen atom) or containing two heteroatoms (e.g. two oxygen atoms or one oxygen atom and one nitrogen atom or two nitrogen atoms). Particular examples of C.sub.3-6heterocycloalkyl comprising one oxygen atom include oxiranyl, oxetanyl, 3-dioxolanyl, morpholinyl, 1,4-oxathianyl, tetrahydropyranyl, 1,4-thioxanyl and 1,3,5-trioxanyl. Particular examples of C.sub.3-5heterocycloalkyl comprising one nitrogen atom include pyrrolidinyl, pyrazolidinyl, imidazolidinyl, thiazolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl.

[0101] The heterocycloalkyl groups may have the following structures:

##STR00009## ##STR00010##

wherein each Q is independently selected from O, N or S, such as O or N. When Q is N, as required by valency, the nitrogen atom(s) may be connected to a hydrogen atom to form an NH group. Alternatively the nitrogen atom(s) may be substituted (such as one nitrogen atom is substituted), for example by C.sub.1-4alkyl, C(O)H, C(O)C.sub.1-4alkyl, C(O)OC.sub.1-4alkyl, C(O)OC.sub.1-4alkylaryl such as C(O)OBz, C(O)NHC.sub.1-4alkyl, C(O)NHC.sub.1-4alkylaryl such as C(O)NHBz, an Fmoc group, C(O)C.sub.1-4haloalkyl, C(O)OC.sub.1-4haloalkyl or C(O)NHC.sub.1-4haloalkyl such as C(O)OtBu. When any Q is S, the S atoms can be substituted (such as one S atom is substituted) by one or two oxygen atoms (i.e. S(O) or S(O).sub.2).

Alternatively, any sulphur atom(s) in the C.sub.3-6heterocycloalkyl ring is not substituted.

[0102] When the heterocycloalkyl is formed from R.sub.4 and R.sub.5 together with the carbon atom to which they are attached, suitably any heteroatom is not directly connected to the carbon to which R.sub.4 and R.sub.5 are attached. Thus suitably, when the heterocycloalkyl is formed from R.sub.4 and R.sub.5 together with the carbon atom to which they are attached, the heterocycloalkyl may be:

##STR00011##

wherein each Q is independently O, N or S such as O or N. When Q is N, as required by valency, the nitrogen atom(s) may be connected to a hydrogen atom to form an NH group. Alternatively the nitrogen atom(s) may be substituted (such as one nitrogen atom is substituted), for example by C.sub.1-4alkyl, C(O)H, C(O)C.sub.1-4alkyl, C(O)OC.sub.1-4alkyl, C(O)OC.sub.1-4alkylaryl such as C(O)OBz, C(O)NHC.sub.1-4alkyl, C(O)NHC.sub.1-4alkylaryl such as C(O)NHBz, an Fmoc group, C(O)C.sub.1-4haloalkyl, C(O)OC.sub.1-4haloalkyl or C(O)NHC.sub.1-4haloalkyl such as C(O)OtBu. When any Q is S, the S atom(s) can be substituted (such as one S atom is substituted) by one or two oxygen atoms (i.e. S(O) or S(O).sub.2). Alternatively, any sulphur atom(s) in the C.sub.3-6heterocycloalkyl ring is not substituted.

[0103] When R.sub.4 and/or R.sub.5 is CoalkyleneC.sub.3-6heterocycloalkyl, any heteroatom in the heterocycloalkyl may not be directly connected to the carbon to which R.sub.4 and R.sub.5 are connected.

[0104] The term 'alkynyl' as used herein, such as in C.sub.2-4alkynyl such as in C.sub.2alkynyl is an unbranched hydrocarbon chain containing the specified number of carbons (e.g. 2, 3 or 4 carbons, such as two carbons), two of which carbon atoms are linked by a carbon-carbon triple bond.

[0105] The term 'halo' or 'halogen' as used herein, refers to fluorine, chlorine, bromine or iodine. Particular examples of halo are fluorine and chlorine, especially fluorine.

[0106] The term 'haloalkyl' as used herein, such as in C.sub.1-6haloalkyl, such as in C.sub.1-2haloalkyl or C.sub.1-4haloalkyl, whether alone or forming part of a larger group such as an Ohaloalkyl group, such as in OC.sub.1-6haloalkyl, such as in OC.sub.1-2haloalkyl or OC.sub.1-4haloalkyl, is a straight or a branched fully saturated hydrocarbon chain containing the specified number of carbon atoms and at least one halogen atom, such as fluoro or chloro, especially fluoro.

An example of haloalkyl is CF.sub.3. Further examples of haloalkyl are CHF.sub.2 and CH.sub.2CF.sub.3. Examples of Ohaloalkyl include OCF.sub.3, OCHF.sub.2 and OCH.sub.2CF.sub.3.

[0107] The term '6-membered aryl' as used herein refers to a phenyl ring.

[0108] The term '6-membered heteroaryl' as used herein refers to 6-membered aromatic rings containing at least one heteroatom (e.g. nitrogen). Exemplary 6-membered heteroaryls include one nitrogen atom (pyridinyl), two nitrogen atoms (pyridazinyl, pyrimidinyl or pyrazinyl) and three nitrogen atoms (triazinyl).

[0109] The phrase 'in the para position relative to the amide' as used herein, such as in relation to the position of Ar₂, means that compounds with the following substructure are formed:

##STR00012##

wherein W may be N, CH or CR.sub.10, and Y may be N, CH or CR.sub.12 as required by the definitions provided for compounds of formula (I). W may also be CR.sub.11 as allowed by the definitions provided for compounds of formula (I).

[0110] The term 'meta' as used herein, such as when used in respect of defining the position of R.sub.12 on Ar₂ is with respect to Ar₁ means:

##STR00013##

[0111] The term 'ortho' as used herein, such as when used in respect of defining the position of R.sub.12 on Ar₂ is with respect to Ar₁ means:

##STR00014##

[0112] In one embodiment of the invention R.sub.1 is C.sub.1-5alkyl such as C.sub.1-4alkyl. When R.sub.1 is C.sub.1-5alkyl, R.sub.1 is methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, isobutyl, sec-butyl or tert-butyl) or pentyl (e.g. n-pentyl, sec-pentyl, 3-pentyl, sec-isopentyl or active pentyl). When R.sub.1 is C.sub.1-4alkyl, R.sub.1 is methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl, sec-butyl or tert-butyl).

[0113] In a second embodiment of the invention R.sub.1 is C.sub.1-3alkyleneOC.sub.1-2alkyl such as C.sub.1-2alkyleneOC.sub.1-2alkyl. R.sub.1 may be C.sub.1alkyleneOC.sub.1alkyl. R.sub.1 may be C.sub.1alkyleneOC.sub.2alkyl. R.sub.1 may be C.sub.2alkyleneOC.sub.1alkyl. R.sub.1 may be C.sub.2alkyleneOC.sub.2alkyl. R.sub.1 may be C.sub.2alkyleneOC.sub.1alkyl. R.sub.1 may be C.sub.2alkyleneOC.sub.2alkyl.

[0114] In a third embodiment of the invention R.sub.1 is C.sub.0-2alkyleneC.sub.3-5cycloalkyl which cycloalkyl is optionally substituted by CH.sub.3 such as C.sub.0-1alkyleneC.sub.3-4cycloalkyl which cycloalkyl is optionally substituted by CH.sub.3. In some embodiments, R.sub.1 is C.sub.0-2alkyleneC.sub.3-5cycloalkyl such as C.sub.0-1alkyleneC.sub.3-4cycloalkyl. In other embodiments, R.sub.1 is C.sub.0-2alkyleneC.sub.3-5cycloalkyl which cycloalkyl is substituted by CH.sub.3 such as C.sub.0-1alkyleneC.sub.3-4cycloalkyl which cycloalkyl is substituted by CH.sub.3. R.sub.1 may be C.sub.3-5cycloalkyl, which cycloalkyl is optionally substituted by CH.sub.3 such as C.sub.3-4cycloalkyl, which cycloalkyl is optionally substituted by CH.sub.3. R.sub.1 may be C.sub.1alkyleneC.sub.3-5cycloalkyl, which cycloalkyl is optionally substituted by CH.sub.3. R.sub.1 may be C.sub.1alkyleneC.sub.3-4cycloalkyl, which cycloalkyl is optionally substituted by CH.sub.3. R.sub.1 may be C.sub.2alkyleneC.sub.3-5cycloalkyl, which cycloalkyl is optionally substituted by CH.sub.3. R.sub.1 may be C.sub.2alkyleneC.sub.3-4cycloalkyl, which cycloalkyl is optionally substituted by CH.sub.3. R.sub.1 may be C.sub.0-2alkyleneC.sub.3cycloalkyl, which cycloalkyl is optionally substituted by CH.sub.3. R.sub.1 may be C.sub.0-1alkyleneC.sub.3cycloalkyl, which cycloalkyl is optionally substituted by CH.sub.3. R.sub.1 may be C.sub.0-2alkyleneC.sub.4cycloalkyl, which cycloalkyl is optionally substituted by CH.sub.3. R.sub.1 may be C.sub.0-1alkyleneC.sub.4cycloalkyl, which cycloalkyl is optionally substituted by CH.sub.3. R.sub.1 may be C.sub.0-2alkyleneC.sub.5cycloalkyl, which cycloalkyl is optionally substituted by CH.sub.3. R.sub.1 may be C.sub.0-1alkyleneC.sub.5cycloalkyl, which cycloalkyl is optionally substituted by CH.sub.3. Suitably, where C.sub.0-2alkyleneC.sub.3-

5cycloalkyl such as C.sub.0-1alkyleneC.sub.3-4cycloalkyl is optionally substituted by CH.sub.3, the CH.sub.3 is at the point of attachment of the C.sub.3-5cycloalkyl to the C.sub.0-2alkylene such as at the point of attachment of the C.sub.3-4cycloalkyl to the C.sub.0-1alkylene.

[0115] Suitably R.sub.1 is cyclopropyl.

[0116] In a fourth embodiment of the invention, R.sub.1 is CF.sub.3.

[0117] In one embodiment R.sub.3 is H. In a second embodiment R.sub.3 is CH.sub.3. In a third embodiment, R.sub.3 is halo. In an example, R.sub.3 is F. In a second example, R.sub.3 is Cl. In a fourth embodiment, R.sub.3 is OC.sub.1-2alkyl. Suitably R.sub.3 is OCH.sub.3. Suitably, R.sub.3 is OCH.sub.2CH.sub.3. In a fifth embodiment, R.sub.3 is CF.sub.3.

[0118] Suitably, R.sub.3 is H.

[0119] In one embodiment, R.sub.4 is H. In a second embodiment R.sub.4 is C.sub.1-6alkyl such as C.sub.1-4alkyl, i.e. methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl, sec-butyl or tert-butyl). R.sub.4 may also be pentyl (e.g. n-pentyl, sec-pentyl, 3-pentyl, sec-isopentyl or active pentyl) or hexyl (e.g. n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl and 2,3-dimethylbutyl). In a third embodiment, R.sub.4 is C.sub.0-2alkyleneC.sub.3-6cycloalkyl such as C.sub.0-2alkyleneC.sub.3-5cycloalkyl, such as C.sub.0-2alkyleneC.sub.3cycloalkyl, C.sub.0-2alkyleneC.sub.4cycloalkyl, C.sub.0-2alkyleneCsubcycloalkyl, CoalkyleneC.sub.3-5cycloalkyl, C.sub.1alkyleneC.sub.3-5cycloalkyl and C.sub.2alkyleneC.sub.3-5cycloalkyl. R.sub.4 may also be C.sub.0-2alkyleneC.sub.5cycloalkyl, C.sub.0alkyleneC.sub.3-6cycloalkyl, C.sub.1alkyleneC.sub.3-6Cycloalkyl and C.sub.2alkyleneC.sub.3-6cycloalkyl. In a fourth embodiment R.sub.4 is C.sub.1-3alkyleneOC.sub.1-3alkyl, in particular C.sub.1-2alkyleneOC.sub.1-2alkyl such as C.sub.1alkyleneOC.sub.1alkyl, C.sub.2alkyleneOC.sub.1alkyl, C.sub.1alkyleneOC.sub.2alkyl or C.sub.2alkyleneOC.sub.2alkyl. In a fifth embodiment R.sub.4 is C.sub.1-6alkylOH such as C.sub.1-4alkylOH such as C.sub.1alkylOH, C.sub.2alkylOH, C.sub.5alkylOH or C.sub.4alkylOH wherein C.sub.1-4alkyl is methyl, ethyl, propyl (n-propyl or isopropyl) and butyl (n-butyl, isobutyl, sec-butyl or tert-butyl). R.sub.4 may also be C.sub.5alkylOH or C.sub.6alkylOH. In a sixth embodiment, R.sub.4 is C.sub.1-6haloalkyl such as C.sub.1-4haloalkyl such as C.sub.1haloalkyl (e.g. CF.sub.3), C.sub.2haloalkyl (e.g. CH.sub.2CF.sub.3), C.sub.3haloalkyl (e.g. CH.sub.2CH.sub.2CF.sub.3) or C.sub.4haloalkyl (e.g. CH.sub.2CH.sub.2CH.sub.2CF.sub.3). R.sub.4 may also be C.sub.5haloalkyl (e.g. CH.sub.2CH.sub.2CH.sub.2CH.sub.2CF.sub.3) or C.sub.6haloalkyl (e.g. CH.sub.2CH.sub.2CH.sub.2CH.sub.2CH.sub.2CF.sub.3). In a seventh embodiment, R.sub.4 is C.sub.0-2alkyleneC.sub.3-6heterocycloalkyl such as C.sub.0-2alkyleneC.sub.3heterocycloalkyl, C.sub.0-2alkyleneC.sub.4heterocycloalkyl, C.sub.0-2alkyleneC.sub.5heterocycloalkyl, C.sub.0-2alkyleneC.sub.6heterocycloalkyl, CoalkyleneC.sub.3-6heterocycloalkyl, ChalkyleneC.sub.3-6heterocycloalkyl and C.sub.2alkyleneC.sub.3-6heterocycloalkyl. Suitably the heterocycloalkyl of a C.sub.0-2alkyleneC.sub.3-6heterocycloalkyl group is a heterocyclopropyl, heterocyclobutyl, heterocyclopentyl or heterocyclohexyl ring such as a heterocyclohexyl ring. Suitably, the heterocyclopentyl ring is tetrahydrofuranyl or pyrrolidinyl. Suitably, the heterocyclohexyl ring is tetrahydropyranyl or piperidinyl. Any nitrogen atom such as one nitrogen atom in the C.sub.3-6heterocycloalkyl ring may be substituted, for example by C.sub.1-4alkyl, C(O)H, C(O)C.sub.1-4alkyl, C(O)OC.sub.1-4alkyl, C(O)OC.sub.1-4alkylaryl such as C(O)OBz, C(O)NHC.sub.1-4alkyl, C(O)NHC.sub.1-4alkylaryl such as C(O)NHBz, an Fmoc group, C(O)C.sub.1-4haloalkyl, C(O)OC.sub.1-4haloalkyl or C(O)NHC.sub.1-4haloalkyl such as C(O)OtBu. Suitably, any nitrogen atom in the C.sub.3-6heterocycloalkyl ring is not substituted. In an eighth embodiment, R.sub.4 and R.sub.5 together with the carbon atom to which they are attached form a C.sub.3-6cycloalkyl or C.sub.3-6heterocycloalkyl ring. Suitably R.sub.4 and R.sub.5 together with the carbon atom to which they are attached form a C.sub.3-6cycloalkyl ring, such as a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl ring. Suitably R.sub.4 and R.sub.5 together with the carbon atom to which they are attached form a C.sub.3-6heterocycloalkyl ring, such as a heterocyclopropyl, heterocyclobutyl, heterocyclopentyl or heterocyclohexyl ring.

Suitably, the heterocyclopentyl ring is tetrahydrofuranyl or pyrrolidinyl. Suitably, the heterocyclohexyl ring is tetrahydropyranyl or piperidinyl. Any nitrogen atom such as one nitrogen atom in the C.sub.3-6heterocycloalkyl ring may be substituted, for example by C.sub.1-4alkyl, C(O)H, C(O)C.sub.1-4alkyl, C(O)OC.sub.1-4alkyl, C(O)OC.sub.1-4alkylaryl such as C(O)OBz, C(O)NHC.sub.1-4alkyl, C(O)NHC.sub.1-4alkylaryl such as C(O)NHBz, an Fmoc group, C(O)C.sub.1-4haloalkyl, C(O)OC.sub.1-4haloalkyl or C(O)NHC.sub.1-4haloalkyl such as C(O)OtBu. Suitably, any nitrogen atom in the C.sub.3-6heterocycloalkyl ring is not substituted. [0120] Suitably R.sub.4 is H, CH.sub.3 or ethyl, in particular CH.sub.3 or ethyl. Suitably, R.sub.4 and R.sub.5 together with the carbon atom to which they are attached form a C.sub.3-6cycloalkyl ring, such as a cyclopropyl ring.

[0121] In one embodiment, R.sub.5 is H. In a second embodiment R.sub.5 is C.sub.1-6alkyl such as C.sub.1-4alkyl, i.e. methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl, sec-butyl or tert-butyl). R.sub.5 may also be pentyl (e.g. n-pentyl, sec-pentyl, 3-pentyl, sec-isopentyl and active pentyl) or hexyl (e.g. n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl and 2,3-dimethylbutyl). In a third embodiment, R.sub.5 is C.sub.0-2alkyleneC.sub.3-6cycloalkyl such as C.sub.0-2alkyleneC.sub.3-5cycloalkyl, such as C.sub.0-2alkyleneC.sub.3cycloalkyl, C.sub.0-2alkyleneC.sub.4cycloalkyl, C.sub.0-2alkyleneC.sub.5cycloalkyl, C.sub.0alkyleneC.sub.3-5cycloalkyl, C.sub.1alkyleneC.sub.3-5cycloalkyl and C.sub.2alkyleneC.sub.3-5cycloalkyl. R.sub.5 may also be C.sub.0-2alkyleneC.sub.6cycloalkyl, C.sub.0alkyleneC.sub.3-6cycloalkyl, C.sub.1alkyleneC.sub.3-6cycloalkyl and C.sub.2alkyleneC.sub.3-6cycloalkyl. In a fourth embodiment R.sub.5 is C.sub.1-3alkyleneOC.sub.1-3alkyl, in particular C.sub.1-2alkyleneOC.sub.1-2alkyl such as C.sub.1alkyleneOC.sub.1alkyl, C.sub.2alkyleneOC.sub.1alkyl, C.sub.1alkyleneOC.sub.2alkyl or C.sub.2alkyleneOC.sub.2alkyl. In a fifth embodiment R.sub.5 is C.sub.1-6alkylOH such as C.sub.1-4alkylOH such as C.sub.1alkylOH, C.sub.2alkylOH, C.sub.5alkylOH or C.sub.4alkylOH wherein C.sub.1-4alkyl is methyl, ethyl, propyl (n-propyl or isopropyl) and butyl (n-butyl, isobutyl, sec-butyl or tert-butyl). R.sub.5 may also be C.sub.5alkylOH or C.sub.4alkylOH. In a sixth embodiment, R.sub.5 is C.sub.1-6haloalkyl such as C.sub.1-4haloalkyl such as C.sub.1haloalkyl (e.g. CF.sub.3), C.sub.2haloalkyl (e.g. CH.sub.2CF.sub.3), C.sub.3haloalkyl (e.g. CH.sub.2CH.sub.2CF.sub.3), C.sub.4haloalkyl (e.g. CH.sub.2CH.sub.2CH.sub.2CF.sub.3). R.sub.5 may also be C.sub.5haloalkyl (e.g. CH.sub.2CH.sub.2CH.sub.2CH.sub.2CF.sub.3) or C.sub.5haloalkyl (e.g. CH.sub.2CH.sub.2CH.sub.2CH.sub.2CH.sub.2CF.sub.3). In a seventh embodiment, R.sub.5 is C.sub.0-2alkyleneC.sub.3-6heterocycloalkyl such as C.sub.0-2alkyleneC.sub.5heterocycloalkyl, C.sub.0-2alkyleneC.sub.4heterocycloalkyl, C.sub.0-2alkyleneC.sub.5heterocycloalkyl, C.sub.0-2alkyleneC.sub.6heterocycloalkyl, C.sub.0alkyleneC.sub.3-6heterocycloalkyl, C.sub.1alkyleneC.sub.3-6heterocycloalkyl and C.sub.2alkyleneC.sub.3-6heterocycloalkyl. Suitably the heterocycloalkyl is a heterocyclopropyl, heterocyclobutyl, heterocyclopentyl or heterocyclohexyl ring such as a heterocyclohexyl ring. Suitably, the heterocyclopentyl ring is tetrahydrofuranyl or pyrrolidinyl. Suitably, the heterocyclohexyl ring is tetrahydropyranyl or piperidinyl. Any nitrogen atom such as one nitrogen in the C.sub.3-6heterocycloalkyl ring may be substituted, for example by C.sub.1-4alkyl, C(O)H, C(O)C.sub.1-4alkyl, C(O)OC.sub.1-4alkyl, C(O)OC.sub.1-4alkylaryl such as C(O)OBz, C(O)NHC.sub.1-4alkyl, C(O)NHC.sub.1-4alkylaryl such as C(O)NHBz, an Fmoc group, C(O)C.sub.1-4haloalkyl, C(O)OC.sub.1-4haloalkyl or C(O)NHC.sub.1-4haloalkyl such as C(O)OtBu. Suitably, any nitrogen atom in the C.sub.3-6heterocycloalkyl ring is not substituted.

[0122] Suitably R.sub.5 is H, CH.sub.3 or ethyl, in particular CH.sub.3 or ethyl. Suitably, R.sub.4 and R.sub.5 together with the carbon atom to which they are attached form a C.sub.3-6cycloalkyl ring, such as a cyclopropyl ring.

[0123] Suitably R.sub.4 is H, CH.sub.3 or ethyl and R.sub.5 is H, CH.sub.3 or ethyl, in particular R.sub.4 is CH.sub.3 or ethyl and R.sub.5 is CH.sub.3 or ethyl. For example, R.sub.4 and R.sub.5

are H, R.sub.4 and R.sub.5 are methyl or R.sub.4 and R.sub.5 are ethyl.

[0124] Suitably, R.sub.4 is CH.sub.2CH.sub.2OCH.sub.3 and R.sub.5 is H.

[0125] In one embodiment, R.sub.6 is H. In another embodiment, R.sub.6 is C.sub.1-3alkyl, in particular CH.sub.3.

[0126] In one embodiment Ar1 is a 6-membered aryl, i.e. phenyl. In a second embodiment Ar1 is a 6-membered heteroaryl, in particular containing one nitrogen atom (pyridyl) or two nitrogen atoms (pyridazinyl, pyrimidinyl or pyrazinyl).

[0127] In particular Ar1 is phenyl or 2-pyridyl, such as phenyl. The position numbering for Ar1 is in respect of the amide, with the carbon at the point of attachment designated position 1 and other numbers providing the relative location of the nitrogen atoms, for example:

##STR00015##

[0128] In one embodiment R.sub.10 is H. In a second embodiment R.sub.10 is halo, for example fluoro or chloro. In a third embodiment R.sub.10 is C.sub.1-3alkyl, i.e. CH.sub.3, ethyl or propyl (e.g. n-propyl or iso-propyl). In a fourth embodiment R.sub.10 is OC.sub.1-2alkyl, such as OCH.sub.3 or ethoxy. In a fifth embodiment, R.sub.10 is C.sub.1-2haloalkyl, such as CF.sub.3 or CH.sub.2CF.sub.3. In a sixth embodiment R.sub.10 is OC.sub.1-2haloalkyl, such as OCF.sub.3. In a seventh embodiment R.sub.10 is CN.

[0129] Suitably R.sub.10 is H, fluoro, OCH.sub.3, CH.sub.3 or CF.sub.3, in particular H or fluoro, especially H.

[0130] Suitably R.sub.10 is attached at the ortho position of Ar1 relative to the amide (i.e. proximal to the amide).

[0131] In one embodiment R.sub.11 is H. In a second embodiment R.sub.11 is F. In a third embodiment, R.sub.11 is Cl. In a fourth embodiment R.sub.11 is CH.sub.3. In a fifth embodiment R.sub.11 is CH.sub.2CH.sub.3. In a sixth embodiment R.sub.11 is OCH.sub.3. In a seventh embodiment R.sub.11 is CF.sub.3. In an eighth embodiment R.sub.11 is OCF.sub.3. In a ninth embodiment R.sub.11 is CN.

[0132] In one embodiment, R.sub.11 is in the ortho position relative to the amide. In another embodiment, R.sub.11 is in the meta position relative to the amide.

[0133] In one embodiment Ar2 is a 6-membered aryl, i.e. phenyl. In a second embodiment Ar2 is a 6-membered heteroaryl, in particular containing one nitrogen atom (pyridyl) or two nitrogen atoms (pyridazinyl, pyrimidinyl or pyrazinyl).

[0134] The position numbering for Ar2 is in respect of the point of attachment to Ar1, for example:

##STR00016##

[0135] In particular Ar2 is 3-pyridyl or 2,5-pyrazinyl, especially 2,5-pyrazinyl.

[0136] In one embodiment R.sub.12 is H. In a second embodiment R.sub.12 is halo, for example fluoro or chloro. In a third embodiment R.sub.12 is C.sub.1-4alkyl, i.e. methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl, sec-butyl or tert-butyl). In a fourth embodiment, R.sub.12 is C.sub.2-4alkynyl such as C.sub.2alkynyl (i.e. C \equiv CH). In a fifth embodiment, R.sub.12 is C(=O)C.sub.1-2alkyl, such as C(=O)C.sub.1alkyl or C(=O)C.sub.2alkyl. In a sixth embodiment R.sub.12 is OC.sub.0-2alkyleneC.sub.3-5cycloalkyl, such as OC.sub.3-5cycloalkyl (e.g. cyclopropoxy or cyclobutoxy), OC.sub.1alkyleneC.sub.3-5cycloalkyl or OC.sub.2alkyleneC.sub.3-5cycloalkyl. In a seventh embodiment R.sub.12 is OC.sub.1-4alkyl, such as OCH.sub.3, ethoxy, iso-propoxy or n-propoxy. In an eighth embodiment, R.sub.12 is C.sub.1-3alkyleneOC.sub.1-3alkyl in particular C.sub.1-2alkyleneOC.sub.1-2alkyl such as C.sub.1alkyleneOC.sub.1alkyl, C.sub.2alkyleneOC.sub.1alkyl, C.sub.1alkyleneOC.sub.2alkyl or C.sub.2alkyleneOC.sub.2alkyl. In a ninth embodiment R.sub.12 is C.sub.1-4haloalkyl, such as CF.sub.3. In a tenth embodiment R.sub.12 is OC.sub.1-4haloalkyl, such as OCF.sub.3, OCHF.sub.2 or OCH.sub.2CF.sub.3. In an eleventh embodiment R.sub.12 is CN. In an eleventh embodiment R.sub.12 is OC.sub.0-2alkyleneC.sub.3-5cycloalkyl, such as OC.sub.3-5cycloalkyl (e.g. cyclopropoxy or cyclobutoxy), OC.sub.1alkyleneC.sub.3-5cycloalkyl or OC.sub.2alkyleneC.sub.3-5cycloalkyl. In a twelfth

embodiment R.sub.12 is OCH.sub.2CH.sub.2N (CH.sub.3).sub.2. In a thirteenth embodiment R.sub.12 is OH. In a fourteenth embodiment R.sub.12 is C.sub.1-4alkylOH, such as CH.sub.2OH or C (CH.sub.3).sub.2OH. In a fifteenth embodiment R.sub.12 is NR.sub.23R.sub.24. In a sixteenth embodiment R.sub.12 is SO.sub.2CH.sub.3. In a seventeenth embodiment R.sub.12 is C(O)N(CH.sub.3).sub.2. In an eighteenth embodiment R.sub.12 is NHC(O)C.sub.1-3alkyl such as NHC(O)CH.sub.3. In a nineteenth embodiment R.sub.12 is a C.sub.3-6heterocycloalkyl comprising (such as containing) one nitrogen located at the point of attachment to Ar₂, such as a C.sub.5heterocycloalkyl, in particular pyrrolidinyl, or a C.sub.6heterocycloalkyl such as morpholinyl. In a twentieth embodiment, R.sub.12 together with a nitrogen atom to which it is attached forms an N-oxide (N^{sup.+}—O^{sup.-}).

[0137] In one embodiment, R.sub.23 is H. In another embodiment, R.sub.23 is C.sub.1-2alkyl i.e. CH.sub.3 or CH.sub.2CH.sub.3.

[0138] In one embodiment, R.sub.24 is H. In another embodiment, R.sub.24 is C.sub.1-2alkyl i.e. CH.sub.3 or CH.sub.2CH.sub.3.

[0139] R.sub.12 is suitably H, fluoro, chloro, CH.sub.3, Et, OCH.sub.3, OEt, OiPr, CF.sub.3 or OCH.sub.2CF.sub.3. In particular, R.sub.12 is fluoro, chloro, CH.sub.3, OCH.sub.3, OEt, OiPr or CF.sub.3, for example chloro, OEt, OiPr or CF.sub.3 such as chloro, OEt or CF.sub.3.

[0140] R.sub.12 is suitably attached at the meta position of Ar₂. Alternatively, R.sub.12 is attached at the ortho position of Ar₂.

[0141] The present invention provides N-oxides of the compound of formula (I). Suitably, when R.sub.12 together with a nitrogen atom to which it is attached forms an N-oxide (N^{sup.+}—O^{sup.-}), the example following structures are formed:

##STR00017##

[0142] Throughout the specification Ar₁ and Ar₂ may be depicted as follows:

##STR00018##

[0143] Ar₁ may also be depicted as follows:

##STR00019##

[0144] All depictions with respect to Ar₁ are equivalent and all depictions with respect to Ar₂ are equivalent, unless the context requires otherwise, depictions of Ar₁ and Ar₂ should not be taken to exclude the presence of heteroatoms or substitutions.

[0145] The present invention provides the compounds described in any one of Examples R1 to R71.

[0146] The present invention also provides the compounds described in any one of Examples R72 to R93.

[0147] The present invention provides the following compounds: [0148] N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-5-phenylpicolinamide; [0149] N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-4-(pyridin-3-yl)benzamide; [0150] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide; [0151] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide (R enantiomer); [0152] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide (S enantiomer); [0153] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0154] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide; [0155] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-methoxybenzamide; [0156] N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-[1,1'-biphenyl]-4-carboxamide; [0157] N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0158] N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide; [0159] N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0160] N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-4-(6-

isopropoxy-pyrazin-2-yl)benzamide; [0161] N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-4-(6-ethoxypyrazin-2-yl)benzamide; [0162] N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide; [0163] N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(5-fluoropyridin-3-yl)benzamide; [0164] N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(5-methylpyridin-3-yl)benzamide; [0165] N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(pyridin-3-yl)benzamide; [0166] N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0167] 4-(6-chloropyrazin-2-yl)-N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)benzamide; [0168] N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(6-methylpyrazin-2-yl)benzamide; [0169] N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(pyrazin-2-yl)benzamide; [0170] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-5-(6-ethoxypyrazin-2-yl)-3-fluoropicolinamide; [0171] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-5-(6-(trifluoromethyl)pyrazin-2-yl)picolinamide; [0172] 5-(6-chloropyrazin-2-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)picolinamide; [0173] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-5-(6-ethoxypyrazin-2-yl)picolinamide; [0174] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-[2,2'-bipyridine]-5-carboxamide; [0175] 4-(5-chloropyridin-3-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)benzamide; [0176] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide; [0177] 4-(5-chloropyridin-3-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluorobenzamide; [0178] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(5-fluoropyridin-3-yl)benzamide; [0179] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methoxy-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide; [0180] 4-(5-acetylpyridin-3-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)benzamide; [0181] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide; [0182] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(5-fluoropyridin-3-yl)benzamide; [0183] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(5-methylpyridin-3-yl)benzamide; [0184] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(5-methoxypyridin-3-yl)benzamide; [0185] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(pyridin-3-yl)benzamide; [0186] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxamide; [0187] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethylpyrazin-2-yl)-2-fluorobenzamide; [0188] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0189] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(6-isopropoxy-pyrazin-2-yl)benzamide; [0190] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)benzamide; [0191] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0192] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-methylbenzamide; [0193] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-(trifluoromethyl)benzamide; [0194] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methoxy-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0195] 4-(6-chloropyrazin-2-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methoxybenzamide; [0196] 4-(6-cyanopyrazin-2-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methoxybenzamide; [0197] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0198] 4-(6-chloropyrazin-2-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)benzamide; [0199] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-methylpyrazin-2-yl)benzamide; [0200] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-methoxypyrazin-2-

yl)benzamide; [0201] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)benzamide; [0202] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-isopropoxypyrazin-2-yl)benzamide; [0203] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-(2,2,2-trifluoroethoxy) pyrazin-2-yl)benzamide; [0204] N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(pyrazin-2-yl)benzamide; [0205] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-fluoropyridin-3-yl)benzamide; [0206] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-methylpyridin-3-yl)benzamide; [0207] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(pyridin-3-yl)benzamide; [0208] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide; [0209] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-fluoro-N-methylbenzamide; [0210] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-2-fluoro-4-(6-isopropoxypyrazin-2-yl)benzamide; [0211] 4-(6-chloropyrazin-2-yl)-N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)benzamide; [0212] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-methylpyrazin-2-yl)benzamide; [0213] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(pyrazin-2-yl)benzamide; [0214] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-fluoropyridin-3-yl)benzamide (R enantiomer); [0215] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-fluoropyridin-3-yl)benzamide (S enantiomer); [0216] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide (R enantiomer); and [0217] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide (S enantiomer); [0218] or a salt and/or solvate thereof and/or derivative thereof.

[0219] The invention also provides the following compounds: [0220] N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)-5-(6-ethoxypyrazin-2-yl)picolinamide; [0221] N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-5-(6-ethoxypyrazin-2-yl)picolinamide; [0222] N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide; [0223] N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide; [0224] N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)-2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0225] N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0226] N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0227] N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0228] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-5-(6-ethoxypyrazin-2-yl)picolinamide; [0229] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-4-(pyridin-3-yl)benzamide; [0230] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide; [0231] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0232] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0233] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(5-fluoropyridin-3-yl)benzamide; [0234] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(6-ethylpyrazin-2-yl)-2-fluorobenzamide; [0235] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide; [0236] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide; [0237] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-2-fluoro-4-(6-isopropoxypyrazin-2-yl)benzamide; [0238] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(6-ethoxypyrazin-2-yl)benzamide; [0239] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)ethyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide; [0240] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(6-ethoxypyrazin-2-yl)-2-

fluorobenzamide (R enantiomer); and [0241] N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide (S enantiomer); [0242] or a salt and/or solvate thereof and/or derivative thereof.

[0243] The compounds of the invention may be provided in the form of a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof. In particular, the compound of formula (I) may be provided in the form of a pharmaceutically acceptable salt and/or solvate, such as a pharmaceutically acceptable salt.

[0244] Compounds of the invention of particular interest are those demonstrating an IC₅₀ of 1 μ M or lower, especially 100 nM or lower, in respect of CTPS1 enzyme, using the methods of the examples (or comparable methods).

[0245] Compounds of the invention of particular interest are those demonstrating a selectivity for CTPS1 over CTPS2 of 2-30 fold, suitably >30-60 fold or more suitably >60 fold, using the methods of the examples (or comparable methods).

[0246] It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Non-pharmaceutically acceptable salts of the compounds of formula (I) may be of use in other contexts such as during preparation of the compounds of formula (I). Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art.

Pharmaceutically acceptable salts include those described by Berge et al. (1977). Such pharmaceutically acceptable salts include acid and base addition salts. Pharmaceutically acceptable acid additional salts may be formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates or formates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention.

[0247] Certain compounds of formula (I) form acid or base addition salts with one or more equivalents of the acid or base. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

[0248] The compounds of formula (I) may be prepared in crystalline or non-crystalline form and, if crystalline, may optionally be solvated, e.g. as the hydrate. This invention includes within its scope stoichiometric solvates (e.g. hydrates) as well as compounds containing variable amounts of solvent (e.g. water).

[0249] It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

[0250] As used herein “pharmaceutically acceptable derivative” includes any pharmaceutically acceptable prodrug such as an ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

[0251] It is to be understood that the present invention encompasses all isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

[0252] The present disclosure includes all isotopic forms of the compounds of the invention provided herein, whether in a form (i) wherein all atoms of a given atomic number have a mass number (or mixture of mass numbers) which predominates in nature (referred to herein as the “natural isotopic form”) or (ii) wherein one or more atoms are replaced by atoms having the same atomic number, but a mass number different from the mass number of atoms which predominates in nature (referred to herein as an “unnatural variant isotopic form”). It is understood that an atom

may naturally exist as a mixture of mass numbers. The term “unnatural variant isotopic form” also includes embodiments in which the proportion of an atom of given atomic number having a mass number found less commonly in nature (referred to herein as an “uncommon isotope”) has been increased relative to that which is naturally occurring e.g. to the level of >20%, >50%, >75%, >90%, >95% or >99% by number of the atoms of that atomic number (the latter embodiment referred to as an “isotopically enriched variant form”). The term “unnatural variant isotopic form” also includes embodiments in which the proportion of an uncommon isotope has been reduced relative to that which is naturally occurring. Isotopic forms may include radioactive forms (i.e. they incorporate radioisotopes) and non-radioactive forms. Radioactive forms will typically be isotopically enriched variant forms.

[0253] An unnatural variant isotopic form of a compound may thus contain one or more artificial or uncommon isotopes such as deuterium (²H or D), carbon-11 (¹¹C), carbon-13 (¹³C), carbon-14 (¹⁴C), nitrogen-13 (¹³N), nitrogen-15 (¹⁵N), oxygen-15 (¹⁵O), oxygen-17 (¹⁷O), oxygen-18 (¹⁸O), phosphorus-32 (³²P), sulphur-35 (³⁵S), chlorine-36 (³⁶Cl), chlorine-37 (³⁷Cl), fluorine-18 (¹⁸F) iodine-123 (¹²³I), iodine-125 (¹²⁵I) in one or more atoms or may contain an increased proportion of said isotopes as compared with the proportion that predominates in nature in one or more atoms.

[0254] Unnatural variant isotopic forms comprising radioisotopes may, for example, be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ³H, and carbon-14, i.e. ¹⁴C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Unnatural variant isotopic forms which incorporate deuterium i.e. ²H or D may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Further, unnatural variant isotopic forms may be prepared which incorporate positron emitting isotopes, such as ¹¹C, ¹⁸F, ¹⁵O and ¹³N, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0255] In one embodiment, the compounds of the invention are provided in a natural isotopic form.

[0256] In one embodiment, the compounds of the invention are provided in an unnatural variant isotopic form. In a specific embodiment, the unnatural variant isotopic form is a form in which deuterium (i.e. ²H or D) is incorporated where hydrogen is specified in the chemical structure in one or more atoms of a compound of the invention. In one embodiment, the atoms of the compounds of the invention are in an isotopic form which is not radioactive. In one embodiment, one or more atoms of the compounds of the invention are in an isotopic form which is radioactive. Suitably radioactive isotopes are stable isotopes. Suitably the unnatural variant isotopic form is a pharmaceutically acceptable form.

[0257] In one embodiment, a compound of the invention is provided whereby a single atom of the compound exists in an unnatural variant isotopic form. In another embodiment, a compound of the invention is provided whereby two or more atoms exist in an unnatural variant isotopic form.

[0258] Unnatural isotopic variant forms can generally be prepared by conventional techniques known to those skilled in the art or by processes described herein e.g. processes analogous to those described in the accompanying Examples for preparing natural isotopic forms. Thus, unnatural isotopic variant forms could be prepared by using appropriate isotopically variant (or labelled) reagents in place of the normal reagents employed in the Examples. Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

[0259] In general, the compounds of formula (I) may be made according to the organic synthesis

techniques known to those skilled in this field, as well as by the representative methods set forth below, those in the Examples, and modifications thereof.

General Routes

[0260] Generic routes by which compound examples of the invention may be conveniently prepared are summarised below.

##STR00020##

[0261] The thiazol-4-yl(propan-2-yl)benzamide derivatives of formula (I) in which R.sub.1, R.sub.3, R.sub.4, R.sub.5, Ar.sub.1 and Ar.sub.2 are defined above may be prepared as shown in Scheme 1 by sulfonation of the commercial amine such as (VII) followed by double Grignard addition to ethyl 2-(cyclopropanesulfonamido)thiazole-4-carboxylate (VI) in an aprotic solvent such as THF to form intermediates of formula (V). A Ritter type reaction may then be undertaken using an alkyl nitrile, such as 2-chloroacetonitrile in the presence of an acid such as H.sub.2SO.sub.4. This intermediate of formula (IV) can be deprotected by reaction with thiourea in a protic solvent such as ethanol in the presence of acetic acid and heated under reflux to yield the free benzylamine derivative (II). A carboxylic acid precursor (III) (commercially available or prepared in two steps, as in Scheme 4) is reacted with an activating agent such as HATU, T3P or Ghosez's reagent (1-chloro-N,N,2-trimethylprop-1-en-1-amine), to generate a reactive, electrophilic carboxylic acid derivative, followed by subsequent reaction with benzylamine of formula (II), to yield the desired amide derivative of general formula (I).

##STR00021##

[0262] The thiazol-4-yl (propan-2-yl)benzamide derivatives of formula (I) in which R.sub.1, R.sub.3, R.sub.4, Ar.sub.1 and Ar.sub.2 are defined above may be prepared by two different routes as shown in Scheme 2. The two routes then converge at compounds of general formula (IX) where they are then taken on to the final analogues by a two-step process.

[0263] ROUTE A: Reduction of the ester of general formula (VI) using a reducing agent such as DIBAL-H yields the aldehyde of general formula (IX) (R.sub.4 is H). It will be understood by persons skilled in the art that such reactions need to be carefully controlled to avoid over-reduction.

[0264] ROUTE B: The alkyl ester of formula (VI) may be conveniently hydrolysed by exposure to a suitable inorganic base, for example lithium hydroxide, in an aqueous mixture of aprotic and protic solvents, such as THF: methanol: water. The carboxylic acid derivative (XI) can then be converted to the Weinreb amide by employing a coupling agent, for example, HATU in the presence of a suitable base, such as DIPEA in a solvent such as DMF. The Weinreb amide derivative (X) can then be exposed to a nucleophile such as EtM gBr in an aprotic solvent such as THF to yield the corresponding ketone of the general formula (IX).

[0265] A reductive amination may be undertaken using (2,4-dimethoxyphenyl)methanamine and a reducing agent such as sodium triacetoxyborohydride (STAB). This reaction can be carried out on the ketone of general formula (IX) (when R.sub.4 is other than H) or the aldehyde of general formula (IX) (when R.sub.4 is H), if the des-alkyl linker is desired. The intermediate of formula (VIII) may then be deprotected using a strong acid, such as TFA. Such reactions may be heated to 70° C. to yield the free benzylamine derivative (II). An amide coupling can then be undertaken as in Scheme 1.

##STR00022##

[0266] Compounds of formula (XIII) may be obtained by a general process as shown in Scheme 3 whereby a carboxylic acid precursor (XIV) is reacted with an activating agent such as HATU, T3P or Ghosez's reagent, to generate a reactive, electrophilic carboxylic acid derivative, followed by subsequent reaction with an amine of formula (II). Intermediates of formula (XIII) are then converted to a compound of general formula (I) by coupling under Suzuki conditions with an aromatic halide of general formula (XII), of which X is defined in Scheme 3 and represents a dihydroxyboryl or dialkyloxyboryl group, such as a 4,4,5,5-tetramethyl-1,3,3,2-dioxaborolan-2-yl group. The couplings according to the Suzuki method are performed, for example, by heating in the

presence of a catalyst such as bis(diphenylphosphino)ferrocene]dichloropalladium(II).CH.sub.2Cl.sub.2 adduct and an inorganic base such as potassium carbonate in a solvent mixture of dioxane and water under an inert atmosphere such as a nitrogen atmosphere. It will be understood by persons skilled in the art that many catalysts and conditions can be employed for such couplings.

##STR00023##

[0267] Intermediates of formula (III) where Ar.sub.2 is an unsubstituted or substituted 2-pyrazine ring or 3-pyridyl ring, may be synthesised as shown in Scheme 4 by coupling under Suzuki conditions of an aromatic halide of general formula (XII), of which R.sub.10 and R.sub.12 are defined above and Z represents a halide such as Br or Cl, to a boronate of general formula (XVI) where X denotes a dihydroxyboryl or dialkyloxyboryl group, such as a 4,4,5,5-tetramethyl-1,3,3,2-dioxaborolan-2-yl group. The couplings according to the Suzuki method are performed, for example, by heating in the presence of a catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II).Math.CH.sub.2Cl.sub.2 adduct and an inorganic base such as cesium carbonate in a solvent mixture of dioxane and water under an inert atmosphere such as a nitrogen atmosphere. The carboxylic acids of general formula (III) are obtained by either deprotection of the t-butyl ester using a strong acid, such as TFA in a solvent of CH.sub.2Cl.sub.2, hydrolysis of the methyl ester using an alkali metal hydroxide such as NaOH in a solvent mixture such as THF/MeOH or hydrolysis of the nitrile using a strong acid such as concentrated HCl. Compounds of formula (III-A) may also be made using this method.

##STR00024##

[0268] The thiazol-4-yl (propan-2-yl)benzamide derivatives of formula (I) in which R.sub.1, R.sub.3, R.sub.4, R.sub.5, Ar.sub.1 and Ar.sub.2 are defined above may be prepared by the route as shown in Scheme 5. Intermediate 2-bromthiazole esters of general formula (XVII) can be mono or bis-alkylated by alkyl halides such as 1-bromo-2-methoxyethane in the presence of a strong base such as sodium hydride to yield esters of general formula (XVIII) which may be conveniently hydrolysed by exposure to a suitable inorganic base, for example lithium hydroxide, in an aqueous mixture of aprotic and protic solvents, such as THF: methanol: water. The intermediate acyl azide, which may be formed from carboxylate (XIX) and diphenylphosphoryl azide in toluene and tert-butanol in the presence of a weak base such as trimethylamine undergoes a Curtius rearrangement at elevated temperatures such as 100° C. to yield an isocyanate that reacts with the alcohol present to give the carbamate protected amines of formula (XX). Palladium catalysed sulfonamidation of intermediate (XX) may be achieved using a catalytic system such as [Pd(allyl)Cl].sub.2 and a phosphine mono-dentate ligand such as t-BuX Phos in the presence of a primary sulphonamide to obtain compounds of the formula (XXI).

[0269] The intermediate of formula (XXI) may then be deprotected using a strong acid, such as HCl to yield the free benzylamine derivatives of formula (II) or salts thereof such as HCl salts. An amide coupling can then be undertaken as in Scheme 1 to give compounds of formula (I).

Inter Mediates of the Invention

[0270] The present invention also relates to novel intermediates in the synthesis of compounds of formula (I) such as compounds of formula (II)-(XXI) such as (II)-(XVI). Particular intermediates of interest are those of the following general formulae, wherein the variable groups and associated preferences are as defined previously for compounds of formula (I): [0271] a compound of formula (II):

##STR00025## [0272] a compound of formula (III):

##STR00026##

and [0273] a compound of formula (VIII):

##STR00027##

[0274] Also of interest are compounds of formula (III-A):

##STR00028##

[0275] Suitably, the intermediate is not:

##STR00029##

[0276] Suitably, at least one of R.sub.10, R.sub.11 and R.sub.12 is other than H.

[0277] Included as an aspect of the invention are all novel intermediates described in the examples, including: [0278] Intermediates INTE1 to INTE20; and [0279] Intermediates INTF 1 to INTF53.

[0280] A Iso included as an aspect of the invention are all novel intermediates described in the examples, including: [0281] Intermediates INTE21 to INTE 39.

[0282] Included as an aspect of the invention are salts such as pharmaceutically acceptable salts of any one of the intermediates disclosed herein, such as any one of compounds of formulae (II)-(XXI).

Therapeutic Methods

[0283] Compounds of formula (I) of the present invention have utility as inhibitors of CTPS1.

[0284] Suitably, the compounds of formula (I) of the present invention are selective for CTPS1 over CTPS2.

[0285] Therefore, the invention also provides a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof, for use as a medicament, in particular in the treatment or prophylaxis of a disease or disorder wherein an inhibitor of CTPS1 is beneficial, for example those diseases and disorders mentioned herein below.

[0286] The invention provides a method for the treatment or prophylaxis of a disease or disorder wherein an inhibitor of CTPS1 is beneficial, for example those diseases and disorders mentioned herein below, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof.

[0287] The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof (e.g. salt) and/or derivative, in the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder wherein an inhibitor of CTPS1 is beneficial, for example those diseases and disorders mentioned herein below.

[0288] More suitably, the disease or disorder wherein an inhibitor of CTPS1 is beneficial is a disease or disorder wherein a reduction in T-cell and/or B-cell proliferation would be beneficial.

[0289] The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof, for use in the inhibition of CTPS1 in a subject.

[0290] The invention provides a method for the inhibition of CTPS1 in a subject, which comprises administering to the subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof.

[0291] The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof (e.g. salt) and/or derivative, in the manufacture of a medicament for the inhibition of CTPS1 in a subject.

[0292] The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof, for use in the reduction of T-cell and/or B-cell proliferation in a subject.

[0293] The invention provides a method for the reduction of T-cell and/or B-cell proliferation in a subject, which comprises administering to the subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof.

[0294] The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof (e.g. salt) and/or derivative, in the manufacture of a medicament for the reduction of T-cell and/or B-cell proliferation in a subject.

[0295] More suitably, the disease or disorder wherein an inhibitor of CTPS1 is beneficial is a disease or disorder wherein a reduction in T-cell and/or B-cell proliferation would be beneficial.

[0296] The term 'treatment' or 'treating' as used herein includes the control, mitigation, reduction,

or modulation of the disease state or its symptoms.

[0297] The term 'prophylaxis' or 'preventing' is used herein to mean preventing symptoms of a disease or disorder in a subject or preventing recurrence of symptoms of a disease or disorder in an afflicted subject and is not limited to complete prevention of an affliction.

[0298] Suitably, the disease or disorder is selected from rejection of transplanted cells and tissues, Graft-related diseases or disorders, allergies and autoimmune diseases.

[0299] In one embodiment the disease or disorder is the rejection of transplanted cells and tissues. The subject may have been transplanted with a graft selected from the group consisting of heart, kidney, lung, liver, pancreas, pancreatic islets, brain tissue, stomach, large intestine, small intestine, cornea, skin, trachea, bone, bone marrow (or any other source of hematopoietic precursor cells and stem cells including hematopoietic cells mobilized from bone marrow into peripheral blood or umbilical cord blood cells), muscle, or bladder. The compounds of the invention may be of use in preventing or suppressing an immune response associated with rejection of a donor tissue, cell, graft or organ transplant in a subject.

[0300] In a further embodiment the disease or disorder is a Graft-related disease or disorder. Graft-related diseases or disorders include graft versus host disease (GVHD), such as GVHD associated with bone marrow transplantation, and immune disorders resulting from or associated with rejection of organ, tissue, or cell graft transplantation (e.g., tissue or cell allografts or xenografts), including, e.g., grafts of skin, muscle, neurons, islets, organs, parenchymal cells of the liver, etc, and Host-Versus-Graft-Disease (HVGD). The compounds of the invention may be of use in preventing or suppressing acute rejection of such transplant in the recipient and/or for long-term maintenance therapy to prevent rejection of such transplant in the recipient (e.g., inhibiting rejection of insulin-producing islet cell transplant from a donor in the subject recipient suffering from diabetes). Thus the compounds of the invention have utility in preventing Host-Versus-Graft-Disease (HVGD) and Graft-Versus-Host-Disease (GVHD).

[0301] A CTPS1 inhibitor may be administered to the subject before, after transplantation and/or during transplantation. In some embodiments, the CTPS1 inhibitor may be administered to the subject on a periodic basis before and/or after transplantation.

[0302] In another embodiment, the disease or disorder is an allergy.

[0303] In additional embodiments the immune related disease or disorder is an autoimmune disease. As used herein, an "autoimmune disease" is a disease or disorder directed at a subject's own tissues. Examples of autoimmune diseases include, but are not limited to Addison's Disease, Adult-onset Still's disease, Alopecia Areata, Alzheimer's disease, Anti-neutrophil Cytoplasmic Antibodies (ANCA)-Associated Vasculitis, Ankylosing Spondylitis, Anti-phospholipid Syndrome (Hughes' Syndrome), Aplastic Anemia, Arthritis, Asthma, Atherosclerosis, Atherosclerotic plaque, Atopic Dermatitis, Autoimmune Hemolytic Anemia, Autoimmune Hepatitis, Autoimmune Hypophysitis (Lymphocytic Hypophysitis), Autoimmune Inner Ear Disease, Autoimmune Lymphoproliferative Syndrome, Autoimmune Myocarditis, Autoimmune Neutropenia, Autoimmune Oophoritis, Autoimmune Orchitis, Auto-Inflammatory Diseases requiring an immunosuppressive treatment, Azospermia, Behcet's Disease, Berger's Disease, Bullous Pemphigoid, Cardiomyopathy, Cardiovascular disease, Celiac disease including Refractory Celiac Disease (type I and type II), Chronic Fatigue Immune Dysfunction Syndrome (CFIDS), Chronic Idiopathic Polyneuritis, Chronic Inflammatory Demyelinating Polyneuropathy (CIPD), Chronic Relapsing Polyneuropathy (Guillain-Barré syndrome), Churg-Strauss Syndrome (CSS), Cicatricial Pemphigoid, Cold Agglutinin Disease (CAD), chronic obstructive pulmonary disease (COPD), CREST Syndrome, Cryoglobulin Syndromes, Cutaneous Lupus, Dermatitis Herpetiformis, Dermatomyositis, Eczema, Epidermolysis Bullosa Acquisita, Essential Mixed Cryoglobulinemia, Evan's Syndrome, Exophthalmos, Fibromyalgia, Goodpasture's Syndrome, Grave's disease, Hemophagocytic Lymphohistiocytosis (HLH) (including Type 1 Hemophagocytic Lymphohistiocytosis), Histiocytosis/Histiocytic Disorders, Hashimoto's Thyroiditis, Idiopathic

Pulmonary Fibrosis, Idiopathic Thrombocytopenia Purpura (ITP), IgA Nephropathy, Immunoproliferative Diseases or Disorders, Inflammatory Bowel Disease (IBD), Interstitial Lung Disease, Juvenile Arthritis, Juvenile Idiopathic Arthritis (JIA), Kawasaki's Disease, Lambert-Eaton Myasthenic Syndrome, Lichen Planus, Localized Scleroderma, Lupus Nephritis, Ménière's Disease, Microangiopathic Hemolytic Anemia, Microscopic Polyangiitis, Miller Fisher Syndrome/Acute Disseminated Encephalomyeloradiculopathy, Mixed Connective Tissue Disease, Multiple Sclerosis (MS), Muscular Rheumatism, Myalgic Encephalomyelitis (ME), Myasthenia Gravis, Ocular Inflammation, Pemphigus Foliaceus, Pemphigus Vulgaris, Pernicious Anemia, Polyarteritis Nodosa, Polychondritis, Polyglandular Syndromes (Whitaker's syndrome), Polymyalgia Rheumatica, Polymyositis, Primary Agammaglobulinemia, Primary Biliary Cirrhosis/Autoimmune Cholangiopathy, Primary Glomerulonephritis, Primary Sclerosing Cholangitis, Psoriasis, Psoriatic Arthritis, Pure Red Cell Anemia, Raynaud's Phenomenon, Reiter's Syndrome/Reactive Arthritis, Relapsing Polychondritis, Restenosis, Rheumatic Fever, Rheumatic Disease, Rheumatoid Arthritis, Sarcoidosis, Schmidt's Syndrome, Scleroderma/Systemic Sclerosis, Sjögren's Syndrome, Stiff-Man Syndrome, The Sweet Syndrome (Febrile Neutrophilic Dermatoses), Systemic Lupus Erythematosus (SLE), Systemic Scleroderma, Takayasu Arteritis, Temporal Arteritis/Giant Cell Arteritis, Thyroiditis, Type 1 diabetes, Type 2 diabetes, Uveitis, Vasculitis, Vitiligo, Wegener's Granulomatosis, and X-linked lymphoproliferative disease.

[0304] Of particular interest are diseases and disorders which are mainly driven by T-cell activation and proliferation, including: [0305] diseases and disorders which are not linked to alloreactivity including: [0306] Alopecia areata, atopic dermatitis, eczema, psoriasis, lichen planus, psoriatic arthritis, vitiligo; [0307] Uveitis; [0308] Ankylosing spondylitis, Reiter's syndrome/reactive arthritis; [0309] Aplastic anemia, autoimmune lymphoproliferative syndrome/disorders, hemophagocytic lymphohistiocytosis; [0310] Type 1 diabetes; and [0311] Refractory celiac disease; [0312] Acute rejection of grafted tissues and transplanted organs; acute graft versus host disease (GVHD) after transplantation of bone marrow cells or any other source of allogeneic cells including hematopoietic precursors cells and/or stem cells.

[0313] Also of interest are diseases and disorders which are driven by both T- and B-cell activation and proliferation, with an important involvement of B-cells, including: [0314] diseases and disorders for which the involvement of pathogenic auto-antibodies is well characterized, including: [0315] Allergy; [0316] Cicatricial pemphigoid, bullous pemphigoid, epidermolysis bullosa acquisita, pemphigus foliaceus, pemphigus vulgaris, dermatitis herpetiformis; [0317] ANCA-associated vasculitis and microscopic polyangiitis, vasculitis, Wegener's granulomatosis; Churg-Strauss syndrome (CSS), polyarteritis nodosa, cryoglobulin syndromes and essential mixed cryoglobulinemia; [0318] Systemic lupus erythematosus (SLE), antiphospholipid syndrome (Hughes' syndrome), cutaneous lupus, lupus nephritis, mixed connective tissue disease; [0319] Thyroiditis, Hashimoto thyroiditis, Grave's disease, exophthalmos; [0320] Autoimmune hemolytic anemia, autoimmune neutropenia, ITP, pernicious anaemia, pure red cell anaemia, microangiopathic hemolytic anemia; [0321] Primary glomerulonephritis, Berger's disease, Goodpasture's syndrome, IgA nephropathy; and [0322] Chronic idiopathic polyneuritis, chronic inflammatory demyelinating polyneuropathy (CIPD), chronic relapsing polyneuropathy (Guillain-Barré syndrome), Miller Fisher syndrome, Stiff man syndrome, Lambert-Eaton myasthenic syndrome, myasthenia gravis. [0323] diseases and disorders for which the involvement of B-cells is less clearly characterized (although sometimes illustrated by the efficacy of anti-CD20 monoclonal antibodies or intravenous immunoglobulin infusions) and may not correspond or be limited to the production of pathogenic antibodies (nevertheless, non-pathogenic antibodies are sometimes described or even often present and used as a diagnosis biomarker), including: [0324] Addison's disease, autoimmune oophoritis and azoospermia, polyglandular syndromes (Whitaker's syndrome), Schmidt's syndrome; [0325] Autoimmune myocarditis, cardiomyopathy, Kawasaki's disease; [0326] Rheumatoid arthritis, Sjögren's syndrome, mixed connective tissue disease,

polymyositis and dermatomyositis; polychondritis; [0327] Primary glomerulonephritis; [0328] Multiple sclerosis; [0329] Autoimmune hepatitis, primary biliary cirrhosis/autoimmune cholangiopathy, [0330] Hyper acute rejection of transplanted organs; [0331] Chronic rejection of graft or transplants; [0332] Chronic Graft versus Host reaction/disease after transplantation of bone marrow cells or hematopoietic precursor cells.

[0333] Additionally of interest are diseases and disorders for which the mechanism is shared between activation/proliferation of T-cells and activation/proliferation of innate immune cells and other inflammatory cellular subpopulations (including myeloid cells such as macrophages or granulocytes) and resident cells (such as fibroblasts and endothelial cells), including: [0334] COPD, idiopathic pulmonary fibrosis, interstitial lung disease, sarcoidosis; [0335] Adult onset Still's disease, juvenile idiopathic arthritis, Systemic sclerosis, CREST syndrome where B cells and pathogen antibodies may also play a role; the Sweet syndrome; Takayasu arteritis, temporal arteritis/giant cell arteritis; [0336] Ulcerative cholangitis, inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis, primary sclerosing cholangitis.

[0337] Also of interest are diseases and disorders for which the mechanism remains poorly characterized but involves the activation and proliferation of T-cells, including: [0338] Alzheimer's disease, cardiovascular syndrome, type 2 diabetes, restenosis, chronic fatigue immune dysfunction syndrome (CFIDS). [0339] Autoimmune Lymphoproliferative disorders, including: [0340] Autoimmune Lymphoproliferative Syndrome and X-linked lymphoproliferative disease.

[0341] Suitably the disease or disorder is selected from: inflammatory skin diseases such as psoriasis or lichen planus; acute and/or chronic GVHD such as steroid resistant acute GVHD; acute lymphoproliferative syndrome; systemic lupus erythematosus, lupus nephritis or cutaneous lupus; or transplantation. In addition, the disease or disorder may be selected from myasthenia gravis, multiple sclerosis, and scleroderma/systemic sclerosis.

[0342] The compounds of formula (I) may be used in the treatment of cancer.

[0343] Thus, in one embodiment there is provided is a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, for use in the treatment of cancer.

[0344] Further, there is provided a method for treating cancer in a subject, by administering to a subject in need thereof a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof.

[0345] Additionally provided is the use of a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, in the manufacture of a medicament for the treatment of cancer in a subject.

[0346] Suitably the cancer is a haematological cancer, such as Acute myeloid leukemia, Angioimmunoblastic T-cell lymphoma, B-cell acute lymphoblastic leukemia, Sweet Syndrome, T-cell Non-Hodgkins lymphoma (including natural killer/T-cell lymphoma, adult T-cell leukaemia/lymphoma, enteropathy type T-cell lymphoma, hepatosplenic T-cell lymphoma and cutaneous T-cell lymphoma), T-cell acute lymphoblastic leukemia, B-cell Non-Hodgkins lymphoma (including Burkitt lymphoma, diffuse large B-cell lymphoma, Follicular lymphoma, Mantle cell lymphoma, Marginal Zone lymphoma), Hairy Cell Leukemia, Hodgkin lymphoma, Lymphoblastic lymphoma, Lymphoplasmacytic lymphoma, Mucosa-associated lymphoid tissue lymphoma, Multiple myeloma, Myelodysplastic syndrome, Plasma cell myeloma, Primary mediastinal large B-cell lymphoma, chronic myeloproliferative disorders (such as chronic myeloid leukemia, primary myelofibrosis, essential thrombocytemia, polycythemia vera) or chronic lymphocytic leukemia.

[0347] Alternatively, the cancer is a non-haematological cancer, such as selected from the group consisting of bladder cancer, breast cancer, melanoma, neuroblastoma, malignant pleural mesothelioma and sarcoma, such as breast cancer and melanoma.

[0348] In addition, compounds of formula (I) may be used in enhancing recovery from vascular

injury or surgery and reducing morbidity and mortality associated with neointima and restenosis in a subject. Vascular injury may occur in any vessel in the subject, such as a coronary artery, a renal artery, a carotid artery, a dialysis fistulae artery or a peripheral artery.

[0349] The compounds of formula (I) may be used in preventing, reducing, or inhibiting neointima formation. The compounds of formula (I) may be used in preventing or reducing the occurrence of restenosis, for example following surgery.

[0350] Furthermore, the compounds of formula (I) may be used in conjunction with a medical device. A medical device may be treated prior to insertion or implantation with an effective amount of a compound of formula (I) or a composition comprising a compound of formula (I) in order to prevent, reduce, or inhibit neointima formation following insertion or implantation of the device or graft into the subject. The device can be a device that is inserted into the subject transiently, or a device that is implanted permanently. In some embodiments, the device is a surgical device. Examples of medical devices include, but are not limited to, needles, cannulas, catheters, shunts, balloons, and implants such as stents and valves.

[0351] Suitably, the compound of formula (I) may be used in conjunction with angioplasty. The medical device may be a balloon.

[0352] Suitably the subject is a mammal, in particular the subject is a human.

Pharmaceutical Compositions

[0353] For use in therapy the compounds of the invention are usually administered as a pharmaceutical composition. The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof, and a pharmaceutically acceptable carrier or excipient.

[0354] In one embodiment, there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof, for use in the treatment or prophylaxis of a disease or disorder as described herein.

[0355] In a further embodiment, there is provided a method for the prophylaxis or treatment of a disease or disorder as described herein, which comprises administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof.

[0356] The invention also provides the use of a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof (e.g. salt) and/or derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder as described herein.

[0357] The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives thereof may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

[0358] The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives thereof may be administered topically, for example to the eye, gut or skin. Thus, in an embodiment there is provided a pharmaceutical composition comprising a compound of the invention optionally in combination with one or more topically acceptable diluents or carriers.

[0359] A pharmaceutical composition of the invention may be delivered topically to the skin. Compositions suitable for transdermal administration include ointments, gels and patches. Such a pharmaceutical composition may also suitably be in the form of a cream, lotion, foam, powder, paste or tincture.

[0360] The pharmaceutical composition may suitably include vitamin D3 analogues (e.g. calcipotriol and maxacalcitol), steroids (e.g. fluticasone propionate, betamethasone valerate and clobetasol propionate), retinoids (e.g. tazarotene), coal tar and dithranol. Topical medicaments are often used in combination with each other (e.g. a vitamin D3 and a steroid) or with further agents

such as salicylic acid.

[0361] A pharmaceutical composition of the invention may be delivered topically to the eye. Such a pharmaceutical composition may suitably be in the form of eye drops or an ointment.

[0362] A pharmaceutical composition of the invention may be delivered topically to the gut. Such a pharmaceutical composition may suitably be delivered orally, such as in the form of a tablet or a capsule, or rectally, such as in the form of a suppository.

[0363] Suitably, delayed release formulations are in the form of a capsule.

[0364] The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives thereof which are active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

[0365] A liquid formulation will generally consist of a suspension or solution of the active ingredient (such as a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof) in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

[0366] A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

[0367] A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient (such as a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof) can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

[0368] Typical parenteral compositions consist of a solution or suspension of the active ingredient (such as a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof) in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

[0369] Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a fluoro-chloro-hydrocarbon or hydrofluorocarbon. Aerosol dosage forms can also take the form of pump-atomisers.

[0370] Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

[0371] Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

[0372] Suitably, the composition is in unit dose form such as a tablet, capsule or ampoule.

[0373] The composition may for example contain from 0.1% to 100% by weight, for example from 10 to 60% by weight, of the active material, depending on the method of administration. The composition may contain from 0% to 99% by weight, for example 40% to 90% by weight, of the carrier, depending on the method of administration. The composition may contain from 0.05 mg to

2000 mg, for example from 1.0 mg to 500 mg, of the active material, depending on the method of administration. The composition may contain from 50 mg to 1000 mg, for example from 100 mg to 400 mg of the carrier, depending on the method of administration. The dose of the compound used in the treatment or prophylaxis of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 mg to 1000 mg, more suitably 1.0 mg to 500 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

[0374] The invention provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable, salt, solvate and/or derivative thereof (e.g. a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof) together with a further pharmaceutically acceptable active ingredient or ingredients.

[0375] The invention provides a compound of formula (I), for use in combination with a further pharmaceutically acceptable active ingredient or ingredients.

[0376] When the compounds are used in combination with other therapeutic agents, the compounds may be administered separately, sequentially or simultaneously by any convenient route.

[0377] Optimal combinations may depend on the disease or disorder. Possible combinations include those with one or more active agents selected from the list consisting of: 5-aminosalicylic acid, or a prodrug thereof (such as sulfasalazine, olsalazine or bisalazide); corticosteroids (e.g. prednisolone, methylprednisolone, or budesonide); immunosuppressants (e.g. cyclosporin, tacrolimus, sirolimus, methotrexate, azathioprine mycophenolate mofetil, leflunomide, cyclophosphamide, 6-mercaptopurine or anti-lymphocyte (or thymocyte) globulins); anti-TNF- α antibodies (e.g., infliximab, adalimumab, certolizumab pegol or golimumab); anti-IL 12/IL 23 antibodies (e.g., ustekinumab); anti-IL 6 or anti-IL 6R antibodies, anti-IL 17 antibodies or small molecule IL 12/IL23 inhibitors (e.g., apilimod); Anti- α -4- β -7 antibodies (e.g., vedolizumab); MAdCAM-1 blockers (e.g., PF-00547659); antibodies against the cell adhesion molecule α -4-integrin (e.g., natalizumab); antibodies against the IL 2 receptor α subunit (e.g., daclizumab or basiliximab); JAK inhibitors including JAK 1 and JAK 3 inhibitors (e.g., tofacitinib, baricitinib, R348); Syk inhibitors and prodrugs thereof (e.g., fostamatinib and R-406); Phosphodiesterase-4 inhibitors (e.g., tetomilast); HM PL-004; probiotics; Dersalazine; semapimod/CPSI-2364; and protein kinase C inhibitors (e.g. A EB-071).

[0378] For cancer, the further pharmaceutically acceptable active ingredient may be selected from anthracyclins such as doxorubicin; anti-mitotic agents such as vinblastine, paclitaxel and docetaxel; alkylating agents, for example cisplatin, carboplatin, dacarbazine and cyclophosphamide; antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea; intercalating agents for example adriamycin and bleomycin; topoisomerase inhibitors for example etoposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; P13 kinase inhibitors for example idelalisib; mTOR inhibitors for example everolimus and temsirolimus; proteasome inhibitors for example bortezomib; histone deacetylase inhibitors for example panobinostat or vorinostat; and hedgehog pathway blockers such as vismodegib.

[0379] The further pharmaceutically acceptable active ingredient may be selected from tyrosine kinase inhibitors such as, for example, axitinib, dasatinib, erlotinib, imatinib, nilotinib, pazopanib and sunitinib.

[0380] Anticancer antibodies may be included in a combination therapy and may be selected from the group consisting of olaratumab, daratumumab, necitumumab, dinutuximab, trastuzumab emtansine, pertuzumab, obinutuzumab, brentuximab, ofatumumab, panitumumab, catumaxomab, bevacizumab, cetuximab, tositumomab, trastuzumab, gentuzumab ozogamycin and rituximab.

[0381] Compounds or pharmaceutical compositions of the invention may also be used in combination with radiotherapy.

[0382] Some of the combinations referred to above may conveniently be presented for use in the

form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. The individual components of combinations may also be administered separately, through the same or different routes.

[0383] When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Medical Devices

[0384] In an embodiment, compounds of the invention or pharmaceutical compositions comprising said compounds may be formulated to permit incorporation into the medical device, thus providing application of the compound or composition directly to the site to prevent or treat conditions disclosed herein.

[0385] In an embodiment, the compounds of the invention or pharmaceutical composition thereof is formulated by including it within a coating onto the medical device. There are various coatings that can be utilized such as, for example, polymer coatings that can release the compound over a prescribed time period. The compound, or a pharmaceutical composition thereof, can be embedded directly within the medical device. In some embodiments, the compound is coated onto or within the device in a delivery vehicle such as a microparticle or liposome that facilitates its release and delivery. In some embodiments, the compound or pharmaceutical composition is miscible in the coating.

[0386] In some embodiments, the medical device is a vascular implant such as a stent. Stents are utilized in medicine to prevent or eliminate vascular restrictions. The implants may be inserted into a restricted vessel whereby the restricted vessel is widened. Excessive growth of the adjacent cells following vascular implantation results in a restriction of the vessel particularly at the ends of the implants which results in reduced effectiveness of the implants. If a vascular implant is inserted into a human artery for the elimination of for example an arteriosclerotic stenosis, intima hyperplasia can occur within a year at the ends of the vascular implant and results in renewed stenosis ("restenosis").

[0387] Accordingly, in some embodiments, the stents are coated or loaded with a composition including a compound of the invention or pharmaceutical composition thereof and optionally a targeting signal, a delivery vehicle, or a combination thereof. Many stents are commercially available or otherwise known in the art.

[0388] In some embodiments, the stent is a drug-eluting stent. Various drug eluting stents that simultaneously deliver a therapeutic substance to the treatment site while providing artificial radial support to the wall tissue are known in the art. Endoluminal devices including stents are sometimes coated on their outer surfaces with a substance such as a drug releasing agent, growth factor, or the like. Stents have also been developed having a hollow tubular structure with holes or ports cut through the sidewall to allow drug elution from a central lumen. Although the hollow nature of the stent allows the central lumen to be loaded with a drug solution that is delivered via the ports or holes in the sidewall of the stent, the hollow tubular structure may not have suitable mechanical strength to provide adequate scaffolding in the vessel.

[0389] In some embodiments, the devices are also coated or impregnated with a compound of the invention, or pharmaceutical composition thereof and one or more additional therapeutic agents, including, but not limited to, antiplatelet agents, anticoagulant agents, anti-inflammatory agents, antimicrobial agents, antimetabolic agents, additional anti-neointima agents, additional antiproliferative agents, immunomodulators, antiproliferative agents, agents that affect migration and extracellular matrix production, agents that affect platelet deposition or formation of thrombus,

and agents that promote vascular healing and re-endothelialization, such as those and others described in Sousa et al. (2003) and Salu et al. (2004).

[0390] Examples of antithrombin agents include, but are not limited to, Heparin (including low molecular heparin), R-Hirudin, Hirulog, Argatroban, Efegatran, Tick anticoagulant peptide, and Ppack.

[0391] Examples of antiproliferative agents include, but are not limited to, Paclitaxel (Taxol), QP-2 Vincristin, Methotrexat, Angiopeptin, Mitomycin, BCP 678, Antisense c-myc, A BT 578, Actinomycin-D, RestenA SE, 1-Chlor-deoxyadenosin, PCNA Ribozym, and Celecoxib.

[0392] Examples of anti-restenosis agents include, but are not limited to, immunomodulators such as Sirolimus

[0393] (Rapamycin), Tacrolimus, Biores, Mizoribin, Cyclosporin, Interferon- γ lb, Leflunomid, Tranilast, Corticosteroide, Mycophenolic acid and Biphosphonate.

[0394] Examples of anti-migratory agents and extracellular matrix modulators include, but are not limited to Halofuginone, Propyl-hydroxylase-Inhibitors, C-Proteinase-Inhibitors, MMP-Inhibitors, Batimastat, Probucol.

[0395] Examples of antiplatelet agents include, but are not limited to, heparin.

[0396] Examples of wound healing agents and endothelialization promoters include vascular epithelial growth factor ("VEGF"), 17-Estradiol, Tkase-Inhibitors, BCP 671, Statins, nitric oxide ("NO")-Donors, and endothelial progenitor cell ("EPC")-antibodies.

[0397] Besides coronary applications, drugs and active agents may be incorporated into the stent or stent coating for other indications. For example, in urological applications, antibiotic agents may be incorporated into the stent or stent coating for the prevention of infection. In gastroenterological and urological applications, active agents may be incorporated into the stent or stent coating for the local treatment of carcinoma. It may also be advantageous to incorporate in or on the stent a contrast agent, radiopaque markers, or other additives to allow the stent to be imaged in vivo for tracking, positioning, and other purposes. Such additives could be added to the absorbable composition used to make the stent or stent coating, or absorbed into, melted onto, or sprayed onto the surface of part or all of the stent. Preferred additives for this purpose include silver, iodine and iodine labeled compounds, barium sulfate, gadolinium oxide, bismuth derivatives, zirconium dioxide, cadmium, tungsten, gold tantalum, bismuth, platinum, iridium, and rhodium. These additives may be, but are not limited to, micro- or nano-sized particles or nano particles. Radio-opacity may be determined by fluoroscopy or by x-ray analysis.

[0398] A compound of the invention and one or more additional agents, or pharmaceutical composition thereof, can be incorporated into the stent, either by loading the compound and one or more additional agents, or pharmaceutical composition thereof into the absorbable material prior to processing, and/or coating the surface of the stent with the agent(s). The rate of release of agent may be controlled by a number of methods including varying the following the ratio of the absorbable material to the compound and one or more additional agents, or pharmaceutical composition, the molecular weight of the absorbable material, the composition of the compound and one or more additional agents, or pharmaceutical composition, the composition of the absorbable polymer, the coating thickness, the number of coating layers and their relative thicknesses, and/or the compound and one or more additional agents, or pharmaceutical composition concentration. Top coats of polymers and other materials, including absorbable polymers, may also be applied to active agent coatings to control the rate of release. For example, P4HB can be applied as a top coat on a metallic stent coated with P4HB including an active agent to retard the release of the active agent.

[0399] The invention is further exemplified by the following non-limiting examples.

EXAMPLES

[0400] Abbreviations used herein are defined below. Any abbreviations not defined are intended to convey their generally accepted meaning.

Abbreviations

[0401] AcOH glacial acetic acid [0402] AIM e3 trimethylaluminium [0403] aq aqueous [0404] Ar aromatic ring [0405] BEH ethylene bridged hybrid [0406] Bispin bis (pinacolato)diboron; 4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi-1,3,2-dioxaborolane [0407] Bz benzyl (CH₂.sub.2-phenyl) [0408] BOC tert-butyloxycarbonyl protecting group [0409] Cs.sub.2CO.sub.3 cesium carbonate [0410] CSH charged surface hybrid [0411] d doublet [0412] DCM dichloromethane [0413] DIBAL-H diisobutylaluminium hydride [0414] DIPEA N,N-diisopropylethylamine [0415] dioxane 1,4-dioxane [0416] DMF N,N-dimethylformamide [0417] DMSO dimethyl sulfoxide [0418] DPPA diphenylphosphoryl azide [0419] dppf 1,1'-bis(diphenylphosphino) ferrocene [0420] (ES+) electrospray ionisation, positive mode [0421] (ES-) electrospray ionisation, negative mode [0422] ESI electrospray ionisation [0423] Et ethyl [0424] EtM gBr ethyl magnesium bromide [0425] EtOAc ethyl acetate [0426] EtOH ethanol [0427] Fmoc fluorenylmethyloxycarbonyl [0428] g grams [0429] HATU 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate [0430] HCl hydrochloric acid [0431] HPLC high performance liquid chromatography [0432] hr(s) hour(s) [0433] H.sub.2SO.sub.4 sulfuric acid [0434] IC.sub.50 50% inhibitory concentration [0435] K.sub.2CO.sub.3 potassium carbonate [0436] LCMS liquid chromatography-mass spectrometry [0437] LiOH lithium hydroxide [0438] (M+H).sup.+ protonated molecular ion [0439] (M-H).sup.- unprotonated molecular ion [0440] M molar concentration [0441] mL millilitre [0442] mm millimeter [0443] mmol millimole [0444] MgSO.sub.4 magnesium sulfate [0445] Me methyl [0446] MeCN acetonitrile [0447] MeMgBr methyl magnesium bromide [0448] MeOH methanol [0449] MHz megahertz [0450] min(s) minute(s) [0451] MSD mass selective detector [0452] m/z mass-to-charge ratio [0453] N.sub.2 nitrogen gas [0454] NH.sub.3 ammonia [0455] NH.sub.4Cl ammonium chloride [0456] NaH sodium hydride [0457] Na.sub.2SO.sub.4 sodium sulfate [0458] NaHCO.sub.3 sodium bicarbonate [0459] nM nanomolar [0460] nm nanometre [0461] NMR nuclear magnetic resonance (spectroscopy) [0462] PDA photodiode array [0463] PdCl.sub.2(dppf).Math.CH.sub.2Cl.sub.2 [1,1'-bis(diphenylphosphino) ferrocene]dichloropalladium (II) dichloromethane [0464] prep HPLC preparative high performance liquid chromatography [0465] Ph phenyl [0466] pos/neg positive/negative [0467] q quartet [0468] RT room temperature [0469] Rt retention time [0470] RP reverse phase [0471] S singlet [0472] S.sub.NAr nucleophilic aromatic substitution [0473] sat saturated [0474] SCX solid supported cation exchange (resin) [0475] t triplet [0476] T3P 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide [0477] TBME tert-butyl methyl ether [0478] TFA trifluoroacetic acid [0479] TMSOK potassium trimethylsilanolate [0480] THF tetrahydrofuran [0481] UPLC ultra performance liquid chromatography [0482] UV ultraviolet [0483] v/v volume/volume [0484] VWD variable wave detector [0485] wt weight [0486] μ m micrometre [0487] μ M micromolar [0488] μ L microlitre

General Procedures

[0489] All starting materials and solvents were obtained either from commercial sources or prepared according to the literature. Unless otherwise stated all reactions were stirred. Organic solutions were routinely dried over anhydrous magnesium sulfate or sodium sulfate.

Hydrogenations were performed on a Thales H-cube flow reactor under the conditions stated.

[0490] Column chromatography was performed on pre-packed silica (230-400 mesh, 40-63 μ m) cartridges using the amount indicated. SCX was purchased from Supelco and treated with 1 M hydrochloric acid prior to use. Unless stated otherwise the reaction mixture to be purified was first diluted with MeOH and made acidic with a few drops of AcOH. This solution was loaded directly onto the SCX and washed with MeOH.

[0491] The desired material was then eluted by washing with 0.7 M NH₃ in MeOH.

Preparative Reverse Phase High Performance Liquid Chromatography (HPLC)

Prep HPLC

Acidic Prep

[0492] Waters X-Select CSH column C18, 5 μ m (19 \times 50 mm), flow rate 28 mL min⁻¹ eluting with a H₂O-MeCN gradient containing 0.1% v/v formic acid over 6.5 min using UV detection at 254 nm.

Basic Prep

[0493] Waters X-Bridge Prep column C18, 5 μ m (19 \times 50 mm), flow rate 28 mL min⁻¹ eluting with a 10 mM NH₄HCO₃—MeCN gradient over 6.5 min using UV detection at 254 nm.

Prep Chiral HPLC

[0494] Chiral Method A: Chiralpak® IA (Daicel Ltd.) column (2 \times 25 cm), flow rate 13.5 mL min⁻¹ eluting with a mixture of (30%) EtOH in a 4:1 mixture of heptane+0.2% TFA and CHCl₃, UV detection at 254 nm. Samples were loaded onto the column via an at-column dilution pump, pumping (EtOH) (1.5 mL min⁻¹) for the duration of the run, giving a combined flow rate of 15 mL min⁻¹.

[0495] Chiral Method B: Chiralpak® IA (Daicel Ltd.) column (2 \times 25 cm), flow rate 13.5 mL min⁻¹ eluting with a mixture of (40%) EtOH in a 4:1 mixture of heptane+0.2% TFA and CHCl₃, UV detection at 254 nm. Samples were loaded onto the column via an at-column dilution pump, pumping (EtOH) (1.5 mL min⁻¹) for the duration of the run, giving a combined flow rate of 15 mL min⁻¹.

Analytical Methods

Reverse Phase HPLC Conditions for the LCMS Analytical Methods

HPLC Acidic: Acidic LCMS 4 Minute (5-95%)

[0496] Analytical LCMS was carried out using a Waters X-Select CSH C18, 2.5 μ m, 4.6 \times 30 mm column eluting with a gradient of 0.1% formic acid in MeCN in 0.1% formic acid in water. The gradient from 5-95% 0.1% formic acid in MeCN occurred between 0.00-3.00 minutes at 2.5 mL/min with a flush from 3.01-3.5 minutes at 4.5 mL/min. A column re-equilibration to 5% MeCN was from 3.60-4.00 minutes at 2.5 mL/min. UV spectra of the eluted peaks were measured using an Agilent 1260 Infinity VWD at 254 nm. Mass spectra were measured using an Agilent 6120 MSD running with positive/negative switching.

HPLC Basic: Basic LCMS 4 Minute (5-95%)

[0497] Analytical LCMS was carried out using a Waters X-Select BEH C18, 2.5 μ m, 4.6 \times 30 mm column eluting with a gradient of MeCN in aqueous 10 mM ammonium bicarbonate. The gradient from 5-95% MeCN occurred between 0.00-3.00 minutes at 2.5 mL/min with a flush from 3.01-3.5 minutes at 4.5 mL/min. A column re-equilibration to 5% MeCN was from 3.60-4.00 minutes at 2.5 mL/min. UV spectra of the eluted peaks were measured using an Agilent 1260 Infinity VWD at 254 nm. Mass spectra were measured using an Agilent 6120 MSD running with positive/negative switching.

Reverse Phase HPLC Conditions for the UPLC Analytical Methods

UPLC Acidic: Acidic UPLC3 Minute

[0498] Analytical UPLC/MS was carried out using a Waters Acquity CSH C18, 1.7 μ m, 2.1 \times 30 mm column eluting with a gradient of 0.1% formic acid in MeCN in 0.1% formic acid in water. The gradient was structured with a starting point of 5% MeCN held from 0.0-0.11 minutes. The gradient from 5-95% occurred between 0.11-2.15 minutes with a flush from 2.15-2.56 minutes. A column re-equilibration to 5% MeCN was from 2.56-2.83 minutes. UV spectra of the eluted peaks were measured using an Acquity PDA and mass spectra were recorded using an Acquity QDa detector with ESI positive/negative switching.

UPLC Basic: Basic UPLC3 Minute

[0499] Analytical UPLC/MS was carried out using a Waters Acquity BEH C18, 1.7 μ m, 2.1 \times 30 mm column eluting with a gradient of MeCN in aqueous 10 mM ammonium bicarbonate. The gradient was structured with a starting point of 5% MeCN held from 0.0-0.11 minutes. The gradient from 5-95% occurred between 0.11-2.15 minutes with a flush from 2.15-2.56 minutes. A column re-equilibration to 5% MeCN was from 2.56-2.83 minutes. UV spectra of the eluted peaks were measured using an Acquity PDA and mass spectra were recorded using an Acquity QDa

detector with ESI positive/negative switching.

[0500] Column temperature was 40° C. in all runs. Injection volume was 3 μ L and the flow rate was 0.77 mL/min. PDA scan from 210-400 nm was conducted on all runs.

Normal Phase HPLC Conditions for the Chiral Analytical Methods

[0501] Chiral IA method 1: Chiral HPLC (Daicel Chiralpak IA, 5 μ m, 4.6 \times 250 mm, 1.0 mL/min, 5-95% (gradient over 45 min) EtOH (0.2% TFA) in [4:1 heptane (0.2% TFA): CHCl₃.sub.3].

[0502] Chiral IA method 2: Chiral HPLC (Daicel Chiralpak IA, 5 μ m, 4.6 \times 250 mm, 1.0 mL/min, Isocratic 40% EtOH (0.2% TFA) in [4:1 heptane (0.2% TFA): CHCl₃.sub.3].

[0503] Chiral IC method 1: Chiral HPLC (Daicel Chiralpak IA, 5 μ m, 4.6 \times 250 mm, 0.5 mL/min, Isocratic 70% EtOH (0.2% TFA) in [4:1 iso-hexane (0.2% TFA): CHCl₃].

[0504] ¹H NMR Spectroscopy ¹H NMR spectra were acquired on a Bruker Avance III spectrometer at 400 M Hz or Bruker Avance III HD spectrometer at 500 M Hz using residual undeuterated solvent as reference and unless specified otherwise were run in DMSO-d₆.sub.6.

Preparation of Intermediates

[0505] Known synthetic intermediates were procured from commercial sources or were obtained using published literature procedures. Additional intermediates were prepared by the representative synthetic processes described herein.

Ethyl 2-(cyclopropanesulfonamido)thiazole-4-carboxylate INTE 1

##STR00030##

[0506] A solution of ethyl 2-aminothiazole-4-carboxylate (6.49 g, 37.7 mmol) and cyclopropanesulfonyl chloride (4 mL, 39.5 mmol) in pyridine (15 mL) was warmed to 40° C. and stirred for 48 hrs. The reaction mixture was taken up in DMSO (20 mL) and the crude product was purified by reverse phase chromatography on C18 silica (330 g column, 10-20% MeCN/10 mM ammonium bicarbonate) to afford the product which was then taken up in EtOAc (300 mL) and washed with 1 M HCl (aq, 300 mL) and brine (150 mL). The organic layer was dried (Na₂SO₄.sub.4), filtered and concentrated to afford ethyl 2-(cyclopropanesulfonamido)thiazole-4-carboxylate (4.7 g, 15.31 mmol, 41% yield) as an orange oil; Rt 1.36 min (HPLC acidic); m/z 277 (M+H).sup.+(ES.sup.+); ¹H NMR (400 M Hz, DMSO-d₆.sub.6) δ 13.14 (s, 1H), 7.72 (s, 1H), 4.28 (q, J=7.1 Hz, 2H), 2.72-2.58 (m, 1H), 1.29 (t, J=7.1 Hz, 3H), 1.01-0.81 (m, 4H).

N-(4-Formylthiazol-2-yl)cyclopropanesulfonamide INTE 2

##STR00031##

[0507] A solution of ethyl 2-(cyclopropanesulfonamido)thiazole-4-carboxylate INTE 1 (1.0 g, 3.62 mmol) in DCM (10 mL) was cooled to -78° C. whereupon DIBAL-H (1 M in DCM) (14.5 mL, 14.5 mmol) was added dropwise over 30 mins. The reaction was then stirred at this temperature for 2 hrs. MeOH (1.5 mL) was added cautiously before the reaction mixture was allowed to warm to RT. DCM (50 mL) was then added, followed by 1 M HCl (aq, 90 mL) with vigorous stirring. The mixture was stirred for 10 mins before being passed through a phase separator and further extracting with DCM (50 mL). The organic layers were combined and concentrated onto silica (2 g) and the crude product was purified by chromatography on silica (40 g column, 20-80% EtOAc/iso-hexanes) to afford N-(4-formylthiazol-2-yl)cyclopropanesulfonamide (122 mg, 0.5 mmol, 14% yield) as a colourless gum; Rt 0.53 min (UPLC acidic); m/z 233 (M+H).sup.+(ES.sup.+); ¹H NMR (400 MHz, DMSO-d₆.sub.6) δ 13.17 (s, 1H), 9.52 (s, 1H), 8.06 (s, 1H), 2.73-2.57 (m, 1H), 1.04-0.67 (m, 4H).

2-(Cyclopropanesulfonamido)thiazole-4-carboxylic acid INTE 3

##STR00032##

[0508] A solution of ethyl 2-(cyclopropanesulfonamido)thiazole-4-carboxylate INTE 1 (1.3 g, 4.70 mmol) in 2 M LiOH (aq, 4.70 mL, 9.41 mmol), MeOH (1 mL) and THF (6 mL) was stirred at RT. The reaction mixture was part concentrated (to approx. 6 mL) then acidified with 1 M HCl (aq, 12 mL). The aqueous layer was then extracted with EtOAc (3 \times 20 mL), then the organic phases were combined, dried (Na₂SO₄ 4), filtered and concentrated to afford 2-

(cyclopropanesulfonamido)thiazole-4-carboxylic acid (910 mg, 3.59 mmol, 76% yield) as a colourless solid; Rt 0.65 min (UPLC acidic); m/z 249 (M+H).sup.+(ES.sup.+); .sup.1H NMR (400 MHZ, DMSO-d.sub.6) δ 13.83-12.58 (br. s, 2H), 7.61 (s, 1H), 2.67-2.58 (m, 1H), 1.07-0.73 (m, 4H).

2-(Cyclopropanesulfonamido)-N-methoxy-N-methylthiazole-4-carboxamide INTE 4

##STR00033##

[0509] A solution of 2-(cyclopropanesulfonamido)thiazole-4-carboxylic acid INTE3 (910 mg, 3.67 mmol) and N,O-dimethylhydroxylamine hydrochloride (358 mg, 3.67 mmol) in DMF (6 mL) was treated with DIPEA (2.2 mL, 12.8 mmol) and stirred for 5 mins before HATU (1.3 g, 3.67 mmol) was added, the reaction mixture was stirred at RT for 20 hrs. The reaction mixture was taken up in 1 M HCl (aq, 50 mL) which was extracted with EtOAc (3×50 mL). The organic phases were combined, dried (Na.sub.2SO.sub.4), filtered and concentrated onto silica (5 g). The crude product was purified by chromatography on silica (24 g column, 0-100% EtOAc/iso-hexanes) to afford 2-(cyclopropanesulfonamido)-N-methoxy-N-methylthiazole-4-carboxamide (786 mg, 2.64 mmol, 72% yield) as a colourless solid; Rt 0.73 min (UPLC acidic); m/z 292 (M+H).sup.+(ES.sup.+); .sup.1H NMR (400 MHZ, DMSO-d.sub.6) δ 12.75 (s, 1H), 7.58 (s, 1H), 3.73 (s, 3H), 3.26 (s, 3H), 2.68-2.58 (m, 1H), 1.00-0.84 (m, 4H).

N-(4-Propionylthiazol-2-yl)cyclopropanesulfonamide INTE 5

##STR00034##

[0510] A suspension of 2-(cyclopropanesulfonamido)-N-methoxy-N-methylthiazole-4-carboxamide INTE 4 (2.5 g, 8.58 mmol) in THF (100 mL) at 40° C. was treated dropwise with 2 M EtM gCl (THF, 8.6 mL, 17.2 mmol). The reaction mixture was maintained at 40° C. for 18 hrs. The reaction mixture was quenched by addition of NH.sub.4Cl (sat. aq, 30 mL) followed by EtOAc (50 mL) and water (20 mL). The phases were partitioned and the aqueous layer was extracted with EtOAc (50 mL), the organic phases were combined, dried (Na.sub.2SO.sub.4), filtered and concentrated onto silica (10 g). The crude product was purified by chromatography on silica (24 g column, 0-50% EtOAc/iso-hexanes) to afford N-(4-propionylthiazol-2-yl)cyclopropanesulfonamide (1.9 g, 5.84 mmol, 68% yield) as an off white gum; Rt 1.24 min (HPLC acidic); m/z 261 (M+H).sup.+(ES.sup.+); .sup.1H NMR (400 M Hz, DMSO-d.sub.6) δ 12.92 (s, 1H), 7.95 (s, 1H), 2.86 (q, J=7.2 Hz, 2H), 2.68-2.58 (m, 1H), 1.05 (t, J=7.2 Hz, 3H), 0.97-0.80 (m, 4H).

N-(4-acetylthiazol-2-yl)cyclopropanesulfonamide INTE 21

##STR00035##

[0511] Prepared as for INTE 1 using commercial 1-(2-aminothiazol-4-yl) ethanone to afford N-(4-acetylthiazol-2-yl)cyclopropanesulfonamide (30% yield) as a yellow gum. Rt 1.00 (HPLC acidic); m/z 247 (M+H).sup.+(ES.sup.+); .sup.1H NMR (500 M Hz, DMSO-d.sub.6) δ 12.92 (s, 1H), 7.98 (s, 1H), 2.70-2.58 (m, 1H), 2.43 (s, 3H), 1.00-0.80 (m, 4H).

##STR00036##

[0512] A solution of aldehyde/ketone (1 eq.) in THF was treated with AcOH (1 eq.), amine (1 eq.) and a reducing agent such as STAB (1.2 eq.) and stirred at RT for 1 hr. The reaction mixture was quenched by addition of MeOH then loaded directly on to SCX (1 g/mmol of substrate), washed with MeOH and the product was eluted with 1 M NH.sub.3 in MeOH. The crude product was then concentrated onto silica and purified by normal phase chromatography.




TABLE-US-00001 TABLE 1 The following intermediates were made according to Method A.

Synthesis Method, [LCMS Method], Name/Structure m/z (All examples containing chiral centres (M + H).sup.+, .sup.1H NMR Chemical Shift Data INT are racemates unless stated) (Rt/min)

(DMSO-d.sub.6 unless stated) INTE6 N-(4-(((2,4- Using 7.23 (d, J = 8.3 Hz, 1H), 6.56 (d, J = dimethoxybenzyl)amino)methyl)thiazol-2- INTE2 2.4 Hz, 1H), 6.52 (d, J = 2.4 Hz,

yl)cyclopropanesulfonamide [00037]  [HPLC acidic], 384 (0.99). 1H), 6.50

(d, J = 2.3 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.74 (s, 2H), 3.63-3.61 (m, 2H), 2.49-2.45 (m, 1H), 0.89-0.72 (m, 4H), zwitterion, 2 × N—H not observed. INTE7 N-(4-(1-((2,4- Using 7.18 (d, J = 8.3


Hz, 1H), 6.59-6.37 dimethoxybenzyl)amino)propyl)thiazol-2- INTE5 (m, 3H), 3.76 (s, 3H), 3.75 (s, 3H), yl)cyclopropanesulfonamide [00038]  embedded image [UPLC acidic], 412 (0.62). 3.64-3.43 (m, 3H), 2.58-2.52 (m, 1H), 1.76-1.57 (m, 2H), 0.91- 0.81 (m, 4H), 0.78 (t, J = 7.4 Hz, 3H), 2 × N—H not observed. INTE8 N-(4-(1-((4- Using 12.11 (v. br. s, 1H), 7.26-7.18 (m, methoxybenzyl)(methyl)amino)propyl)thiazol- INTE5, 2H), 6.91-6.83 (m, 2H), 6.58 (s, 2-yl)cyclopropanesulfonamide [00039]  embedded image [HPLC basic], 396 (1.63). 1H), 3.73 (s, 3H), 3.55-3.42 (m, 2H), 3.39-3.26 (m, 1H), 2.65- 2.57 (m, 1H), 1.99 (s, 3H), 1.91- 1.57 (m, 2H), 0.97-0.84 (m, 5H), 0.75-0.65 (m, 2H). INTE22 N-(4-(1-((2,4- Using None recorded dimethoxybenzyl)amino)ethyl)thiazol-2- INTE21 yl)cyclopropanesulfonamide [00040]  embedded image [HPLC basic], 398 (1.43).



##STR00041##

[0513] Benzylamine derivative (1 eq.) was dissolved in TFA (50 eq.) and heated to 70° C. for 1-24 hrs. The reaction was allowed to cool to RT, then was loaded on to SCX (1 g/mmol of substrate) and washed with MeOH. The required compound was eluted with 1% NH.sub.3 in MeOH.

TABLE-US-00002 TABLE 2 The following intermediates were made according to Method B. Synthesis Method, [LCMS Name/Structure Method], (All examples containing chiral m/z (M + H).sup.+, .sup.1H NMR Chemical Shift Data INT centres are racemates unless stated) (Rt/min)

(DMSO-d.sub.6 unless stated) INTE9 N-(4-(aminomethyl)thiazol-2- yl)cyclopropanesulfonamide [00042]  embedded image Using INTE6, [UPLC basic], 234 (0.23). 6.44 (s, 1H), 3.79-3.70 (m, 2H), 2.46-2.33 (m, 1H), 0.85-0.75 (m, 2H), 0.74-0.61 (m, 2H), 3 x NH not observed. INTE10 N-(4-

(1-aminopropyl)thiazol-2- yl)cyclopropanesulfonamide [00043]  embedded image Using INTE7, [HPLC basic], 262 (M + H).sup.+ (ES+); (0.51). 8.00 (v. br. s, 3H), 6.43 (s, 1H), 3.98-3.73 (m, 1H, obscured by impurity), 2.42-2.28 (m, 1H), 1.92-1.62 (m, 2H), 0.95-0.40 (m, 7H). INTE11 N-(4-(1-(methylamino)propyl)thiazol- 2-yl)cyclopropanesulfonamide [00044]

 embedded image Using INTE8, [HPLC acidic], 276 (0.34). 6.49 (s, 1H), 3.70-3.57 (m, 1H), 2.44-2.34 (m, 1H), 2.32 (s, 3H), 1.82-1.69 (m, 2H), 0.84- 0.74 (m, 5H), 0.74-0.66 (m, 2H), 2 x NH not observed INTE23 N-(4-(1-aminoethyl)thiazol-2- yl)cyclopropanesulfonamide [00045]  embedded image Using INTE21, No Data recorded 6.39 (d, J = 0.8 Hz, 1H), 4.16-4.02 (m, 1H), 2.46-2.26 (m, 1H), 1.41 (d, J = 6.7 Hz, 3H), 0.84-0.73 (m, 2H), 0.72-0.56 (m, 2H), 3 x exchangeable N-H not observed.

N-(4-(2-Hydroxypropan-2-yl)thiazol-2-yl)cyclopropanesulfonamide INTE 12

##STR00046##

[0514] A solution of ethyl 2-(cyclopropanesulfonamido)thiazole-4-carboxylate INTE 1 (2.7 g, 9.77 mmol) in THF (30 mL) was cooled to 0° C. then MeM gBr (3.4 M in THF, 14.4 mL, 48.9 mmol) was added dropwise, over approx. 20 mins, maintaining the temperature below 10° C. Once addition was complete the reaction mixture was allowed to warm to RT and was stirred for 24 hrs. The reaction mixture was cooled with an ice bath and NH.sub.4Cl (sat. aq, 10 mL) was added cautiously, resulting in precipitate formation. 1 M HCl (aq, 50 mL) was added and the reaction mixture was extracted with EtOAc (3×50 mL). The organic phases were combined, dried (MgSO.sub.4), filtered and concentrated onto silica (10 g). The product was then purified by chromatography on silica (24 g column, 0-100% EtOA c/iso-hexanes) to afford N-(4-(2-hydroxypropan-2-yl)thiazol-2-yl)cyclopropanesulfonamide (1.03 g, 3.53 mmol, 36% yield) as a pale yellow solid: Rt 1.05 min (HPLC acidic); m/z 263 (M+H).sup.+(ES.sup.+); .sup.1H NMR (400 M Hz, DMSO-d.sub.6) δ 12.44 (s, 1H), 6.42 (s, 1H), 5.35 (s, 1H), 2.64-2.54 (m, 1H), 1.40 (s, 6H), 0.96-0.74 (m, 4H).

2-Chloro-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)acetamide INTE 13

##STR00047##

[0515] A mixture of N-(4-(2-hydroxypropan-2-yl)thiazol-2-yl)cyclopropanesulfonamide INTE 12 (500 mg, 1.91 mmol) and 2-chloroacetonitrile (0.72 mL, 11.4 mmol) in AcOH (0.87 mL, 15 mmol) was cooled in an ice bath before H.sub.2SO.sub.4 (0.92 mL, 17.2 mmol) was added. The reaction

was allowed to warm to RT and was stirred for 18 hrs. The solution was poured onto ice water (10 mL) and extracted with DCM (3×10 mL), partitioning with a phase separator. The crude product was purified by chromatography on silica (12 g column, 0-100% EtOAc/iso-hexanes) to afford 2-chloro-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)acetamide (574 mg, 1.61 mmol, 85% yield) as an orange gum; Rt 0.78 min (UPLC acidic); m/z 337 (.sup.35Cl M+H).sup.+ (ES.sup.+); .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 12.46 (s, 1H), 8.29 (s, 1H), 6.44 (s, 1H), 4.11-3.87 (m, 2H), 2.63-2.53 (m, 1H), 1.51 (s, 6H), 0.97-0.83 (m, 4H).

N-(4-(2-A minopropan-2-yl)thiazol-2-yl)cyclopropanesulfonamide INTE 14

##STR00048##

[0516] A suspension of thiourea (154 mg, 2.03 mmol) and 2-chloro-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)acetamide INTE 13 (570 mg, 1.69 mmol) in EtOH (8 mL) was treated with A cOH (1.6 mL, 28.7 mmol) and heated to reflux for 20 hrs. The reaction mixture was allowed to cool to RT. The resulting precipitate was filtered and the filtrate was loaded onto SCX (5 g), washed with MeOH and the required product was isolated by eluting with 1% NH.sub.3 in MeOH to afford N-(4-(2-aminopropan-2-yl)thiazol-2-yl)cyclopropanesulfonamide (479 mg, 1.80 mmol, quant. yield) as a slightly pink solid; Rt 0.50 min (UPLC basic); m/z 262 (M+H).sup.+(ES.sup.+); .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 6.38 (s, 1H), 2.44-2.21 (m, 1H), 1.49 (s, 6H), 0.89-0.35 (m, 4H), 3×H exchangeable protons were very broad and are not reported.

N-(4-(3-hydroxypentan-3-yl)thiazol-2-yl)cyclopropanesulfonamide INTE 15

##STR00049##

[0517] A solution of ethyl 2-(cyclopropanesulfonamido)thiazole-4-carboxylate INTE 1 (3 g, 10.86 mmol) in THF (50 mL) was cooled to 0° C., then EtM gBr (2 M in THF) (27.1 mL, 54.3 mmol) was added dropwise over approx. 20 mins, maintaining the temperature below 20° C. Once addition was complete the reaction mixture was warmed to RT and was stirred for 1 hr after which the reaction mixture was cooled with an ice bath and 1 M HCl (aq, 65 mL) was added cautiously. The aqueous layer was extracted with EtOAc (3×50 mL). The organic phases were combined, dried (Na.sub.2SO.sub.4), filtered and concentrated onto silica (10 g). The product was purified by chromatography on silica (24 g column, 0-100% EtOA c/iso-hexanes) to afford N-(4-(3-hydroxypentan-3-yl)thiazol-2-yl)cyclopropane sulfonamide (2.13 g, 6.97 mmol, 64% yield) as a colourless solid. Rt 0.86 min (UPLC, acidic); m/z 313.2 (M+Na).sup.+(ES.sup.+); .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 12.29 (s, 1H), 6.37 (s, 1H), 4.91 (s, 1H), 2.63-2.53 (m, 1H), 1.82-1.47 (m, 4H), 0.95-0.82 (m, 4H), 0.70 (t, J=7.3 Hz, 6H).

2-Chloro-N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)acetamide INTE 16

##STR00050##

[0518] A mixture of N-(4-(3-hydroxypentan-3-yl)thiazol-2-yl)cyclopropanesulfonamide INTE 15 (2.13 g, 7.33 mmol) and 2-chloroacetonitrile (2.8 mL, 44.5 mmol) in AcOH (3.4 mL, 59.4 mmol) was cooled in an ice bath before sulfuric acid (3.5 mL, 65.7 mmol) was added to afford a solution. The reaction was warmed to RT and was stirred for 18 hrs. The solution was poured onto ice water (100 mL) and extracted with DCM (3×100 mL) partitioning with a phase separator. The material was concentrated onto silica (20 g) and the crude product was purified by chromatography on silica (80 g column, 0-100% EtOA c/iso-hexanes) to afford 2-chloro-N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)acetamide (1.62 g, 4.21 mmol, 57% yield) as a colourless solid. Rt 0.76 min (UPLC, acidic); m/z 366.2 (35Cl M+H).sup.+(ES.sup.+); .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 12.36 (s, 1H), 7.99 (s, 1H), 6.44 (s, 1H), 4.09 (s, 2H), 2.62-2.53 (m, 1H), 2.05-1.86 (m, 2H), 1.80-1.66 (m, 2H), 0.95-0.83 (m, 4H), 0.69 (t, J=7.3 Hz, 6H).

N-(4-(3-aminopentan-3-yl)thiazol-2-yl)cyclopropanesulfonamide INTE 17

##STR00051##

[0519] A solution of thiourea (0.40 g, 5.25 mmol) and 2-chloro-N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)acetamide INTE 16 (1.6 g, 4.37 mmol) in

EtOH (20 mL) was treated with acetic acid (4.3 mL, 75 mmol) and heated to reflux for 18 hrs. The reaction mixture was cooled to RT, the resulting precipitate was filtered and the filtrate was loaded onto SCX (50 g), washed with MeOH and the product was isolated by eluting with 1% NH₃ in MeOH to afford N-(4-(3-aminopentan-3-yl)thiazol-2-yl)cyclopropanesulfonamide (1.05 g, 3.27 mmol, 75% yield) as a colourless solid. Rt 0.56 min (HPLC, basic); m/z 273.0 (M-NH₂+H)⁺ (ES⁺); ¹H NMR (400 MHz, DMSO-d₆) δ 7.70 (v. br s, 3H), 6.34 (s, 1H), 2.41-2.29 (m, 1H), 1.80 (app. q, J=7.4 Hz, 4H), 0.83-0.76 (m, 6H), 0.73-0.60 (m, 4H).

Methyl 2-(2-bromothiazol-4-yl)-4-methoxybutanoate INTE 24

##STR00052##

[0520] To an ice cold solution of commercial methyl 2-(2-bromothiazol-4-yl)acetate (5.0 g, 21.9 mmol) in DMF (30 mL) was added NaH (60 wt % in mineral oil 0.93 g, 23.3 mmol) portion-wise over 5 min. The resulting mixture was allowed to warm to RT under vigorous stirring for 10 min, then cooled to 0° C. before a solution of 1-bromo-2-methoxyethane (2.09 mL, 22.24 mmol) in DMF (15 mL) was added dropwise over 1 min. The resulting mixture was allowed to warm to RT and stirred for 2 hrs. The mixture was carefully poured into sat. NH₄Cl (aq, 100 mL) and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed in vacuo. The crude product was purified by chromatography on silica gel (120 g column, 0-20% EtOAc/iso-hexane) to afford methyl 2-(2-bromothiazol-4-yl)-4-methoxybutanoate (3.35 g, 11.27 mmol, 53% yield) as an orange oil. Rt 1.14 (UPLC acidic); m/z 296 (81Br M+H)⁺ (ES⁺); ¹H NMR (500 MHz, DMSO-d₆) δ 7.59 (s, 1H), 3.96 (t, J=7.5 Hz, 1H), 3.61 (s, 3H), 3.31-3.19 (m, 2H), 3.18 (s, 3H), 2.26-2.14 (m, 1H), 2.09-1.95 (m, 1H).

2-(2-Bromothiazol-4-yl)-4-methoxybutanoic acid INTE 25

##STR00053##

[0521] Prepared as for INTE 3 using methyl 2-(2-bromothiazol-4-yl)-4-methoxybutanoate INTE 24 to afford 2-(2-bromothiazol-4-yl)-4-methoxybutanoic acid (99% yield) as a white solid. Rt 0.92 (UPLC acidic); m/z 280 (.sup.79Br M+H)⁺ (ES⁺); ¹H NMR (500 MHz, DMSO-d₆) δ 12.55 (s, 1H), 7.54 (s, 1H), 3.84 (t, J=7.4 Hz, 1H), 3.30-3.26 (m, 1H), 3.26-3.20 (m, 1H), 3.20 (s, 3H), 2.21-2.12 (m, 1H), 2.02-1.93 (m, 1H).

Ethyl 2-(cyclopropanesulfonamido)-5-methylthiazole-4-carboxylate INTE 26

##STR00054##

[0522] Prepared as for INTE 1 using commercial ethyl 2-amino-5-methylthiazole-4-carboxylate to afford ethyl 2-(cyclopropanesulfonamido)-5-methylthiazole-4-carboxylate (43% yield) as an off-white solid. Rt 1.60 (HPLC acidic); m/z 291 (M+H)⁺ (ES⁺); ¹H NMR (500 MHz, DMSO-d₆) δ 12.78 (s, 1H), 4.27 (q, J=7.1 Hz, 2H), 2.68-2.58 (m, 1H), 2.49 (s, 3H), 1.30 (t, J=7.1 Hz, 3H), 0.98-0.66 (m, 4H).

Methyl 5-chloro-2-(cyclopropanesulfonamido)thiazole-4-carboxylate INTE 27

##STR00055##

[0523] Prepared as for INTE 1 using commercial methyl 2-amino-5-chlorothiazole-4-carboxylate to afford methyl 5-chloro-2-(cyclopropanesulfonamido)thiazole-4-carboxylate (29% yield) as an off-white solid. Rt 1.63 (HPLC acidic); m/z 297 (.sup.35Cl M+H)⁺ (ES⁺); ¹H NMR (500 MHz, DMSO-d₆) δ 13.07 (v. br s, 1H), 3.84 (s, 3H), 2.81-2.68 (m, 1H), 1.03-0.90 (m, 4H).

N-(4-(2-Hydroxypropan-2-yl)-5-methylthiazol-2-yl)cyclopropanesulfonamide INTE 28

##STR00056##

[0524] Prepared as for INTE 12 using ethyl 2-(cyclopropanesulfonamido)-5-methylthiazole-4-carboxylate INTE 26 to afford N-(4-(2-hydroxypropan-2-yl)-5-methylthiazol-2-yl)cyclopropanesulfonamide (37% yield) as an off-white solid. Rt 1.29 (HPLC acidic); m/z 277 (M+H)⁺ (ES⁺); ¹H NMR (500 MHz, DMSO-d₆) δ 11.84 (s, 1H), 5.36 (s, 1H), 2.61-2.51 (m, 1H), 2.27 (s, 3H), 1.43 (s, 6H), 0.90-0.73 (m, 4H).

N-(5-Chloro-4-(2-hydroxypropan-2-yl)thiazol-2-yl)cyclopropanesulfonamide INTE 29

##STR00057##

[0525] Prepared as for INTE 12 using methyl 5-chloro-2-(cyclopropanesulfonamido)thiazole-4-carboxylate INTE 27 to afford N-(5-chloro-4-(2-hydroxypropan-2-yl)thiazol-2-yl)cyclopropanesulfonamide (44% yield) as an off-white solid. Rt 1.57 (HPLC acidic); m/z 297 (35Cl M+H).sup.+(ES.sup.+); .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 12.27 (s, 1H), 5.63 (s, 1H), 2.69-2.59 (m, 1H), 1.49 (s, 6H), 1.01-0.84 (m, 4H).

2-Chloro-N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)acetamide INTE 30

##STR00058##

[0526] Prepared as for INTE 13 using N-(4-(2-hydroxypropan-2-yl)-5-methylthiazol-2-yl)cyclopropanesulfonamide INTE 28 to afford 2-chloro-N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)acetamide (95% yield) as a yellow gum. Rt 1.36 (HPLC acidic); m/z 352 (35Cl M+H).sup.+(ES.sup.+); .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 11.85 (s, 1H), 8.46 (s, 1H), 4.06 (s, 2H), 2.59-2.52 (m, 1H), 2.15 (s, 3H), 1.55 (s, 6H), 0.99-0.83 (m, 4H).

2-Chloro-N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)acetamide INTE 31

##STR00059##

[0527] Prepared as for INTE 13 using N-(5-chloro-4-(2-hydroxypropan-2-yl)thiazol-2-yl)cyclopropanesulfonamide INTE 29 to afford 2-chloro-N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)acetamide (97% yield) as a yellow gum. Rt 1.61 (HPLC acidic); m/z 372 (35Cl M+H).sup.+(ES.sup.+); .sup.1H NMR (500 M Hz, DMSO-d.sub.6) δ 12.33 (s, 1H), 8.59 (s, 1H), 4.07 (s, 2H), 2.74-2.63 (m, 1H), 1.58 (s, 6H), 1.00-0.89 (m, 4H).

N-(4-(2-A minopropan-2-yl)-5-methylthiazol-2-yl)cyclopropanesulfonamide INTE 32

##STR00060##

[0528] Prepared as for INTE 14 using 2-chloro-N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)acetamide INTE 30 to afford N-(4-(2-aminopropan-2-yl)-5-methylthiazol-2-yl)cyclopropanesulfonamide (50% yield) as a white solid. Rt 1.23 (HPLC basic); m/z 276 (M+H).sup.+(ES.sup.+); .sup.1H NMR (500 M Hz, DMSO-d.sub.6) δ 7.87 (s, 3H), 2.39-2.27 (m, 1H), 2.20 (s, 3H), 1.51 (s, 6H), 0.84-0.69 (m, 2H), 0.69-0.56 (m, 2H).

N-(4-(2-A minopropan-2-yl)-5-chlorothiazol-2-yl)cyclopropanesulfonamide INTE 33

##STR00061##

[0529] Prepared as for INTE 14 using 2-chloro-N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)acetamide INT 31 to afford N-(4-(2-aminopropan-2-yl)-5-chlorothiazol-2-yl)cyclopropanesulfonamide (37% yield) as a white solid. Rt 1.23 (HPLC basic); m/z 296 (.sup.35Cl M+H).sup.+(ES.sup.+); .sup.1H NMR (500 M Hz, DMSO-d.sub.6) δ 8.21 (s, 3H), 2.36-2.23 (m, 1H), 1.58 (s, 6H), 0.80-0.73 (m, 2H), 0.73-0.61 (m, 2H).

tert-Butyl (1-(2-bromothiazol-4-yl)cyclopropyl)carbamate INTE 34

##STR00062##

[0530] A suspension of commercial 1-(2-bromothiazol-4-yl)cyclopropanecarboxylic acid (2.95 g, 11.9 mmol) in toluene (30 mL) was treated with t-BuOH (30 mL) and triethylamine (1.8 mL, 12.91 mmol) and then heated to 40° C. whereupon a solution was observed, DPPA (2.7 mL, 11.90 mmol) was then added. The reaction mixture was then heated to 100° C. for 3 hrs then allowed to cool to RT. The reaction mixture was then treated with sat. NaHCO.sub.3(aq, 100 mL) and EtOAc (100 mL). The phases were separated and the organic phase washed with brine (20 mL), dried over Na.sub.2SO.sub.4, filtered and concentrated. The crude product was purified by chromatography on silica gel (40 g column, 0-100% EtOA c/iso-hexane) to afford tert-butyl (1-(2-bromothiazol-4-yl)cyclopropyl)carbamate (1.26 g, 3.55 mmol, 30% yield) as a colourless solid. Rt 1.23 (UPLC acidic); m/z 264 (.sup.79Br M+H-tBu).sup.+(ES.sup.+); .sup.1H NMR (500 M Hz, DMSO-

d.sub.6) δ 7.76 (s, 1H), 7.14 (s, 1H), 1.40 (s, 9H), 1.26-1.21 (m, 2H), 1.12-1.05 (m, 2H).

tert-Butyl (1-(2-bromothiazol-4-yl)-3-methoxypropyl)carbamate INT E 35

##STR00063##

[0531] Prepared as for INTE 34 using 2-(2-bromothiazol-4-yl)-4-methoxybutanoic acid INTE 25 to afford tert-butyl (1-(2-bromothiazol-4-yl)-3-methoxypropyl)carbamate (28% yield) as a colourless solid. Rt 1.38 (UPLC basic); m/z 251 (M+H-tBu).sup.+(ES.sup.+); .sup.1H NMR (500 M Hz, DMSO-d.sub.6) δ 7.37 (s, 1H), 7.32 (d, J=8.7 Hz, 1H), 4.75-4.66 (m, 1H), 3.37-3.24 (m, 2H), 3.20 (s, 3H), 2.05-1.93 (m, 1H), 1.88-1.76 (m, 1H), 1.38 (s, 9H).

tert-Butyl (1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)carbamate INTE 36

##STR00064##

[0532] A suspension of cyclopropanesulfonamide (500 mg, 4.13 mmol), tert-butyl (1-(2-bromothiazol-4-yl)cyclopropyl)carbamate (1.26 g, 3.95 mmol) INTE 34 and Cs.sub.2CO.sub.3 (4.0 g, 12.9 mmol) in dioxane (10 mL) was degassed (N.sub.2). To this suspension was added a degassed (N.sub.2) solution of t-BuX Phos (170 mg, 0.40 mmol) and [Pd(allyl)Cl].sub.2 (75 mg, 0.204 mmol) in dioxane (5 ml). The reaction mixture was stirred at 90° C. for 18 hrs. An additional degassed (N.sub.2) solution of t-BuX Phos (170 mg, 0.400 mmol) and [Pd(allyl)Cl].sub.2 (75 mg, 0.204 mmol) in dioxane (5 mL) was then added to the reaction mixture and the temperature was maintained at 90° C. for 18 hrs. The reaction mixture was cooled to RT then diluted with EtOAc (100 ml) and acidified with 1M HCl (50 mL). The phases were separated and the organic phase washed with brine (50 mL). The organic phase was dried over Na.sub.2SO.sub.4, filtered and concentrated onto silica (5 g). The crude product was purified by chromatography on silica gel (40 g column, 0-100% EtO Ac/iso-hexane) to afford tert-butyl (1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)carbamate (427 mg, 1.13 mmol, 29% yield) as a colourless solid. Rt 1.72 (HPLC acidic); m/z 360 (79Br M+H).sup.+(ES.sup.+); .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 12.12 (s, 1H), 7.57 (s, 1H), 6.27 (s, 1H), 2.61-2.54 (m, 1H), 1.37 (s, 9H), 1.25-1.19 (m, 2H), 1.09-1.00 (m, 2H), 0.99-0.85 (m, 4H).

tert-Butyl (1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)carbamate INTE 37

##STR00065##

[0533] Prepared as for INTE 36 using tert-butyl (1-(2-bromothiazol-4-yl)-3-methoxypropyl)carbamate INT E 35 to afford tert-butyl (1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)carbamate (47% yield) as a colourless solid. Rt 1.71 (HPLC acidic); m/z 392 (M+H).sup.+(ES.sup.+); .sup.1H NMR (500 M Hz, DMSO-d.sub.6) δ 12.48 (s, 1H), 7.17 (d, J=8.7 Hz, 1H), 6.43 (s, 1H), 4.57-4.44 (m, 1H), 3.39-3.25 (m, 2H), 3.21 (s, 3H), 2.63-2.55 (m, 1H), 2.00-1.86 (m, 1H), 1.84-1.67 (m, 1H), 1.39 (s, 9H), 0.99-0.81 (m, 4H).

N-(4-(1-A minocyclopropyl)thiazol-2-yl)cyclopropanesulfonamide, HCl INTE 38

##STR00066##

[0534] tert-Butyl (1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)carbamate (427 mg, 1.13 mmol) INTE 36 was dissolved in 4M HCl in dioxane (5 mL) then stirred at RT for 1 hr. The reaction mixture was then concentrated in vacuo and the residue azeotroped with toluene (5 ml) then MeCN (2×5 mL) to afford N-(4-(1-aminocyclopropyl)thiazol-2-yl)cyclopropanesulfonamide, HCl (340 mg, 0.92 mmol, 82% yield) as a brown solid. Rt 0.25 (HPLC acidic); m/z 260 (M+H).sup.+(ES.sup.+); .sup.1H NMR data not collected.


N-(4-(1-A mino-3-methoxypropyl)thiazol-2-yl)cyclopropanesulfonamide, HCl INTE 39


##STR00067##


[0535] Prepared as for INTE 37 using tert-butyl (1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)carbamate to afford N-(4-(1-amino-3-methoxypropyl)thiazol-2-yl)cyclopropanesulfonamide, HCl (quantitative yield) as a colourless solid. Rt 0.84 (HPLC basic); m/z 292 (M+H).sup.+(ES.sup.+); .sup.1H NMR data not collected.

TABLE-US-00003 TABLE 3 The following intermediates were made according to Method 1a or 1b (see preparation of examples section for details). Synthesis Method, [LCMS Method],

Name/Structure m/z (All examples containing chiral centres (M + H).sup.+, .sup.1H NMR Chemical Shift Data INT are racemates unless stated) (Rt/min) (DMSO-d.sub.6 unless stated)

INTE18 4-Bromo-N-(2-(2- (cyclopropanesulfonamido)thiazol-4- yl)propan-2-yl)-2-methoxybenzamide [00068]  Method 1b, Using INTE 14, [UPLC acidic], 474 (1.27). 12.52 (s, 1H), 8.24 (s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 1.8 Hz, 1H), 7.26 (dd, J = 8.3, 1.8 Hz, 1H), 6.49 (s, 1H), 3.96 (s, 3H), 2.61- 2.54 (m, 1H), 1.61 (s, 6H), 0.94-0.84 (m, 4H).

INTE19 N-(2-(2- (Cyclopropanesulfonamido)thiazol-4- yl)propan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzamide [00069]  Method 1a, Using INTE 14, [UPLC acidic], 492 (1.38). 12.55 (s, 1H), 8.27 (s, 1H), 7.90-7.85 (m, 2H), 7.76-7.71 (m, 2H), 6.46 (s, 1H), 2.60 2.52 (m, 1H), 1.61 (s, 6H), 1.31 (s, 12H), 0.92- 0.79 (m, 4H).

INTE20 N-(2-(2- (Cyclopropanesulfonamido)thiazol-4- yl)propan-2-yl)-2-fluoro-4-(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2- yl)benzamide [00070]  Method 1a, Using INTE 14, [UPLC acidic], 510 (1.44). 12.57 (s, 1H), 8.35-8.27 (m, 1H), 7.78- 7.70 (m, 1H), 7.56-7.50 (m, 1H), 7.43 7.35 (m, 1H), 6.47 (s, 1H), 2.63-2.54 (m, 1H), 1.60 (s, 6H), 1.31 (s, 12H), 0.93-0.82 (m, 4H).

Synthesis of Biaryl Acids and their Intermediates

2-Ethoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazine INTF1

##STR00071##

[0536] To a solution of 2-chloro-6-ethoxypyrazine (10.0 g, 59.9 mmol) in dioxane (200 mL) was successively added bispin (16.7 g, 65.9 mmol), KOAc (23.5 g, 240 mmol) and PdCl.sub.2 (dppf)-CH.sub.2Cl.sub.2 (2.45 g, 3.00 mmol) at RT. The resulting mixture was degassed (N.sub.2) before heating at 110° C. for 2.5 hrs. The mixture was cooled to RT, filtered through celite and the solvent was removed in vacuo. The crude product was purified by chromatography on silica (220 g cartridge, 20-100% EtOA c/iso-hexanes). The crude product was then dissolved in EtOAc (20 mL) and washed with water (3×10 mL). The organic layer was dried (Na.sub.2SO.sub.4), filtered and the solvent was removed in vacuo. The product was re-purified by chromatography on silica (330 g cartridge, 0-100% EtO A c/iso-hexanes) and the product was dissolved in EtOAc (50 mL) and washed with water (4×30 mL). The organic layer was dried (Na.sub.2SO.sub.4), filtered and concentrated in vacuo to afford 2-ethoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazine (2.0 g, 7.60 mmol, 13% yield) as a thick pale yellow oil. .sup.1H NMR (500 M Hz, DMSO-d.sub.6) δ 8.38 (s, 1H), 8.30 (s, 1H), 4.36 (q, J=7.1 Hz, 2H), 1.34 (t, J=7.1 Hz, 3H), 1.32 (s, 12H).

Methyl 4-(6-ethoxypyrazin-2-yl)-2-methylbenzoate INTF2

##STR00072##

[0537] A solution of 2-ethoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazine INTF1 (200 mg, 0.80 mmol), methyl 4-bromo-2-methylbenzoate (183 mg, 0.80 mmol) and Cs.sub.2CO.sub.3 (700 mg, 2.15 mmol) in a mixture of dioxane (5 mL) and water (1 mL) at 35° C. was degassed (N.sub.2) then PdCl.sub.2 (dppf)-CH.sub.2Cl.sub.2 (35 mg, 0.043 mmol) was added. The mixture was degassed (N.sub.2) then heated to 90° C. for 18 hrs. The reaction mixture was concentrated (to approx. 2 mL) then taken up with water (5 mL) and EtOAc (10 mL) and filtered through celite, eluting with EtOAc (20 mL). The phases were then diluted with water (10 mL) and partitioned. The organic phase was washed with brine (10 mL), dried (Na.sub.2SO.sub.4), filtered and concentrated onto silica (1 g). The crude product was purified by chromatography on silica (40 g cartridge, 0-30% EtOAc/iso-hexanes to afford methyl 4-(6-ethoxypyrazin-2-yl)-2-methylbenzoate (124 mg, 0.45 mmol, 56% yield) as a colourless solid. Rt 2.54 min (HPLC, acidic); m/z 273 (M+H).sup.+ (ES.sup.+); .sup.1H NMR (500 MHZ, DMSO-d.sub.6) δ 8.88 (s, 1H), 8.29 (s, 1H), 8.11-8.08 (m, 1H), 8.05 (dd, J=8.2, 1.8 Hz, 1H), 7.95 (d, J=8.2 Hz, 1H), 4.49 (q, J=7.0 Hz, 2H), 3.86 (s, 3H), 2.61 (s, 3H), 1.41 (t, J=7.0 Hz, 3H).

Methyl 2-fluoro-4-(6-vinylpyrazin-2-yl)benzoate INTF3

##STR00073##

[0538] A stirred solution of potassium trifluoro (vinyl) borate (900 mg, 6.72 mmol), 2,6-dichloropyrazine (1 g, 6.71 mmol) and 2 M K.sub.2CO.sub.3 (10 mL, 20.0 mmol) in dioxane (80

mL) at 40° C. was degassed (N.sub.2) then treated with PdCl.sub.2(dppf)-CH.sub.2Cl.sub.2 (274 mg, 0.336 mmol), degassed (N.sub.2), then heated to 80° C. for 4 hrs. The reaction mixture was cooled to RT then (3-fluoro-4-(methoxycarbonyl)phenyl)boronic acid (1.33 g, 6.71 mmol) was added and the reaction mixture was heated to 100° C. for 18 hrs. The reaction mixture was cooled and concentrated (to approx. 10 mL). 1 M HCl (100 mL) and EtOAc (100 mL) were added and the reaction mixture was filtered through celite, further eluting with EtOAc (50 mL). The phases were partitioned and the organic phase was washed with brine (50 mL). The organic phase was dried (MgSO.sub.4), filtered and concentrated onto silica (5 g). The crude product was purified by chromatography on silica (40 g cartridge, 0-50% EtOAc/iso-hexanes) to afford methyl 2-fluoro-4-(6-vinylpyrazin-2-yl)benzoate (490 mg, 1.803 mmol, 27% yield) as a brown gum. Rt 2.24 min (HPLC, acidic); m/z 259 (M+H).sup.+(ES.sup.+); .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 9.27 (s, 1H), 8.83 (s, 1H), 8.19 (d, J=1.0 Hz, 1H), 8.18-8.15 (m, 1H), 8.08-7.99 (m, 1H), 6.98 (dd, J=17.5, 10.9 Hz, 1H), 6.56 (dd, J=17.5, 1.3 Hz, 1H), 5.74 (dd, J=10.9, 1.4 Hz, 1H), 3.90 (s, 3H).









Methyl 4-(6-ethylpyrazin-2-yl)-2-fluorobenzoate INTF4












##STR00074##

[0539] A solution of methyl 2-fluoro-4-(6-vinylpyrazin-2-yl)benzoate INT F 3 (490 mg, 1.88 mmol) in MeOH (10 mL) was prepared. The reaction mixture was hydrogenated in the H-Cube (10% Pd/C, 30×4 mm, full hydrogen, 35° C., 1 mL/min). The reaction mixture was concentrated to afford methyl 4-(6-ethylpyrazin-2-yl)-2-fluorobenzoate (470 mg; 1.77 mmol; 93% yield); Rt 2.27 min (HPLC, acidic); m/z 261 (M+H).sup.+(ES.sup.+); .sup.1H NMR (500 M Hz, DMSO-d.sub.6) δ 9.20 (s, 1H), 8.63 (s, 1H), 8.15-8.09 (m, 2H), 8.07-8.00 (m, 1H), 3.89 (s, 3H), 2.89 (q, J=7.6 Hz, 2H), 1.32 (t, J=7.6 Hz, 3H).

##STR00075##

[0540] A solution of boronic acid (1 eq), aryl halide (1.05 eq.) and CS.sub.2CO.sub.3 (3 eq.) in a mixture of dioxane (40 volumes) and water (6 volumes) was degassed (N.sub.2, 5 mins). PdCl.sub.2(dppf).Math.CH.sub.2Cl.sub.2 (5 mol %) was added and the reaction was further degassed (N.sub.2) before being heated to 90° C. for 18 hrs. The reaction mixture was filtered through celite before an aqueous workup was undertaken, followed by purification by normal phase chromatography.

TABLE-US-00004 TABLE 4 The following intermediates were made according to Method C. Synthesis Method, [LCMS Method], m/z (M + H).sup.+, .sup.1H NMR Chemical Shift Data INT Name/Structure (Rt/min) (DM SO-d.sub.6 unless stated) INTF5 tert-butyl 4-(5-methylpyridin-3-yl) benzoate [00076]  Using Ar2Br, [HPLC acidic], 270 (1.93). 8.75 (d, J = 2.2 Hz, 1H), 8.51- 8.39 (m, 1H), 8.03-7.98 (m, 3H), 7.88-7.82 (m, 2H), 2.4 (s, 3H), 1.57 (s, 9H). INTF6 tert-butyl 4-(5-(trifluoromethyl)pyridin-3- yl)benzoate [00077]  Using Ar2Br, [HPLC acidic], 324 (2.78). 9.27 (d, J = 2.2 Hz, 1H), 9.03 (dd, J = 2.2, 1.0 Hz, 1H), 8.61- 8.41 (m, 1H), 8.22-7.83 (m, 4H), 1.58 (s, 9H). INTF7 tert-butyl 4-(5-fluoropyridin-3-yl)benzoate [00078]  Using Ar2Br, [HPLC acidic], 274 (2.56). 8.87 (d, J = 1.9 Hz, 1H), 8.64 (d, J = 2.7 Hz, 1H), 8.22-8.09 (m, 1H), 8.06-7.98 (m, 2H), 7.98- 7.89 (m, 2H), 1.57 (s, 9H). INTF8 tert-butyl 4-(6-chloropyrazin-2-yl)benzoate [00079]  Using Ar2Cl, [UPLC acidic], 290 .sup.35Cl isotope, (1.53). No .sup.1H NMR recorded. INTF9 tert-butyl 4-(6-(trifluoromethyl)pyrazin-2- yl)benzoate [00080]  Using Ar2Cl, [HPLC acidic], no ionisation (2.83). 9.70 (s, 1H), 9.23 (s, 1H), 8.40- 8.30 (m, 2H), 8.12-8.03 (m, 2H), 1.59 (s, 9H). INTF10 tert-butyl 4-(6-methylpyrazin-2-yl) benzoate [00081]  Using Ar2Cl, [HPLC acidic], 271 (2.54). 9.24-9.02 (m, 1H), 8.57 (s, 1H), 8.44-8.14 (m, 2H), 8.14-7.68 (m, 2H), 2.63-2.52 (m, 3H), 1.57 (s, 9H). INTF11 tert-butyl 4-(6-isopropoxy pyrazin-2- yl)benzoate [00082]  Using Ar2Cl, [UPLC acidic], 315 (1.97). 8.86 (s, 1H), 8.30-8.21 (m, 3H), 8.06-8.02 (m, 2H), 5.41 (hept, J = 6.2 Hz, 1H), 1.58 (s, 9H), 1.40 (d, J = 6.2 Hz, 6H). INTF12 methyl 4-(5-chloropyridin-3-yl) benzoate [00083]  Using Ar2Cl, [HPLC

acidic], 247 .sup.35Cl isotope, (2.20). 8.94 (d, J = 2.0 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.35 (t, J = 2.2 Hz, 1H), 8.10-8.01 (m, 2H), 8.00- 7.89 (m, 2H), 3.89 (s, 3H). INTF13 methyl 2-fluoro-4-(5-(trifluoromethyl)pyridin-3-yl)benzoate [00084]  Using Ar2Cl [HPLC acidic], 300 (2.30). No .sup.1H NMR recorded. INTF14 methyl 4-(5-chloropyridin-3-yl)-2- fluorobenzoate [00085]  Using Ar2Br [HPLC acidic], 266 .sup.35Cl isotope (2.20). No .sup.1H NMR recorded. INTF15 methyl 2-fluoro-4-(6- (trifluoromethyl)pyrazin-2-yl)benzoate [00086]  Using Ar2Cl, [UPLC acidic], 301 (1.53). 9.73 (s, 1H), 9.25 (s, 1H), 8.23- 8.13 (m, 2H), 8.09 (dd, J = 8.5, 7.5 Hz, 1H), 3.90 (s, 3H). INTF16 methyl 4-(6-ethoxypyrazin-2-yl)-2- fluorobenzoate [00087]  Using Ar2Cl, [UPLC acidic], 277 (1.53). 8.94 (s, 1H), 8.34 (s, 1H), 8.12- 8.08 (m, 2H), 8.04-8.00 (m, 1H), 4.50 (q, J = 7.0 Hz, 2H), 3.89 (s, 3H), 1.41 (t, J = 7.0 Hz, 3H). INTF17 methyl 2-fluoro-4-(6-isopropoxy pyrazin-2-yl)benzoate [00088]  Using Ar2Cl, [UPLC acidic], 291 (1.63). 8.91 (s, 1H), 8.28 (s, 1H), 8.13- 7.94 (m, 3H), 5.43 (hept, J = 6.1 Hz, 1H), 3.89 (s, 3H), 1.39 (d, J = 6.2 Hz, 6H). INTF18 tert-butyl 4-(6-ethoxypyrazin-2-yl)benzoate [00089]  Using Ar2Cl, [HPLC acidic], 301 (2.89). 8.87 (s, 1H), 8.30 (s, 1H), 8.26- 8.22 (m, 2H), 8.06-7.98 (m, 2H), 4.48 (q, J = 7.1 Hz, 2H), 1.57 (s, 9H), 1.40 (t, J = 7.0 Hz, 3H). INTF19 methyl 2-fluoro-4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)benzoate [00090]  Using Ar2Cl, [HPLC acidic], 331 (2.44). 9.11 (s, 1H), 8.56 (s, 1H), 8.23 (dd, J = 12.3, 1.7 Hz, 1H), 8.18 (dd, J = 8.2, 1.7 Hz, 1H), 8.06-8.01 (m, 1H), 5.24 (q, J = 9.0 Hz, 2H), 3.90 (s, 3H). INTF20 tert-butyl 4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl) benzoate [00091]  Using Ar2Cl, [UPLC acidic], 355 (2.88) 9.06 (s, 1H), 8.52 (s, 1H), 8.44- 8.24 (m, 2H), 8.06-8.01 (m, 2H), 5.22 (q, J = 9.0 Hz, 2H), 1.58 (s, 9H). INTF21 methyl 4-(6-ethoxypyrazin-2-yl)-2- (trifluoromethyl) benzoate [00092]  Using Ar2Cl, [UPLC acidic], 327 (2.59) 9.01 (d, J = 1.6 Hz, 1H), 8.56-8.52 (m, 2H), 8.37 (d, J = 1.6 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 4.58-4.41 (m, 2H), 3.91 (s, 3H), 1.42 (t, J = 7.0 Hz, 3H). INTF22 methyl 2-methyl-4-(6- (trifluoromethyl)pyrazin-2-yl)benzoate [00093]  Using Ar2Cl, [UPLC acidic], 297 (1.62) 9.69 (s, 1H), 9.21 (s, 1H), 8.19 (d, J = 1.8 Hz, 1H), 8.14 (dd, J = 8.2, 1.8 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H), 3.88 (s, 3H), 2.64 (s, 3H). INTF23 5-(6-ethoxypyrazin-2-yl)-3- fluoropicolinonitrile [00094]  Using Ar2Cl, [HPLC acidic], 245 (2.17) 9.38 (t, J = 1.6 Hz, 1H), 9.05 (s, 1H), 8.76 (dd, J = 10.2, 1.6 Hz, 1H), 8.43 (s, 1H), 4.53 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H).

##STR00095##



[0541] A solution of the ester (1 eq) in DCM (20 volumes) was treated with TFA (10 eq.) and stirred at RT for 3 hrs. The reaction mixture was then concentrated and azeotroped with MeOH and MeCN. No further purification was undertaken.



















##STR00096##

[0542] A solution of the ester (1 eq) in a mixture of THF/MeOH (4/1 volumes) was treated with LiOH (2.2-6 eq.) and stirred between RT and 50° C. for between 3 hrs and 18 hrs. The organic solvents were removed in vacuo then acidified with 1 M HCl and extracted with EtOAc. The organic phases were combined, dried (Na.sub.2SO.sub.4), filtered and concentrated. The products were used directly in the next step with no further purification undertaken.

##STR00097##

[0543] A solution of the ester (1 eq.) in THF (4 volumes) was treated with™ SOK (1 eq.) and stirred at RT for 2 hrs before the reaction mixtures were filtered and washed with iso-hexanes. The products were used directly in the next step with no further purification undertaken.

TABLE-US-00005 TABLE 5 The following intermediates were made according to Method D, E or F. Synthesis Method, [LCMS Method], .sup.1H NMR Chemical Shift m/z (M + H).sup.+, Data INT Name/Structure (Rt/min) (DMSO-d.sub.6 unless stated) INTF24 [00098]  Method D, Using INTF5, [HPLC acidic], 214 (0.95). 9.02-8.94 (m, 1H), 8.70- 8.63 (m, 1H), 8.47 (s, 1H), 8.14-8.06 (m, 2H), 8.00- 7.90 (m, 2H), 2.49 (s, 3H), OH not observed. 4-(5-methylpyridin-3-yl)benzoic acid INTF25 [00099]  Method D, Using INTF6, [HPLC acidic],

268 (2.01). 13.12 (s, 1H), 9.28 (d, J = 2.2 Hz, 1H), 9.03 (dd, J = 2.2, 1.0 Hz, 1H), 8.56 (d, J = 2.2 Hz, 1H), 8.13-8.04 (m, 2H), 8.04-7.86 (m, 2H). 4-(5-(trifluoromethyl)pyridin-3-yl)benzoic acid INTF26 [00100]  Method D, Using INTF7, [HPLC acidic], 218 (1.67). 8.87 (t, J = 1.8 Hz, 1H), 8.64 (d, J = 2.7 Hz, 1H), 8.17 (ddd, J = 10.3, 2.7, 1.8 Hz, 1H), 8.07-8.03 (m, 2H), 7.97-7.90 (m, 2H), OH not observed. 4-(5-fluoropyridin-3-yl)benzoic acid INTF27 [00101]  Method D, Using INTF8, [HPLC acidic], 234 .sup.35Cl isotope, (1.91). No NMR recorded. 4-(6-chloropyrazin-2-yl)benzoic acid INTF28 [00102]  Method D, Using INTF9, [UPLC acidic], 269 (1.33). 13.25 (s, 1H), 9.70 (s, 1H), 9.23 (s, 1H), 8.42-8.20 (m, 2H), 8.20-8.00 (m, 2H). 4-(6-(trifluoromethyl)pyrazin-2-yl)benzoic acid INTF29 [00103]  Method D, Using INTF10, [HPLC acidic], 215 (1.60). 9.13 (s, 1H), 8.57 (s, 1H), 8.31-8.23 (m, 2H), 8.09- 8.04 (m, 2H), 2.59 (s, 3H), OH not observed. 4-(6-methylpyrazin-2-yl)benzoic acid INTF30 [00104]  Method D, Using INTF11, [UPLC acidic], 259 (1.40). 13.13 (s, 1H) 8.87 (s, 1H), 8.27-8.20 (m, 3H), 8.09- 8.05 (m, 2H), 5.43 (p, J = 6.2 Hz, 1H), 1.40 (d, J = 6.2 Hz, 6H). 4-(6-isopropoxy pyrazin-2-yl)benzoic acid INTF31 [00105]  Method F, Using INTF12, [UPLC acidic], 234 .sup.35Cl isotope, ionises as free acid, (1.18). 8.87 (d, J = 2.0 Hz, 1H), 8.59 (d, J = 2.2 Hz, 1H), 8.23 (t, J = 2.2 Hz, 1H), 7.95-7.86 (m, 2H), 7.72-7.55 (m, 2H). potassium 4-(5-chloropyridin-3-yl)benzoate INTF32 [00106]  Method F, Using INTF13, [HPLC acidic], 286 ionises as free acid, (2.01). 9.22 (d, J = 2.2 Hz, 1H), 8.95 (d, J = 2.1 Hz, 1H), 8.48 (d, J = 2.3 Hz, 1H), 7.64-7.45 (m, 3H). potassium 2-fluoro-4-(5- (trifluoromethyl)pyridin-3-yl)benzoate INTF33 [00107]  Method F, Using INTF14, [HPLC acidic], 251 .sup.35Cl isotope, ionises as free acid, (1.88). 8.91-8.85 (m, 1H), 8.63- 8.54 (m, 1H), 8.30-8.20 (m, 1H), 7.59-7.49 (m, 1H), 7.49-7.34 (m, 2H). potassium 4-(5-chloropyridin-3-yl)-2- fluorobenzoate INTF34 [00108]  Method E, Using INTF15, [HPLC acidic], 287 (2.08). 13.53 (s, 1H), 9.72 (s, 1H), 9.25 (s, 1H), 8.19-8.12 (m, 2H), 8.11-7.99 (m, 1H). 2-fluoro-4-(6-(trifluoromethyl)pyrazin-2- yl)benzoic acid INTF35 [00109]  Method E, Using INTF16, [HPLC acidic], 263 (2.07). 13.40 (s, 1H), 8.94 (s, 1H), 8.34 (s, 1H), 8.12-8.03 (m, 2H), 8.03-7.92 (m, 1H), 4.50 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H). 4-(6-ethoxy pyrazin-2-yl)-2-fluorobenzoic acid INTF36 [00110]  Method E, Using INTF17, [HPLC acidic], 277 (2.24). 13.53 (s, 1H), 8.90 (s, 1H), 8.27 (s, 1H), 8.08-7.87 (m, 3H), 5.43 (hept, J = 6.2 Hz, 1H), 1.39 (d, J = 6.2 Hz, 6H). 2-fluoro-4-(6-isopropoxy pyrazin-2-yl)benzoic acid INTF37 [00111]  Method D, Using INTF18, [UPLC acidic], 245 (1.29) 13.15 (v. br. s, 1H), 8.89 (s, 1H), 8.31 (s, 1H), 8.29-8.22 (m, 2H), 8.11-8.01 (m, 2H), 4.51 (q, J = 7.0 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H). 4-(6-ethoxy pyrazin-2-yl)benzoic acid INTF38 [00112]  Method E, Using INTF2, [HPLC acidic], 259 (2.17) 12.97 (s, 1H), 8.87 (s, 1H), 8.29 (s, 1H), 8.07-8.05 (m, 1H), 8.03 (dd, J = 8.2, 1.9 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 4.49 (q, J = 7.0 Hz, 2H), 2.62 (s, 3H), 1.41 (t, J = 7.0 Hz, 3H). 4-(6-ethoxy pyrazin-2-yl)-2-methylbenzoic acid INTF39 [00113]  Method E, Using INTF4, [HPLC acidic], 247 (1.91) 13.40 (s, 1H), 9.19 (s, 1H), 8.63 (s, 1H), 8.13-8.05 (m, 2H), 8.01 (t, J = 7.9 Hz, 1H), 2.89 (q, J = 7.6 Hz, 2H), 1.32 (t, J = 7.6 Hz, 3H). 4-(6-ethylpyrazin-2-yl)-2-fluorobenzoic acid INTF40 [00114]  Method E, Using INTF19, [UPLC acidic], 317 (1.38) 13.44 (s, 1H), 9.10 (s, 1H), 8.55 (s, 1H), 8.23-8.12 (m, 2H), 8.03-7.95 (m, 1H), 5.24 (q, J = 9.0 Hz, 2H). 2-fluoro-4-(6-(2,2,2-trifluoro ethoxy)pyrazin-2- yl)benzoic acid INTF41 [00115]  Method D, Using INTF20 [UPLC acidic], 299 (1.37) 13.16 (s, 1H), 9.06 (s, 1H), 8.52 (s, 1H), 8.41-8.27 (m, 2H), 8.13-8.03 (m, 2H), 5.22 (q, J = 9.0 Hz, 2H). 4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)benzoic acid INTF42 [00116]  Method E, Using INTF21, [UPLC acidic], 313 (2.30) 13.75 (s, 1H), 8.98 (s, 1H), 8.52-8.46 (m, 2H), 8.35 (s, 1H), 7.97 (d, J = 7.9 Hz, 1H), 4.49 (q, J = 7.0 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H). 4-(6-ethoxy pyrazin-2-yl)-2- (trifluoromethyl)benzoic acid INTF43 [00117]  Method E, Using INTF22, [HPLC acidic], 283 (2.20) 13.06 (s, 1H), 9.66 (s, 1H), 9.18 (s, 1H), 8.14-8.11 (m, 1H), 8.09 (dd, J = 8.1, 1.9 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 2.63 (s, 3H). 2-methyl-4-(6-(trifluoromethyl)pyrazin-2-

yl)benzoic acid

5-(6-Ethoxypyrazin-2-yl)-3-fluoropicolinic acid INTF44

##STR00118##

[0544] A suspension of 5-(6-ethoxypyrazin-2-yl)-3-fluoropicolinonitrile INTF23 (630 mg, 2.58 mmol) in conc. HCl (10 mL) was heated to reflux for 1 hr. The reaction mixture was allowed to cool to RT. This was then concentrated in vacuo, then suspended in TBME (20 mL) and filtered, washing with iso-hexanes (10 mL) to afford 5-(6-ethoxypyrazin-2-yl)-3-fluoropicolinic acid (750 mg, 2.28 mmol, 88% yield) as an orange solid. Rt 1.74 min (HPLC, acidic); m/z 264 (M+H).sup.+ (ES.sup.+); .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 9.26 (t, J=1.6 Hz, 1H), 9.02 (s, 1H), 8.54 (dd, J=11.5, 1.6 Hz, 1H), 8.39 (s, 1H), 4.52 (q, J=7.0 Hz, 2H), 1.41 (t, J 10=7.0 Hz, 3H), O—H not observed.

(5-(6-(Trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)methanol INTF45

##STR00119##

[0545] A suspension of (5-bromopyridin-2-yl)methanol (1 g, 5.32 mmol), Bispin (1.5 g, 5.91 mmol) and KOAc (1.6 g, 16.0 mmol) in dioxane (20 mL) was heated to 30° C. then degassed (N.sub.2). PdCl.sub.2 (dppf)-CH.sub.2Cl.sub.2 (0.217 g, 0.266 mmol) was added and the reaction mixture heated to 90° C. for 2 hrs. The reaction mixture was cooled to 40° C. whereupon 2-chloro-6-(trifluoromethyl)pyrazine (0.97 g, 5.32 mmol), Cs.sub.2CO.sub.3 (3.47 g, 10.6 mmol) and water (5 mL) were added. The mixture was degassed (N.sub.2), then PdCl.sub.2 (dppf)-CH.sub.2Cl.sub.2 (0.217 g, 0.266 mmol) was added and the mixture was again degassed (N.sub.2). The reaction mixture was then heated to 90° C. for 18 hrs. The reaction mixture was part concentrated (to approx. 5 mL) then taken up with water (20 mL) and EtOAc (50 mL) and passed through celite, eluting with EtOAc (20 mL). The phases were then diluted with water (20 mL) and partitioned. The organic phase was washed with brine (30 ml), dried (Na.sub.2SO.sub.4), filtered and concentrated onto silica (5 g). The crude product was purified by chromatography on silica (40 g cartridge, 0-100% EtOAc/iso-hexanes) to afford (5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)methanol (980 mg, 3.76 mmol, 71% yield) as an off-white solid. Rt 1.38 min (HPLC, acidic); m/z 256 (M+H).sup.+(ES.sup.+); .sup.1H NMR (500 M Hz, DMSO-d.sub.6) δ 9.69 (s, 1H), 9.28 (d, J=2.3 Hz, 1H), 9.20 (s, 1H), 8.56 (dd, J=8.2, 2.3 Hz, 1H), 7.70 (d, J=8.2 Hz, 1H), 5.59 (t, J=5.8 Hz, 1H), 4.67 (d,J=5.8 Hz, 2H).

(5-(6-Chloropyrazin-2-yl)pyridin-2-yl)methanol INT F 46

##STR00120##

[0546] Prepared as for INTF45 using (5-bromopyridin-2-yl)methanol and 2,6-dichloropyrazine to afford (5-(6-chloropyrazin-2-yl)pyridin-2-yl)methanol (27% yield) as a brown solid. Rt 1.10 min (HPLC, acidic); m/z 222 (35CI M+H).sup.+(ES.sup.+); .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 9.36 (s, 1H), 9.22 (s, 1H), 8.81 (s, 1H), 8.50 (d, J=8.2 Hz, 1H), 7.66 (d, J=8.2 Hz, 1H), 5.57 (t, J=6.0 Hz, 1H), 4.66 (d, J=6.0 Hz, 2H).

(5-(6-Ethoxypyrazin-2-yl)pyridin-2-yl)methanol INT F 47

##STR00121##

[0547] Prepared as for INT F45 using (5-bromopyridin-2-yl)methanol and 2-chloro-6-ethoxypyrazine to afford (5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)methanol (54% yield) as a brown solid. Rt 1.34 min (HPLC, acidic); m/z 232 (M+H).sup.+(ES.sup.+); .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 9.27-9.09 (m, 1H), 8.87 (s, 1H), 8.49 (dd, J=8.2, 2.3 Hz, 1H), 8.29 (s, 1H), 7.62 (d, J=8.2 Hz, 1H), 5.53 (t, J=5.9 Hz, 1H), 4.64 (d, J=5.9 Hz, 2H), 4.50 (q, J=7.1 Hz, 2H), 1.41 (t, J=7.1 Hz, 3H).

5-(6-(Trifluoromethyl)pyrazin-2-yl)picolinaldehyde INTF 48

##STR00122##

[0548] A solution of (5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)methanol INT F 45 (980 mg, 3.84 mmol) in CH.sub.2Cl.sub.2 (15 mL) was treated with manganese dioxide (3 g, 34.5 mmol). The reaction was stirred for 4 hrs at RT then filtered through celite and concentrated onto silica (4

g). The crude product was purified by chromatography on silica (24 g cartridge, 0-100% EtOAc/iso-hexanes) to afford 5-(6-(trifluoromethyl)pyrazin-2-yl)picolinaldehyde (541 mg, 2.04 mmol, 55% yield) as a colourless solid. Rt 1.82 min (HPLC, acidic); m/z 254 (M+H).sup.+ (ES.sup.+); .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 10.09 (s, 1H), 9.82 (s, 1H), 9.60 (dd, J=2.2, 0.8 Hz, 1H), 9.30 (s, 1H), 8.79 (dd, J=8.1, 2.2 Hz, 1H), 8.14 (dd, J=8.1, 0.8 Hz, 1H).
5-(6-Chloropyrazin-2-yl)picolinaldehyde INT F 49

##STR00123##

[0549] Prepared as for INTF48 using (5-(6-chloropyrazin-2-yl)pyridin-2-yl)methanol INTF46 to afford 5-(6-chloropyrazin-2-yl)picolinaldehyde (39% yield) as a colourless solid. Rt 1.63 min (HPLC, acidic); m/z 220 (35Cl M+H).sup.+(ES.sup.+); .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 10.08 (d, J=0.8 Hz, 1H), 9.55 (dd, J=2.2, 0.9 Hz, 1H), 9.50 (s, 1H), 8.92 (s, 1H), 8.74 (ddd, J=8.1, 2.2, 0.9 Hz, 1H), 8.11 (dd, J=8.1, 0.9 Hz, 1H).

5-(6-Ethoxypyrazin-2-yl)picolinaldehyde INT F 50

##STR00124##

[0550] Prepared as for INTF48 using (5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)methanol INTF47 to afford 5-(6-ethoxypyrazin-2-yl)picolinaldehyde (42% yield) as a colourless solid. Rt 1.85 min (HPLC, acidic); m/z 230 (M+H).sup.+(ES.sup.+); .sup.1H NMR (500 M Hz, DMSO-d.sub.6) δ 10.07 (d, J=0.8 Hz, 1H), 9.55 (dd, J=2.2, 0.9 Hz, 1H), 9.03 (s, 1H), 8.73 (ddd, J=8.1, 2.2, 0.8 Hz, 1H), 8.39 (s, 1H), 8.08 (dd, J=8.1, 0.9 Hz, 1H), 4.53 (q, J=7.0 Hz, 2H), 1.42 (t, J=7.0 Hz, 3H).

5-(6-(Trifluoromethyl)pyrazin-2-yl)picolinic acid INTF 51

##STR00125##

[0551] A solution of 5-(6-(trifluoromethyl)pyrazin-2-yl)picolinaldehyde INT F 48 (200 mg, 0.79 mmol) in DMF (2 mL) was treated with oxone (650 mg, 1.06 mmol). The reaction mixture was stirred at RT for 4 days. The reaction mixture was diluted with water (10 mL) and filtered. The filtrate was then taken up in EtOAc (10 mL) and heated to 40° C. to afford a free flowing suspension. This was then treated dropwise with iso-hexanes (10 mL), cooled to RT and filtered to afford 5-(6-(trifluoromethyl)pyrazin-2-yl)picolinic acid (180 mg, 0.56 mmol, 68% yield) as a colourless solid. .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 9.78 (s, 1H), 9.48 (dd, J=2.4, 0.8 Hz, 1H), 9.28 (s, 1H), 8.72 (dd, J=8.2, 2.3 Hz, 1H), 8.24 (dd, J=8.2, 0.8 Hz, 1H), v. br OH observed, not reported.

5-(6-Chloropyrazin-2-yl)picolinic acid INTF 52

##STR00126##

[0552] Prepared as for INTF51 using 5-(6-chloropyrazin-2-yl)picolinaldehyde INTF49 to afford 5-(6-chloropyrazin-2-yl)picolinic acid (82% yield) as a colourless solid. Rt 1.32 min (HPLC, acidic); m/z 236 (.sup.35Cl M+H).sup.+(ES.sup.+); .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ 13.30 (s, 1H), 9.46 (s, 1H), 9.42 (d, J=2.1 Hz, 1H), 8.90 (s, 1H), 8.66 (dd, J=8.2, 2.1 Hz, 1H), 8.21 (d, J=8.2 Hz, 1H).

5-(6-Ethoxypyrazin-2-yl)picolinic acid INTF 53

##STR00127##

[0553] Prepared as for INTF51 using 5-(6-ethoxypyrazin-2-yl)picolinaldehyde INTF50 to afford 5-(6-ethoxypyrazin-2-yl)picolinic acid (71% yield) as a colourless solid. Rt 1.45 min (HPLC, acidic); m/z 246 (M+H).sup.+(ES.sup.+); .sup.1H NMR (500 M Hz, DMSO-d.sub.6) δ 13.31 (s, 1H), 9.46-9.38 (m, 1H), 8.98 (s, 1H), 8.64 (dd, J=8.1, 2.3 Hz, 1H), 8.36 (s, 1H), 8.17 (dd, J=8.1, 0.8 Hz, 1H), 4.51 (q, J=7.0 Hz, 2H), 1.42 (t, J=7.0 Hz, 3H).

Preparation of Examples

##STR00128##

[0554] Method 1a: HATU (1.2 eq.) was added to a solution of appropriate acid (1 eq.), amine (1 eq.) and DIPEA (3 eq.) in DM F (10 volumes) at RT. The reaction was stirred at RT for 18 hrs. The solvent was removed and the crude product was purified by normal phase chromatography, reverse phase chromatography or trituration from an appropriate solvent.

[0555] Method 1b: 1-chloro-N,N,2-trimethylprop-1-en-1-amine (2 eq.) was added to a solution of appropriate acid (1 eq.) in DCM (20 volumes). The reaction mixture was stirred at RT for 2 hrs. The reaction mixture was concentrated in vacuo and the residue dissolved in DCM (20 volumes) before addition of DIPEA (3 eq.) and the appropriate amine (1 eq.). The reaction mixture was stirred at RT for 2 hrs. An aqueous work up was performed and the crude product was purified by normal phase chromatography, reverse phase chromatography or trituration from an appropriate solvent.

[0556] Method 1c: T 3P (50 wt % in EtOAc, 2.5 eq.) was added to a solution of appropriate acid (1 eq.), amine (1 eq.) and pyridine (3 eq.) in a mixture of EtOAc (20 volumes) and DMF (10 volumes). The reaction was stirred for 1 hr at RT. An aqueous work up was performed and the crude product was purified by normal phase chromatography, reverse phase chromatography or trituration from an appropriate solvent.

##STR00129##

[0557] PdCl.sub.2(dppf)-CH.sub.2Cl.sub.2 (10 mol %) or other appropriate catalyst was added to a degassed (N.sub.2, 5 mins) solution of Ar1-B (OR) 2 (1 eq.), Ar2-halide (1 eq.) and K.sub.2CO.sub.3 (3 eq.) in dioxane (10 volumes) and water (1 volumes). The solution was then degassed further (N.sub.2, 5 mins) and heated to 90° C. for 1-2 hrs. The reaction mixture was allowed to cool to RT. An aqueous workup was performed and the crude product was purified by normal phase chromatography, reverse phase chromatography or trituration from an appropriate solvent.

##STR00130##

[0558] A suspension of Ar1-Br (1 eq.), Bispin (1.1 eq.) and KOAc (2 eq.) in dioxane (50 volumes) was degassed (N.sub.2) then charged with PdCl.sub.2(dppf).Math.CH.sub.2Cl.sub.2 (5 mol %) and again degassed (N.sub.2). The reaction mixture was heated to 90° C. for 1-24 hrs, recharging the Pd-catalyst if required. On formation of the boronate ester the reaction was allowed to cool to RT. Ar2-Z (1 eq.) and 2 M K.sub.2CO.sub.3 (aq, 2 eq.) were added, degassed (N.sub.2) and the reaction was then heated to 90° C. for 18 hrs. The reaction was allowed to cool to RT, an aqueous work up was performed and the crude compound was purified by normal phase chromatography.

Representative for Method 1a

N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-4-(pyridin-3-yl)benzamide R1

##STR00131##

[0559] A solution of N-(4-(aminomethyl)thiazol-2-yl)cyclopropanesulfonamide INTE 9 (64 mg, 0.274 mmol), 4-(pyridin-3-yl)benzoic acid (54.6 mg, 0.274 mmol) and DIPEA (0.14 mL, 0.82 mmol) in DMF (0.5 mL) was treated with HATU (110 mg, 0.288 mmol) and stirred at RT for 18 hrs. EtOAc (20 mL) was added and the organic phase was washed with water (10 mL) and brine (10 mL), dried (Na.sub.2SO.sub.4), filtered and concentrated onto silica (300 mg). The crude product was purified by chromatography on silica (12 g column, 0-7% (0.7 M ammonia/MeOH)/DCM). The crude product was further purified by reverse phase chromatography on C18 silica (12 g column, 10-40% MeCN/water 0.1% formic acid) to afford N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-4-(pyridin-3-yl)benzamide (18 mg, 0.041 mmol, 15% yield) as a colourless solid. Rt 1.08 min (HPLC, HPLC Acidic); m/z 415 (M+H).sup.+ (ES.sup.+); .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 12.57 (s, 1H), 9.04-8.94 (m, 2H), 8.62 (dd, J=4.8, 1.6 Hz, 1H), 8.17-8.14 (m, 1H), 8.06-7.98 (m, 2H), 7.92-7.84 (m, 2H), 7.50-7.48 (m, 1H), 6.53 (s, 1H), 4.35-4.33 (m, 2H), 2.64-2.52 (m, 1H), 0.09-0.87 (m, 4H).

Representative for Method 1b

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide R2

##STR00132##

[0560] A suspension of 4-(5-(trifluoromethyl)pyridin-3-yl)benzoic acid INTF 25 (46.2 mg, 0.173 mmol) in DCM (2 mL) was treated with 1-chloro-N,N,2-trimethylprop-1-en-1-amine (0.046 mL, 0.346 mmol) and stirred at RT for 1 hr before being concentrated. The residue was taken up in

DCM (3 mL), treated with DIPEA (0.091 mL, 0.518 mmol) and stirred for 5 mins before N-(4-(1-aminopropyl)thiazol-2-yl)cyclopropanesulfonamide INTE 10 (45 mg, 0.17 mmol) was added and the reaction mixture was stirred at RT for 16 hrs. The reaction mixture was treated with NH₄Cl (sat. aq., 5 mL) and passed through a phase separator, further extracting with DCM (5 mL). The organic phase was concentrated onto silica (500 mg) and the crude product was purified by chromatography on silica [12 g column, 0-100% EtOAc (2% MeOH)/iso-hexanes] to afford N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide (46 mg, 0.085 mmol, 49% yield) as a colourless solid. Rt 1.99 min (HPLC, acidic); m/z 511 (M+H).sup.+(ES.sup.+); .sup.1H NMR (400 M Hz, DMSO-d.sub.6) δ 12.60 (s, 1H), 9.30 (d, J=2.1 Hz, 1H), 9.03 (d, J=2.1 Hz, 1H), 8.74 (d, J=8.3 Hz, 1H), 8.56 (s, 1H), 8.09-7.97 (m, 4H), 6.56 (s, 1H), 4.90 (q, J=7.9 Hz, 1H), 2.64-2.51 (m, 1H), 1.98-1.74 (m, 2H), 0.98-0.81 (m, 7H).

[0561] The racemic mixture R2 was separated by chiral preparative HPLC using chiral method A. A salt exchange (TFA to HCl) was undertaken by adding 1.25 M HCl (EtOH, 2 mL×5) and removing solvent to afford:

Peak 1: Stereochemistry of Product was not Defined R3

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide. HCl R.SUB.3 .(13 mg, 0.023 mmol, 37% yield) was isolated as a colourless solid. Rt=1.30 min (UPLC, acidic); m/z 511 (M+H).SUP.+(ES.SUP.+); .SUP.1.H NMR (500 MHZ, DMSO-d.SUB.6.) δ 12.61 (s, 1H), 9.30 (s, 1H), 9.03 (d, J=2.2 Hz, 1H), 8.75 (d, J=8.3 Hz, 1H), 8.56 (s, 1H), 8.09-8.04 (m, 2H), 8.03-7.98 (m, 2H), 6.57 (s, 1H), 4.94-4.87 (m, 1H), 2.64-2.51 (m, 1H), 1.97-1.74 (m, 2H), 0.96-0.85 (m, 7H). Signal for HCl not observed

[0562] The product was analysed by Chiral HPLC, chiral 1A method 1: [Daicel Chiralpak IA, 5 µm, 4.6×250 mm, 45 min method, 1.0 mL/min, 5-95% (gradient over 45 min) EtOH (0.2% TFA) in iso-hexanes (0.2% TFA)]; Rt=14.8 min, >98% @ 254 nm.

Peak 2: Stereochemistry of Product was not Defined R4

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide. HCl R4 (12 mg, 0.021 mmol, 34% yield) was obtained as a colourless solid. Rt=1.30 min (UPLC, acidic); m/z 511 (M+H).SUP.+(ES.SUP.+); .SUP.1.H NMR (500 M Hz, DMSO-d.SUB.6.) δ 12.61 (s, 1H), 9.30 (d, J=2.2 Hz, 1H), 9.03 (d, J=2.1 Hz, 1H), 8.75 (d, J=8.1 Hz, 1H), 8.56 (s, 1H), 8.08-8.04 (m, 2H), 8.03-7.99 (m, 2H), 6.57 (s, 1H), 4.95-4.85 (m, 1H), 2.64-2.51 (m, 1H), 1.97-1.73 (m, 2H), 0.97-0.82 (m, 7H). Signal for HCl not observed

[0563] The product was analysed by Chiral HPLC, chiral IA method 1: [Daicel Chiralpak IA, 5 µm, 4.6×250 mm, 45 min method, 1.0 mL/min, 5-95% (gradient over 45 min) EtOH (0.2% TFA) in iso-hexanes (0.2% TFA)]; Rt=16.8 min, >98% @ 254 nm.

Representative for Method 1c

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide R5

##STR00133##

[0564] A solution of 4-(6-(trifluoromethyl)pyrazin-2-yl) benzoic acid INTF28 (15.4 mg, 0.057 mmol) and N-(4-(1-aminopropyl)thiazol-2-yl)cyclopropanesulfonamide INTE 10 (15 mg, 0.057 mmol) in DM F (0.25 mL) was treated with pyridine (0.014 mL, 0.172 mmol) and T3P (50% wt. in DMF, 0.125 ml, 0.172 mmol). The reaction mixture was allowed to stir at RT over 16 hrs. The crude product was treated with water (0.05 mL) and purified by reverse phase chromatography on C18 silica (12 g column, 10-50% M eCN/10 mM ammonium bicarbonate) to afford N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide (2.5 mg, 0.004 mmol, 8% yield) as a colourless solid. Rt 1.34 min (UPLC, acidic); m/z 512 (M+H).sup.+(ES.sup.+). .sup.1H NMR (400 MHZ, Chloroform-d) δ 9.30 (s, 1H), 8.95 (s, 1H), 8.18 (d, J=8.3 Hz, 2H), 8.12 (d, J=8.4 Hz, 2H), 8.04 (d, J=8.1 Hz, 1H), 6.51 (s, 1H), 5.09-4.95 (m, 1H), 2.56-2.53 (m, 1H), 2.17-1.89 (m, 2H), 1.32-1.09 (m, 2H), 1.09-0.71 (m, 5H), N—H not observed.

Representative for Method 2a

N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide R6

##STR00134##



[0565] A solution of N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide INTE 20 (80 mg, 0.157 mmol), 2 M potassium carbonate (aq, 0.16 mL, 0.314 mmol) and 2-chloro-6-ethoxypyrazine (25 mg, 0.157 mmol) in MeCN (15 mL) and water (2 mL) was degassed (N.sub.2) at 40° C. whereupon PdCl.sub.2(dppf)-CH.sub.2Cl.sub.2 (6.4 mg, 0.008 mmol) was added to form a suspension. The mixture was degassed (N.sub.2) then heated to 90° C. for 3 hrs. The reaction was cooled to RT, concentrated directly onto silica (1 g) and was purified by chromatography on silica (12 g column, 0-100% EtO Ac/iso-hexanes) to afford N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide (13 mg, 0.025 mmol, 16% yield) as a colourless solid. Rt 1.34 min (UPLC, acidic); m/z 506 (M+H).sup.+(ES.sup.+). .sup.1H NMR (400 M Hz, DMSO-d.sub.6) δ 12.58 (s, 1H), 8.93 (s, 1H), 8.36 (s, 1H), 8.32 (s, 1H), 8.11-7.96 (m, 2H), 7.84 (t, J=7.7 Hz, 1H), 6.50 (d, J=8.5 Hz, 1H), 4.50 (q, J=7.0 Hz, 2H), 2.63-2.54 (m, 1H), 1.63 (s, 6H), 1.41 (t, J=7.0 Hz, 3H), 0.95-0.83 (m, 4H).












Representative for Method 2b












N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-methoxybenzamide R7













##STR00135##









[0566] A suspension of 4-bromo-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methoxybenzamide INTE 18 (100 mg, 0.211 mmol), Bispin (59 mg, 0.232 mmol) and KOAc (41 mg, 0.422 mmol) in dioxane (5 mL) was degassed (N.sub.2) then charged with PdCl.sub.2(dppf)-CH.sub.2Cl.sub.2 (8.6 mg, 0.011 mmol) and degassed (N.sub.2). The reaction mixture was heated to 90° C. for 16 hrs. The reaction mixture was allowed to cool then filtered through celite. This was then recharged with KOAc (41 mg, 0.422 mmol), Bispin (59 mg, 0.232 mmol) and PdCl.sub.2(dppf)-CH.sub.2Cl.sub.2 (8.6 mg, 0.011 mmol), degassed (N.sub.2) then heated to 90° C. for 2 hrs. To the reaction mixture was added 2-chloro-6-ethoxypyrazine (33.4 mg, 0.211 mmol) and 2 M potassium carbonate (aq, 0.21 mL, 0.422 mmol) and heated to 90° C. for 16 hrs. The reaction mixture was allowed to cool to RT then diluted with EtOAc (10 mL) and water (10 mL), filtered over celite eluting with EtOAc (10 mL). The phases were then partitioned, washed with brine (10 mL), dried (Na.sub.2SO.sub.4), filtered and concentrated onto silica (500 mg). The crude product was purified by chromatography on silica (12 g cartridge, 0-100% EtOAc/iso-hexanes). The resulting product was re-purified by preparative HPLC (Varian, Basic (0.1% ammonium bicarbonate), 15-50% MeCN in water) to afford N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-methoxybenzamide (20 mg, 0.037 mmol, 17% yield) as a colourless solid. Rt 2.17 min (HPLC acidic); m/z 518 (M+H).sup.+(ES.sup.+). 1H NMR (500 M Hz, DMSO-d.sub.6) δ 12.56 (s, 1H), 8.94 (s, 1H), 8.39 (s, 1H), 8.30 (s, 1H), 7.91 (d, J=8.1 Hz, 1H), 7.86 (d, J=1.5 Hz, 1H), 7.82 (dd, J=8.1, 1.5 Hz, 1H), 6.49 (s, 1H), 4.50 (q, J=7.0 Hz, 2H), 4.07 (s, 3H), 2.59-2.52 (m, 1H), 1.65 (s, 6H), 1.41 (t, J=7.0 Hz, 3H), 0.95-0.76 (m, 4H).












TABLE-US-00006 TABLE 6 The following final compounds were made according to general methods Synthesis Method, Name/Structure [LCMS (All examples containing chiral Method], centres are racemic unless m/z (M + H).sup.+, .sup.1H NMR Chemical Shift Data R stated) (RT/Min) (DMSO-d6 unless stated) R8 [00136]  embedded image Method 1a, Using INTE9 and commercial acid, [UPLC Basic], 415, (1.23) 12.55 (s, 1H), 9.26 (t, J = 6.2 Hz, 1H), 8.99 (dd, J = 2.3, 0.8 Hz, 1H), 8.31 (dd, J = 8.2, 2.3 Hz, 1H), 8.13 (dd, J = 8.2, 0.8 Hz, 1H), 7.87-7.77 (m, 2H), 7.61-7.53 (m, 2H), 7.52- 7.43 (m, 1H), 6.50 (s, 1H), 4.38 (dd, J = 6.3, 1.2 Hz, 2H), 2.62-2.55 (m, 1H), 0.96-0.81 (m, 4H). N-((2-(cyclopropanesulfon- amido)thiazol-4-yl)methyl)-5-phenylpicolinamide R9 [00137]  embedded image Method 1a, Using INTE9 and commercial











acid [HPLC Basic], 414, (1.72) 12.58 (s, 1H), 8.97 (t, J = 5.6 Hz, 1H), 8.05-7.95 (m, 2H), 7.84-7.70 (m, 4H), 7.55-7.46 (m, 2H), 7.45- 7.36 (m, 1H), 6.53 (s, 1H), 4.34 (d, J = 5.4 Hz, 2H), 2.63-2.54 (m, 1H), 0.93-0.86 (m, 4H). N-((2-(cyclopropanesulfon- amido)thiazol-4-yl)methyl)-[1,1'-biphenyl]-4-carboxamide R10 [00138]  Method 1a, Using INTE9 and INTF34, [UPLC Acidic], 502, (1.24) 12.60 (s, 1H), 9.73 (s, 1H), 9.24 (s, 1H), 9.04-8.78 (m, 1H), 8.23-8.08 (m, 2H), 7.98-7.81 (m, 1H), 6.54 (s, 1H), 4.35 (d, J = 5.6 Hz, 2H), 2.62- 2.55 (m, 1H), 0.94-0.79 (m, 4H). N-((2-(cyclopropanesulfon- amido)thiazol-4-yl)methyl)-2- fluoro-4-(6-(trifluoromethyl)-pyrazin-2-yl)benzamide R11 [00139]  Method 1a, Using INTE9 and INTF35, [UPLC Acidic], 478, (1.22) 12.58 (s, 1H), 8.93 (s, 1H), 8.88- 8.83 (m, 1H), 8.32 (s, 1H), 8.11- 8.04 (m, 2H), 7.88-7.79 (m, 1H), 6.54 (s, 1H), 4.50 (q, J = 7.0 Hz, 2H), 4.34 (d, J = 5.6 Hz, 2H), 2.62- 2.54 (m, 1H), 1.41 (t, J = 7.0 Hz, 3H), 0.93-0.81 (m, 4H). N-((2-(cyclopropanesulfon- amido)thiazol-4-yl) methyl)-4-(6- ethoxypyrazin-2-yl)-2- fluorobenzamide R12 [00140]  Method 1a, Using INTE9 and INTF28, [UPLC Acidic], 484, (1.21) 12.60 (s, 1H), 9.71 (s, 1H), 9.20 (s, 1H), 9.14-9.01 (m, 1H), 8.35-8.31 (m, 2H), 8.11-8.06 (m, 2H), 6.55 (s, 1H), 4.35 (d, J = 5.5 Hz, 2H), 2.61- 2.55 (m, 1H), 0.94-0.77 (m, 4H). N-((2-(cyclopropanesulfon- amido)thiazol-4-yl)methyl)-4-(6- (trifluoromethyl)pyrazin-2- yl)benzamide R13 [00141]  Method 1a, Using INTE9 and INTF30, [UPLC Acidic], 474, (1.28) 12.59 (s, 1H), 9.05-8.99 (m, 1H), 8.87 (s, 1H), 8.26-8.19 (m, 3H), 8.05-8.01 (m, 2H), 6.54 (s, 1H), 5.48-5.37 (m, 1H), 4.35 (d, J = 5.4 Hz, 2H), 2.61-2.55 (m, 1H), 1.39 (d, J = 6.1 Hz, 6H), 0.92-0.82 (m, 4H). N-((2-(cyclopropanesulfon- amido)thiazol-4-yl)methyl)-4-(6- isopropoxypyrazin-2- yl)benzamide R14 [00142]  Method 1a, Using INTE9 and INTE37, [UPLC Acidic], 460, (1.18) 12.60 (s, 1H), 9.03 (t, J = 5.6 Hz, 1H), 8.90 (s, 1H), 8.30 (s, 1H), 8.28- 8.22 (m, 2H), 8.08- 8.00 (m, 2H), 6.54 (s, 1H), 4.51 (q, J = 7.1 Hz, 2H), 4.35 (d, J = 5.4 Hz, 2H), 2.61- 2.55 (m, 1H), 1.42 (t, J = 7.0 Hz, 3H), 0.95-0.84 (m, 4H). N-((2-(cyclopropanesulfon- amido)thiazol-4-yl)methyl)-4-(6- ethoxypyrazin-2-yl)benzamide R15 [00143]  Method 1b, Using INTE17 and INTF25, [HPLC acidic], 539, (2.13) 12.52 (s, 1H), 9.30 (d, J = 2.1 Hz, 1H), 9.02 (dd, J = 2.1, 0.9 Hz, 1H), 8.56 (s, 1H), 8.12-7.95 (m, 5H), 6.50 (s, 1H), 2.60-2.53 (m, 1H), 2.27-2.13 (m, 2H), 1.91-1.70 (m, 2H), 0.93-0.85 (m, 4H), 0.77-0.69 (m, 6H). N-(3-(2-(cyclopropanesulfon- amido)thiazol-4-yl)pentan-3-yl)- 4-(5-(trifluoromethyl)pyridin-3- yl)benzamide R16 [00144]  Method 1b, Using INTE17 and INTF26, [HPLC Acidic], 489, (1.9) 12.50 (s, 1H), 8.89 (t, J = 1.8 Hz, 1H), 8.62 (d, J = 2.7 Hz, 1H), 8.17 (ddd, J = 10.3, 2.8, 1.9 Hz, 1H), 8.07- 7.98 (m, 3H), 7.97-7.86 (m, 2H), 6.48 (s, 1H), 2.60-2.52 (m, 1H), 2.29-2.15 (m, 2H), 1.87-1.71 (m, 2H), 0.92-0.82 (m, 4H), 0.73 (t, J = 7.3 Hz, 6H). N-(3-(2-(cyclopropanesulfon- amido)thiazol-4-yl)pentan-3-yl)- 4-(5-fluoropyridin-3- yl)benzamide R17 [00145]  Method 1b, Using INTE17 and INTF24, [HPLC acidic], 485, (1.36) 12.50 (s, 1H), 8.77 (d, J = 2.2 Hz, 1H), 8.46 (dd, J = 2.0, 0.8 Hz, 1H), 8.08-7.96 (m, 4H), 7.89-7.79 (m, 2H), 6.49 (s, 1H), 2.61-2.55 (m, 1H), 2.40 (s, 3H), 2.29-2.12 (m, 2H), 1.88-1.75 (m, 2H), 0.94-0.83 (m, 4H), 0.73 (t, J = 7.2 Hz, 6H). N-(3-(2-(cyclopropanesulfon- amido)thiazol-4-yl)pentan-3-yl)- 4-(5-methylpyridin-3- yl)benzamide R18 [00146]  Method 1b, Using INTE17 and commercial acid, [HPLC Acidic], 471, (1.36) 12.50 (s, 1H), 8.98 (dd, J = 2.4, 0.9 Hz, 1H), 8.62 (dd, J = 4.8, 1.6 Hz, 1H), 8.20-8.12 (m, 1H), 8.07-7.97 (m, 3H), 7.91-7.82 (m, 2H), 7.53 (ddd, J = 8.1, 4.8, 0.9 Hz, 1H), 6.49 (s, 1H), 2.61-2.54 (m, 1H), 2.28- 2.12 (m, 2H), 1.89-1.73 (m, 2H), 0.94-0.82 (m, 4H), 0.74 (t, J = 7.3 Hz, 6H). N-(3-(2-(cyclopropanesulfon- amido)thiazol-4-yl)pentan-3-yl)- 4-(pyridin-3- yl)benzamide R19 [00147]  Method 1b, Using INTE17 and INTF28, [UPLC acidic], 540, (1.44) 12.53 (s, 1H), 9.72 (s, 1H), 9.21 (s, 1H), 8.35-8.28 (m, 2H), 8.17-8.04 (m, 3H), 6.51 (s, 1H), 2.59-2.53 (m, 1H), 2.28-2.14 (m, 2H), 1.87-1.74 (m, 2H), 0.92-0.84 (m, 4H), 0.74 (t, J = 7.4 Hz, 6H). N-(3-(2-(cyclopropanesulfon- amido)thiazol-4-yl)pentan-3-yl)- 4-(6- (trifluoromethyl)pyrazin-2- yl)benzamide R20 [00148]  Method 1b, Using INTE17 and INTF27, [HPLC acidic], 506 .sup.35Cl isotope, (2.06) 12.52 (s, 1H), 9.38 (s, 1H), 8.81 (s, 1H), 8.29-8.21 (m, 2H), 8.15-8.02 (m, 3H), 6.49 (s, 1H), 2.60-2.50 (m, 1H), 2.28-2.12 (m,











2H), 1.90-1.72 (m, 2H), 0.92-0.82 (m, 4H), 0.78-0.61 (m, 6H). 4-(6-chloropyrazin-2-yl)-N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)benzamide R21 [00149]  Method 1b, Using INTE17 and INTF29, [HPLC Acidic], 486, (1.89) 12.52 (s, 1H), 9.15 (s, 1H), 8.57 (s, 1H), 8.28-8.20 (m, 2H), 8.08-8.01 (m, 3H), 6.50 (s, 1H), 2.60 (s, 3H), 2.60-2.54 (m, 1H), 2.26-2.16 (m, 2H), 1.86-1.76 (m, 2H), 0.92-0.84 (m, 4H), 0.74 (t, J = 7.4 Hz, 6H). N-(3-(2-(cyclopropanesulfon- amido)thiazol-4-yl)pentan-3-yl)- 4-(6-methylpyrazin-2- yl)benzamide R22 [00150]  Method 1b, Using INTE17 and commercial acid, [HPLC Acidic], 472, (1.77) 12.51 (s, 1H), 9.35 (d, J = 1.5 Hz, 1H), 8.77 (dd, J = 2.5, 1.5 Hz, 1H), 8.67 (d, J = 2.5 Hz, 1H), 8.28-8.22 (m, 2H), 8.08-8.00 (m, 3H), 6.49 (s, 1H), 2.59-2.51 (m, 1H), 2.26-2.14 (m, 2H), 1.86-1.72 (m, 2H), 0.92- 0.84 (m, 4H), 0.73 (t, J = 7.3 Hz, 6H). N-(3-(2-(cyclopropanesulfon- amido)thiazol-4-yl)pentan-3-yl)- 4-(pyrazin-2-yl)benzamide R23 [00151]  Method 1a, Using INTE14 and INTF44 [HPLC Acidic], 507, (1.99) 12.60 (s, 1H), 9.24 (d, J = 1.4 Hz, 1H), 9.02 (s, 1H), 8.59-8.46 (m, 2H), 8.39 (s, 1H), 6.54 (s, 1H), 4.52 (q, J = 7.0 Hz, 2H), 2.63-2.53 (m, 1H), 1.67 (s, 6H), 1.41 (t, J = 7.0 Hz, 3H), 0.93-0.85 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 5-(6-ethoxypyrazin-2-yl)-3-fluoropicolinamide R24 [00152]  Method 1a, Using INTE14 and INTF51 [HPLC Acidic], 513, (2.06) 12.64 (s, 1H), 9.80 (s, 1H), 9.47 (d, J = 2.1 Hz, 1H), 9.29 (s, 1H), 8.76 (dd, J = 8.2, 2.2 Hz, 1H), 8.51 (s, 1H), 8.21 (d, J = 8.2 Hz, 1H), 6.58 (s, 1H), 2.60-2.53 (m, 1H), 1.71 (s, 6H), 0.94-0.79 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido) thiazol-4-yl)propan-2-yl)- 5-(6-(trifluoromethyl)pyrazin-2- yl)picolinamide R25 [00153]  Method 1a, Using INTE14 and INTF52, [HPLC Acidic], 479 .sup.35Cl isotope, (1.92) 12.62 (s, 1H), 9.46 (s, 1H), 9.39 (d, J = 2.2 Hz, 1H), 8.89 (s, 1H), 8.69 (dd, J = 8.2, 2.2 Hz, 1H), 8.51 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 6.55 (s, 1H), 2.60-2.53 (m, 1H), 1.70 (s, 6H), 0.91-0.81 (m, 4H). 5-(6-chloropyrazin-2-yl)-N-(2-(2-(cyclopropanesulfonamido) thiazol-4-yl)propan-2- yl)picolinamide R26 [00154]  Method 1a, Using INTE14 and INTF53 [HPLC Acidic], 489, (2.04) 12.62 (s, 1H), 9.41 (d, J = 2.2 Hz, 1H), 8.99 (s, 1H), 8.69 (dd, J = 8.2, 2.2 Hz, 1H), 8.47 (s, 1H), 8.37 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 6.56 (s, 1H), 4.51 (q, J = 7.0 Hz, 2H), 2.59-2.53 (m, 1H), 1.70 (s, 6H), 1.41 (t, J = 7.0 Hz, 3H), 0.95-0.83 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 5-(6-ethoxypyrazin-2- yl)picolinamide R27 [00155]  Method 1a, Using INTE14 and commercial acid [HPLC Acidic], 444, (1.39) 12.59 (s, 1H), 9.13 (d, J = 2.2 Hz, 1H), 8.81-8.74 (m, 1H), 8.59 (s, 1H), 8.51-8.45 (m, 2H), 8.45 (s, 1H), 8.09-7.92 (m, 1H), 7.52 (ddd, J = 7.5, 4.7, 1.2 Hz, 1H), 6.52 (s, 1H), 2.62-2.54 (m, 1H), 1.65 (s, 6H), 0.96-0.84 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- [2,2'-bipyridine]-5-carboxamide R28 [00156]  Method 1a, Using INTE14 and INTF31, [UPLC Acidic], 477 .sup.35Cl isotope, (1.2) 12.57 (s, 1H), 8.98-8.93 (m, 1H), 8.72-8.65 (m, 1H), 8.40-8.32 (m, 2H), 8.04-7.97 (m, 2H), 7.97-7.89 (m, 2H), 6.46 (s, 1H), 2.63-2.53 (m, 1H), 1.64 (s, 6H), 0.94-0.82 (m, 4H). 4-(5-chloropyridin-3-yl)-N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2- yl)benzamide R29 [00157]  Method 2a, Using INTE20 and commercial coupling partner, [UPLC Acidic], 529, (1.32) 12.59 (s, 1H), 9.31 (d, J = 2.2 Hz, 1H), 9.04-9.01 (m, 1H), 8.60 (s, 1H), 8.39 (s, 1H), 7.92 (d, J = 11.9 Hz, 1H), 7.89-7.82 (m, 2H), 6.49 (s, 1H), 2.62-2.54 (m, 1H), 1.63 (s, 6H), 0.94-0.84 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 2-fluoro-4-(5-(trifluoromethyl)pyridin-3- yl)benzamide R30 [00158]  Method 1a, Using INTE14 and INTF33, [UPLC Acidic], 495 .sup.35Cl isotope, (1.24) 12.59 (s, 1H), 8.98 (d, J = 2.1 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.40 (t, J = 2.2 Hz, 1H), 8.37 (s, 1H), 7.87- 7.81 (m, 2H), 7.78 (dd, J = 8.1, 1.7 Hz, 1H), 6.48 (s, 1H), 2.62-2.54 (m, 1H), 1.63 (s, 6H), 0.96-0.81 (m, 4H). 4-(5-chloropyridin-3-yl)-N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 2-fluorobenzamide R31 [00159]  Method 2a, Using INTE20 and commercial coupling partner, [UPLC Acidic], 479, (1.15) 12.58 (s, 1H), 8.91 (d, J = 1.9 Hz, 1H), 8.64 (d, J = 2.6 Hz, 1H), 8.37 (s, 1H), 8.27-8.15 (m, 1H), 7.88- 7.74 (m, 3H), 6.49 (s, 1H), 2.65- 2.51 (m, 1H), 1.62 (s, 6H), 0.94- 0.81 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 2-

fluoro-4-(5-fluoropyridin-3-yl)benzamide R32 [00160]  embedded image Method 2b, Using INTE18 and commercial coupling partner, [HPLC Acidic], 541, (2.16) 12.56 (s, 1H), 9.31 (d, J = 2.2 Hz, 1H), 9.02 (dd, J = 2.1, 0.9 Hz, 1H), 8.59 (t, J = 2.3 Hz, 1H), 8.51-8.26 (m, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 1.7 Hz, 1H), 7.54 (dd, J = 8.1, 1.7 Hz, 1H), 6.48 (s, 1H), 4.08 (s, 3H), 2.59-2.53 (m, 1H), 1.65 (s, 6H), 0.94-0.78 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 2-methoxy-4-(5- (trifluoromethyl)pyridin-3- yl)benzamide R33 [00161]  embedded image Method 2a, Using INTE19 and commercial coupling partner, [HPLC acidic], 457, (1.04) 12.55 (s, 1H), 8.49 (dd, J = 4.8, 1.8 Hz, 1H), 8.30 (s, 1H), 8.00-7.91 (m, 2H), 7.62 (dd, J = 7.7, 1.8 Hz, 1H), 7.53-7.47 (m, 2H), 7.33 (dd, J = 7.7, 4.8 Hz, 1H), 6.46 (s, 1H), 2.60- 2.52 (m, 1H), 2.44 (s, 3H), 1.63 (s, 6H), 0.94-0.77 (m, 4H). N-(2-(2- (cyclopropanesulfonamido) thiazol-4-yl)propan-2-yl)-4-(2- methylpyridin-3-yl)benzamide R34 [00162]  embedded image Method 2a, Using INTE19 and commercial coupling partner, [HPLC acidic], 485, (1.59) 12.57 (s, 1H), 9.19 (d, J = 2.3 Hz, 1H), 9.14 (d, J = 2.0 Hz, 1H), 8.55 (t, J = 2.2 Hz, 1H), 8.34 (s, 1H), 8.08- 8.00 (m, 2H), 7.98-7.91 (m, 2H), 6.47 (s, 1H), 2.72 (s, 3H), 2.61-2.51 (m, 1H), 1.64 (s, 6H), 0.93-0.82 (m, 4H). 4-(5-acetylpyridin-3-yl)-N-(2-(2- (cyclopropanesulfon- amido)thiazol-4-yl)propan-2- yl)benzamide R35 [00163]  embedded image Method 2a, Using INTE19 and commercial coupling partner, [HPLC Basic], 511, (1.79) 12.57 (s, 1H), 9.29 (d, J = 2.1 Hz, 1H), 9.03-8.97 (m, 1H), 8.58-8.50 (m, 1H), 8.36 (s, 1H), 8.06-7.96 (m, 4H), 6.47 (s, 1H), 2.59-2.51 (m, 1H), 1.63 (s, 6H), 0.92-0.80 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 4-(5-(trifluoromethyl)pyridin-3- yl)benzamide R36 [00164]  embedded image Method 2a, Using INTE19 and commercial coupling partner, [HPLC Basic], 461, (1.54) 12.56 (s, 1H), 8.91-8.84 (m, 1H), 8.62 (d, J = 2.7 Hz, 1H), 8.34 (s, 1H), 8.20-8.13 (m, 1H), 8.04-7.97 (m, 2H), 7.96-7.89 (m, 2H), 6.47 (s, 1H), 2.58-2.52 (m, 1H), 1.63 (s, 6H), 0.91-0.83 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 4-(5-fluoropyridin-3- yl)benzamide R37 [00165]  embedded image Method 1b, Using INTE14 and INTF24, [UPLC Acidic], 457, (0.74) 12.55 (s, 1H), 8.77 (d, J = 2.2 Hz, 1H), 8.46 (dd, J = 2.1, 0.8 Hz, 1H), 8.31 (s, 1H), 8.02-7.93 (m, 3H), 7.89-7.81 (m, 2H), 6.48 (s, 1H), 2.61-2.53 (m, 1H), 2.40 (s, 3H), 1.64 (s, 6H), 0.97-0.71 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 4-(5-methylpyridin-3- yl)benzamide R38 [00166]  embedded image Method 1b, Using INTE14 and commercial acid, [UPLC Acidic], 473, (0.9) 12.56 (s, 1H), 8.57 (d, J = 1.9 Hz, 1H), 8.34 (d, J = 2.8 Hz, 1H), 8.31 (s, 1H), 8.05-7.96 (m, 2H), 7.92- 7.83 (m, 2H), 7.70 (dd, J = 2.8, 1.9 Hz, 1H), 6.48 (s, 1H), 3.94 (s, 3H), 2.63-2.50 (m, 1H), 1.64 (s, 6H), 0.96-0.82 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 4-(5-methoxypyridin-3- yl)benzamide R39 [00167]  embedded image Method 1b, Using INTE14 and commercial acid, [HPLC Acidic], 443, (1.18) 12.56 (s, 1H), 8.98 (dd, J = 2.5, 0.9 Hz, 1H), 8.62 (dd, J = 4.7, 1.6 Hz, 1H), 8.31 (s, 1H), 8.17 (ddd, J = 8.0, 2.5, 1.6 Hz, 1H), 8.04-7.96 (m, 2H), 7.90-7.82 (m, 2H), 7.53 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 6.48 (s, 1H), 1.64 (s, 6H), 1.00-0.78 (m, 4H), 1 x CH obscured N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 4-(pyridin-3-yl)benzamide R40 [00168]  embedded image Method 1a, Using INTE14 and commercial acid, [HPLC Acidic], 510, (2.35) 12.57 (s, 1H), 8.33 (s, 1H), 8.11- 8.04 (m, 2H), 8.04-7.99 (m, 2H), 7.91-7.85 (m, 2H), 7.80-7.69 (m, 2H), 6.48 (s, 1H), 2.60-2.54 (m, 1H), 1.64 (s, 6H), 0.93-0.84 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido) thiazol-4-yl)propan-2-yl)- 3'-(trifluoromethyl)-[1,1'- biphenyl]-4- carboxamide R41 [00169]  embedded image Method 1a, Using INTE14 and INTF39, [HPLC Acidic], 490, (1.97) 12.59 (s, 1H), 9.19 (s, 1H), 8.62 (s, 1H), 8.38 (d, J = 2.5 Hz, 1H), 8.13- 8.03 (m, 2H), 7.89-7.82 (m, 1H), 6.50 (s, 1H), 2.96-2.84 (m, 2H), 2.64-2.55 (m, 1H), 1.64 (s, 6H), 1.33 (t, J = 7.6 Hz, 3H), 0.97-0.82 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 4-(6-ethylpyrazin-2-yl)-2- fluorobenzamide R42 [00170]  embedded image Method 2a, Using INTE20 and commercial coupling partner, [UPLC Acidic], 530, (1.36) 12.60 (s, 1H), 9.73 (s, 1H), 9.23 (s, 1H), 8.47 (s, 1H), 8.17-8.08 (m, 2H), 7.95-7.86 (m, 1H), 6.50 (s, 1H), 2.63-2.53 (m, 1H), 1.63 (s, 6H), 0.97-0.73 (m, 4H). N-(2-(2-(cyclopropane sulfonamido)thiazol-4- yl)propan-2-yl)-2- fluoro-4-(6- (trifluoromethyl)pyrazin-2- yl)benzamide R43 [00171]  embedded image Method 1a,

Using INTE14 and INTF36, [UPLC Acidic], 520, (1.42) 12.59 (s, 1H), 8.96-8.79 (m, 1H), 8.42-8.32 (m, 1H), 8.31-8.20 (m, 1H), 8.12-7.95 (m, 2H), 7.89-7.76 (m, 1H), 6.50 (s, 1H), 5.46-5.34 (m, 1H), 2.64-2.55 (m, 1H), 1.71-1.53 (m, 6H), 1.50-1.25 (m, 6H), 0.96-0.85 (m, 4H). N-(2-(2-(cyclopropane sulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(6-isopropoxy-pyrazin-2-yl)benzamide R44 [00172]  Method 1a, Using INTE14 and INTF40, [UPLC Acidic], 560, (1.4) 12.59 (s, 1H), 9.09 (s, 1H), 8.52 (s, 1H), 8.40 (s, 1H), 8.18-8.09 (m, 2H), 7.92-7.82 (m, 1H), 6.50 (s, 1H), 5.24 (q, J = 9.0 Hz, 2H), 2.62-2.55 (m, 1H), 1.63 (s, 6H), 0.98-0.81 (m, 4H). N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)benzamide R45 [00173]  Method 1a, Using INTE14 and INTF43 [HPLC Acidic], 526, (2.09) 12.61 (s, 1H), 9.66 (s, 1H), 9.17 (s, 1H), 8.46 (s, 1H), 8.14-8.02 (m, 2H), 7.71 (d, J = 7.9 Hz, 1H), 6.50 (s, 1H), 2.61-2.55 (m, 1H), 2.42 (s, 3H), 1.62 (s, 6H), 0.94-0.85 (m, 4H). N-(2-(2-(cyclopropane sulfonamido)thiazol-4-yl)propan-2-yl)-2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide R46 [00174]  Method 1a, Using INTE14 and INTF38, [HPLC Acidic], 502, (2.04) 12.58 (s, 1H), 8.84 (s, 1H), 8.38 (s, 1H), 8.26 (s, 1H), 8.01-7.93 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H), 6.49 (s, 1H), 4.49 (q, J = 7.0 Hz, 2H), 2.56-2.51 (m, 1H), 2.40 (s, 3H), 1.61 (s, 6H), 1.41 (t, J = 7.0 Hz, 3H), 0.95-0.81 (m, 4H). N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxy-pyrazin-2-yl)-2-methylbenzamide R47 [00175]  Method 1a, Using INTE14 and INTF42, [HPLC Acidic], 556, (2.17) 12.63 (s, 1H), 8.99 (s, 1H), 8.73 (s, 1H), 8.50 (dd, J = 8.1, 1.7 Hz, 1H), 8.43 (d, J = 1.6 Hz, 1H), 8.34 (s, 1H), 7.98 (d, J = 8.1 Hz, 1H), 6.53 (s, 1H), 4.50 (q, J = 7.0 Hz, 2H), 2.62-2.56 (m, 1H), 1.59 (s, 6H), 1.41 (t, J = 7.0 Hz, 3H), 0.95-0.85 (m, 4H). N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxy-pyrazin-2-yl)-2-(trifluoromethyl)benzamide R48 [00176]  Method 2b Using INTE18 and commercial coupling partner, [HPLC Acidic], 542, (2.2) 12.55 (s, 1H), 9.75 (s, 1H), 9.21 (s, 1H), 8.38 (s, 1H), 7.95-7.70 (m, 3H), 6.51 (s, 1H), 4.07 (s, 3H), 2.59-2.54 (m, 1H), 1.65 (s, 6H), 0.96-0.80 (m, 4H). N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methoxy-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide R49 [00177]  Method 2b, Using INTE18 and commercial coupling partner, [HPLC Acidic], 508 .sup.35Cl isotope, (2.07) 12.55 (s, 1H), 9.42 (s, 1H), 8.82 (s, 1H), 8.37 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.86-7.81 (m, 2H), 6.51 (s, 1H), 4.06 (s, 3H), 2.60-2.51 (m, 1H), 1.64 (s, 6H), 1.02-0.74 (m, 4H). 4-(6-chloropyrazin-2-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methoxybenzamide R50 [00178]  Method 2b, Using INTE18 and commercial coupling partner, [HPLC Acidic], 499, (1.94) 12.55 (s, 1H), 9.70 (s, 1H), 9.23 (s, 1H), 8.39 (s, 1H), 7.96-7.82 (m, 3H), 6.51 (s, 1H), 4.07 (s, 3H), 2.62-2.53 (m, 1H), 1.64 (s, 6H), 0.96-0.74 (m, 4H). 4-(6-cyanopyrazin-2-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methoxybenzamide R51 [00179]  Method 1b, Using INTE14 and INTF28, [UPLC Acidic], 512, (1.31) 12.59 (s, 1H), 9.72 (s, 1H), 9.21 (s, 1H), 8.42 (s, 1H), 8.34-8.27 (m, 2H), 8.13-8.04 (m, 2H), 6.50 (s, 1H), 2.62-2.54 (m, 1H), 1.65 (s, 6H), 0.93-0.86 (m, 4H). N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide R52 [00180]  Method 1b, Using INTE14 and INTF27, [HPLC acidic], 478 .sup.35Cl isotope, (1.87) 12.58 (s, 1H), 9.39 (s, 1H), 8.82 (s, 1H), 8.40 (s, 1H), 8.29-8.21 (m, 2H), 8.09-8.03 (m, 2H), 6.48 (s, 1H), 2.54-2.50 (m, 1H), 1.64 (s, 6H), 0.94-0.76 (m, 4H). 4-(6-chloropyrazin-2-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)benzamide R53 [00181]  Method 1b, Using INTE14 and INTF29, [HPLC Acidic], 458, (1.68) 12.58 (s, 1H), 9.15 (s, 1H), 8.56 (s, 1H), 8.35 (s, 1H), 8.28-8.20 (m, 2H), 8.06-7.98 (m, 2H), 6.49 (s, 1H), 2.63-2.55 (m, 4H), 1.64 (s, 6H), 0.96-0.79 (m, 4H). N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-methylpyrazin-2-yl)benzamide R54 [00182]  Method 2a, Using INTE19 and commercial coupling partner, [HPLC Basic], 474, (1.63) 12.57 (s, 1H), 8.93 (s, 1H), 8.34 (s, 1H), 8.32 (s, 1H), 8.27-8.23 (m, 2H), 8.06-7.94 (m, 2H), 6.48 (s, 1H), 4.04 (s, 3H), 2.54-2.51 (m, 1H), 1.63 (s, 6H), 0.93-0.82 (m, 4H). N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-

(6-methoxypyrazin-2-yl)benzamide R55 [00183]  embedded image Method 2a, Using INTE19 and commercial coupling partner, [HPLC Basic], 488, (1.79) 12.56 (s, 1H), 8.91 (s, 1H), 8.33 (s, 1H), 8.29 (s, 1H), 8.25-8.20 (m, 2H), 8.04-7.98 (m, 2H), 6.47 (s, 1H), 4.50 (q, J = 7.0 Hz, 2H), 2.59- 2.53 (m, 1H), 1.63 (s, 6H), 1.41 (t, J = 7.0 Hz, 3H), 0.92-0.81 (m, 4H). N-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 4-(6-ethoxypyrazin-2- yl)benzamide R56 [00184]  embedded image Method 1a, Using INTE14 and INTF30, [UPLC Basic], 502, (1.2) 12.57 (s, 1H), 8.89 (s, 1H), 8.34 (s, 1H), 8.27-8.17 (m, 3H), 8.04-7.98 (m, 2H), 6.48 (s, 1H), 5.49- 5.24 (m, 1H), 2.60-2.53 (m, 1H), 1.64 (s, 6H), 1.40 (d, J = 6.2 Hz, 6H), 0.92- 0.78 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 4-(6-isopropoxypyrazin-2- yl)benzamide R57 [00185]  embedded image Method 1a, Using INTE14 and INTF41, [UPLC Acidic], 542, (1.38) 12.58 (s, 1H), 9.08 (s, 1H), 8.50 (s, 1H), 8.37 (s, 1H), 8.34-8.25 (m, 2H), 8.08-7.99 (m, 2H), 6.49 (s, 1H), 5.23 (q, J = 9.0 Hz, 2H), 2.60- 2.54 (m, 1H), 1.64 (s, 6H), 0.96- 0.83 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 4-(6-(2,2,2- trifluoroethoxy)pyrazin-2- yl)benzamide R58 [00186]  embedded image Method 1b, Using INTE14 and commercial acid, [HPLC Acidic], 444, (1.59) 12.57 (s, 1H), 9.35 (d, J = 1.6 Hz, 1H), 8.76 (dd, J = 2.5, 1.5 Hz, 1H), 8.67 (d, J = 2.5 Hz, 1H), 8.36 (s, 1H), 8.29-8.22 (m, 2H), 8.09-7.95 (m, 2H), 6.48 (s, 1H), 2.60-2.52 (m, 1H), 1.63 (s, 6H), 0.91-0.83 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propan-2-yl)- 4-(pyrazin-2-yl)benzamide R59 [00187]  embedded image Method 1b, Using INTE10 and INTF26, [HPLC acidic], 461, (1.74) 12.60 (s, 1H), 8.91-8.88 (m, 1H), 8.72 (d, J = 8.3 Hz, 1H), 8.64 (d, J = 2.7 Hz, 1H), 8.21-8.16 (m, 1H), 8.08- 8.02 (m, 2H), 7.99-7.92 (m, 2H), 6.56 (s, 1H), 4.94- 4.85 (m, 1H), 2.64-2.55 (m, 1H), 1.97-1.72 (m, 2H), 0.97-0.76 (m, 7H). RACEMIC, N-(1-(2- (cyclopropanesulfonamido) thiazol-4-yl)propyl)-4-(5- fluoropyridin-3-yl)benzamide R60 [00188]  embedded image Method 1b, Using INTE10 and INTF24, [HPLC acidic], 457, (1.22) 12.57 (s, 1H), 8.76 (d, J = 2.3 Hz, 1H), 8.68 (d, J = 8.2 Hz, 1H), 8.46 (dd, J = 2.0, 0.8 Hz, 1H), 8.06-7.95 (m, 3H), 7.90-7.82 (m, 2H), 6.54 (s, 1H), 4.94-4.83 (m, 1H), 2.62-2.55 (m, 1H), 2.39 (s, 3H), 1.97-1.71 (m, 2H), 0.97-0.81 (m, 7H). RACEMIC, N-(1-(2- (cyclopropanesulfonamido) thiazol-4-yl)propyl)-4-(5- methylpyridin-3-yl)benzamide R61 [00189]  embedded image Method 1b, Using INTE10 and commercial acid, [HPLC acidic], 443, (1.2) 12.58 (s, 1H), 9.00-8.96 (m, 1H), 8.72- 8.66 (m, 1H), 8.63 (dd, J = 4.7, 1.6 Hz, 1H), 8.20-8.14 (m, 1H), 8.05-8.01 (m, 2H), 7.91-7.85 (m, 2H), 7.53 (dd, J = 7.9, 4.6 Hz, 1H), 6.55 (s, 1H), 4.95-4.83 (m, 1H), 2.64-2.55 (m, 1H), 1.98-1.71 (m, 2H), 0.99-0.81 (m, 7H). RACEMIC, N-(1-(2- (cyclopropanesulfonamido) thiazol-4-yl)propyl)-4-(pyridin-3- yl)benzamide R62 [00190]  embedded image Method 1a, Using INTE10 and INTF35, [HPLC Acidic], 506, (2.12) 12.63 (s, 1H), 8.93 (s, 1H), 8.71 (d, J = 8.3 Hz, 1H), 8.33 (s, 1H), 8.11- 8.01 (m, 2H), 7.79 (t, J = 7.8 Hz, 1H), 6.55 (s, 1H), 4.93-4.82 (m, 1H), 4.51 (q, J = 7.0 Hz, 2H), 2.62- 2.55 (m, 1H), 1.94-1.81 (m, 1H), 1.81-1.66 (m, 1H), 1.42 (t, J = 7.0 Hz, 3H), 1.01-0.83 (m, 7H). RACEMIC, N-(1-(2- (cyclopropanesulfonamido) thiazol-4-yl)propyl)-4-(6- ethoxypyrazin-2-yl)-2- fluorobenzamide R63 [00191]  embedded image Method 1a, Using INTE11 and INTF35, [HPLC Acidic], 520, (2.22) 12.75 (s, 1H), 8.90 (d, J = 5.1 Hz, 1H), 8.31 (d, J = 4.7 Hz, 1H), 8.15- 7.98 (m, 2H), 7.69 (s, 1H), 6.73 (s, 1H), 5.50 (s, 1H), 4.53-4.47 (m, 2H), 2.66- 2.62 (m, 4H), 2.11-1.74 (m, 2H), 1.45-1.35 (m, 3H), 0.99- 0.84 (m, 7H). RACEMIC, N-(1-(2- (cyclopropanesulfonamido) thiazol-4-yl)propyl)-4-(6- ethoxypyrazin-2-yl)-2-fluoro-N- methylbenzamide R64 [00192]  embedded image Method 1a, Using INTE10 and INF36 [HPLC Acidic], 520, (2.24) 12.62 (s, 1H), 8.90 (s, 1H), 8.70 (d, J = 8.3 Hz, 1H), 8.27 (s, 1H), 8.10- 7.97 (m, 2H), 7.78 (t, J = 7.8 Hz, 1H), 6.54 (s, 1H), 5.45-5.33 (m, 1H), 4.87 (q, J = 7.9 Hz, 1H), 2.62- 2.54 (m, 1H), 1.96-1.83 (m, 1H), 1.81-1.64 (m, 1H), 1.39 (d, J = 6.1 Hz, 6H), 0.98-0.80 (m, 7H). RACEMIC, N-(1-(2- (cyclopropanesulfonamido) thiazol-4-yl)propyl)-2-fluoro-4-(6- isopropoxypyrazin-2- yl)benzamide R65 [00193]  embedded image Method 1b, Using INTE10 and INTF27 [HPLC acidic], 478 .sup.35Cl isotope, (1.91) 12.60 (s, 1H), 9.38 (d, J = 0.6 Hz, 1H), 8.82 (s, 1H), 8.76 (d, J = 8.2 Hz, 1H), 8.31-8.20 (m, 2H), 8.07 (d, J = 8.4 Hz, 2H), 6.55 (s, 1H), 4.90 (q, J = 8.5, 7.9 Hz, 1H), 2.62- 2.52 (m, 1H), 2.00-1.60 (m, 2H), 0.97-0.81 (m, 7H).

RACEMIC, 4-(6-chloropyrazin-2-yl)-N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)benzamide R66 [00194]  Method 1b, Using INTE10 and INTF29 [HPLC Acidic], 458, (1.73) 12.59 (s, 1H), 9.13 (s, 1H), 8.72 (d, J = 8.2 Hz, 1H), 8.56 (s, 1H), 8.28-8.21 (m, 2H), 8.07-8.00 (m, 2H), 6.56 (s, 1H), 4.94-4.84 (m, 1H), 2.62-2.50 (m, 4H), 2.01-1.67 (m, 2H), 0.96-0.85 (m, 7H). RACEMIC, N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-methylpyrazin-2-yl)benzamide R67 [00195]  Method 1b Using INTE10 and commercial acid, [HPLC Acidic], 444, (1.81) 12.59 (s, 1H), 9.35 (d, J = 1.5 Hz, 1H), 8.77 (dd, J = 2.5, 1.5 Hz, 1H), 8.74 (d, J = 8.2 Hz, 1H), 8.67 (d, J = 2.4 Hz, 1H), 8.30-8.24 (m, 2H), 8.11-7.99 (m, 2H), 6.56 (s, 1H), 4.89 (q, J = 7.8 Hz, 1H), 2.62-2.54 (m, 1H), 1.98-1.72 (m, 2H), 0.96-0.79 (m, 7H). RACEMIC, N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(pyrazin-2-yl)benzamide R68 [00196]  Method 1b, Using INTE10 and INTF26, Separation using chiral method A, [UPLC acidic], 461, (1.13) Chiral IA method 1: Peak 1 RT 21.4 mins 12.60 (s, 1H), 8.89 (t, J = 1.8 Hz, 1H), 8.72 (d, J = 8.3 Hz, 1H), 8.64 (d, J = 2.7 Hz, 1H), 8.21-8.16 (m, 1H), 8.08-8.02 (m, 2H), 7.99-7.92 (m, 2H), 6.56 (s, 1H), 4.90 (q, J = 8.2 Hz, 1H), 2.64-2.55 (m, 1H), 1.97-1.72 (m, 2H), 0.97-0.76 (m, 7H). SINGLE ENANTIOMER- stereochemistry unassigned, N-(1-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propyl)-4-(5- fluoropyridin-3-yl)benzamide R69 [00197]  Method 1b, Using INTE10 and INTF26, Separation using chiral method A [UPLC acidic], 461, (1.13) Chiral IA method 1: Peak 2 RT 27.5 mins 12.60 (s, 1H), 8.89 (t, J = 1.8 Hz, 1H), 8.72 (d, J = 8.3 Hz, 1H), 8.64 (d, J = 2.7 Hz, 1H), 8.21-8.16 (m, 1H), 8.08-8.02 (m, 2H), 7.99-7.92 (m, 2H), 6.56 (s, 1H), 4.90 (q, J = 8.2 Hz, 1H), 2.64-2.55 (m, 1H), 1.97-1.72 (m, 2H), 0.97-0.76 (m, 7H). SINGLE ENANTIOMER- stereochemistry unassigned, N-(1-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propyl)-4-(5- fluoropyridin-3-yl)benzamide R70 [00198]  Chiral Sep, Method 1a, Using INTE10 and INTF35, Separation using chiral method B, [HPLC Acidic], 506, (2.11) Chiral IA method 2: Peak 1 RT 16.0 mins 12.62 (s, 1H), 8.93 (s, 1H), 8.70 (dd, J = 8.3, 1.4 Hz, 1H), 8.32 (s, 1H), 8.11-8.03 (m, 2H), 7.80-7.73 (m, 1H), 6.55 (s, 1H), 4.93-4.79 (m, 1H), 4.50 (q, J = 7.0 Hz, 2H), 2.62-2.55 (m, 1H), 1.94-1.82 (m, 1H), 1.80-1.67 (m, 1H), 1.41 (t, J = 7.0 Hz, 3H), 0.98-0.85 (m, 7H). SINGLE ENANTIOMER- stereochemistry unassigned, N-(1-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2- fluorobenzamide R71 [00199]  Chiral Sep, Method 1a, Using INTE10 and INTF35, Separation using chiral method B, [HPLC Acidic], 506, (2.12) Chiral IA method 2: Peak 2 RT 30.2 mins 12.62 (s, 1H), 8.93 (s, 1H), 8.75-8.67 (m, 1H), 8.32 (s, 1H), 8.11-8.01 (m, 2H), 7.83-7.72 (m, 1H), 6.54 (s, 1H), 4.93-4.79 (m, 1H), 4.50 (q, J = 7.0 Hz, 2H), 2.62-2.55 (m, 1H), 1.94-1.81 (m, 1H), 1.79-1.64 (m, 1H), 1.41 (t, J = 7.0 Hz, 3H), 0.98-0.86 (m, 7H). SINGLE ENANTIOMER- stereochemistry unassigned, N-(1-(2-(cyclopropanesulfon- amido)thiazol-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2- fluorobenzamide R72 [00200]  Method 1a using INTE32 and INTF53, [HPLC Acidic], 503, (2.12) 12.07 (s, 1H), 9.40 (d, J = 2.1 Hz, 1H), 9.00 (s, 1H), 8.70 (dd, J = 8.2, 2.2 Hz, 1H), 8.66 (s, 1H), 8.38 (s, 1H), 8.15 (d, J = 8.2 Hz, 1H), 4.52 (q, J = 7.0 Hz, 2H), 2.57-2.53 (m, 1H), 2.19 (s, 3H), 1.75 (s, 6H), 1.42 (t, J = 7.0 Hz, 3H), 0.94-0.79 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)-5-methylthiazol-4-yl)propan-2-yl)-5-(6-ethoxypyrazin-2-yl)picolinamide R73 [00201]  Method 1a using INTE33 and INTF53, [HPLC Acidic], 523 .sup.35Cl isotope, (2.35) 12.52 (s, 1H), 9.40 (d, J = 2.1 Hz, 1H), 9.00 (s, 1H), 8.74-8.67 (m, 2H), 8.38 (s, 1H), 8.15 (d, J = 8.1 Hz, 1H), 4.52 (q, J = 7.0 Hz, 2H), 2.71-2.65 (m, 1H), 1.78 (s, 6H), 1.42 (t, J = 7.0 Hz, 3H), 0.98-0.74 (m, 4H). N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-5-(6-ethoxypyrazin-2-yl)picolinamide R74 [00202]  Method 1a using INTE32 and INTF35, [HPLC Acidic], 520, (2.16) 11.94 (s, 1H), 8.92 (s, 1H), 8.59-8.52 (m, 1H), 8.32 (s, 1H), 8.08-8.02 (m, 2H), 7.80-7.75 (m, 1H), 4.50 (q, J = 7.0 Hz, 2H), 2.62-2.53 (m, 1H), 2.22 (s, 3H), 1.66 (s, 6H), 1.41 (t, J = 7.0 Hz, 3H), 0.95-0.80 (m, 4H). N-(2-(2-(cyclopropanesulfon- amido)-5-methylthiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2- fluorobenzamide R75 [00203]  Method 1a using INTE33 and INTF35, [HPLC Acidic], 540 .sup.35Cl isotope, (2.36) 12.44 (s, 1H),

8.92 (s, 1H), 8.71 (d, J = 1.8 Hz, 1H), 8.33 (s, 1H), 8.11- 8.00 (m, 2H), 7.89-7.66 (m, 1H), 4.50 (q, J = 7.0 Hz, 2H), 2.76-2.61 (m, 1H), 1.69 (s, 6H), 1.41 (t, J = 7.0 Hz, 3H), 1.02-0.90 (m, 4H). N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide R76 [00204]  embedded image Method 1a using INTE32 and INTF43, [HPLC Acidic], 540, (2.16) 11.96 (s, 1H), 9.66 (s, 1H), 9.18 (s, 1H), 8.63 (s, 1H), 8.11-8.01 (m, 2H), 7.66-7.56 (m, 1H), 2.61-2.54 (m, 1H), 2.42 (s, 3H), 2.26 (s, 3H), 1.66 (s, 6H), 0.95-0.86 (m, 4H). N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)-2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide R77 [00205]  embedded image Method 1a using INTE33 and INTF43, [HPLC Acidic], 560 .sup.35Cl isotope, (2.33) 12.45 (s, 1H), 9.66 (s, 1H), 9.18 (s, 1H), 8.79 (s, 1H), 8.18-7.97 (m, 2H), 7.70-7.49 (m, 1H), 2.70-2.66 (m, 1H), 2.43 (s, 3H), 1.69 (s, 6H), 1.02-0.92 (m, 4H). N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide R78 [00206]  embedded image Method 1a using INTE32 and INTF28, [HPLC Acidic], 526, (2.19) 11.98 (s, 1H), 9.71 (s, 1H), 9.21 (s, 1H), 8.59 (s, 1H), 8.33-8.27 (m, 2H), 8.12-8.02 (m, 2H), 2.60-2.54 (m, 1H), 2.18 (s, 3H), 1.69 (s, 6H), 0.92-0.84 (m, 4H). N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide R79 [00207]  embedded image Method 1a using INTE33 and INTF28, [HPLC Acidic], 546 .sup.35Cl isotope, (2.29) 12.47 (s, 1H), 9.71 (s, 1H), 9.21 (s, 1H), 8.74 (s, 1H), 8.39-8.25 (m, 2H), 8.15-7.98 (m, 2H), 2.69-2.64 (m, 1H), 1.72 (s, 6H), 0.97-0.90 (m, 4H). N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide R80 [00208]  embedded image Method 1a using INTE38 and INTF53, [HPLC Acidic], 487, (1.97) 12.41 (s, 1H), 9.40-9.32 (m, 2H), 9.00 (s, 1H), 8.69 (dd, J = 8.2, 2.2 Hz, 1H), 8.38 (s, 1H), 8.16 (d, J = 8.2 Hz, 1H), 6.44 (s, 1H), 4.52 (q, J = 7.0 Hz, 2H), 2.61-2.53 (m, 1H), 1.42 (t, J = 7.0 Hz, 3H), 1.40-1.34 (m, 2H), 1.29-1.23 (m, 2H), 0.93- 0.83 (m, 4H). N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-5-(6-ethoxypyrazin-2-yl)picolinamide R81 [00209]  embedded image Method 1a using INTE38 and Commercial acid, [UPLC Basic], 441, (0.77) 12.32 (s, 1H), 9.14 (s, 1H), 8.97 (d, J = 2.4 Hz, 1H), 8.62 (dd, J = 4.8, 1.6 Hz, 1H), 8.18-8.15 (m, 1H), 8.06- 7.95 (m, 2H), 7.94-7.77 (m, 2H), 7.53 (dd, J = 7.9, 4.8 Hz, 1H), 6.40 (s, 1H), 2.62-2.54 (m, 1H), 1.43- 1.34 (m, 2H), 1.29-1.21 (m, 2H), 0.98-0.78 (m, 4H). N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-4-(pyridin-3-yl)benzamide R82 [00210]  embedded image Method 1a using INTE38 and INTF35, [HPLC Acidic], 504, (2.05) 12.32 (s, 1H), 9.02 (s, 1H), 8.94 (s, 1H), 8.33 (s, 1H), 8.12-8.00 (m, 2H), 7.86-7.78 (m, 1H), 6.44 (s, 1H), 4.51 (q, J = 7.0 Hz, 2H), 2.63- 2.54 (m, 1H), 1.46-1.33 (m, 5H), 1.25-1.15 (m, 2H), 0.96-0.85 (m, 4H). N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide R83 [00211]  embedded image Method 1a using INTE38 and INTF43, [HPLC Acidic], 524, (2.08) 12.31 (s, 1H), 9.67 (s, 1H), 9.18 (s, 1H), 9.04 (s, 1H), 8.10-8.07 (m, 2H), 7.67 (d, J = 7.9 Hz, 1H), 6.47 (s, 1H), 2.63-2.57 (m, 1H), 2.44 (s, 3H), 1.43-1.34 (m, 2H), 1.25-1.18 (m, 2H), 1.00-0.81 (m, 4H). N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide R84 [00212]  embedded image Method 1a using INTE38 and INTF28, [HPLC Acidic], 510, (2.04) 12.37 (s, 1H), 9.72 (s, 1H), 9.29- 9.06 (m, 2H), 8.39-8.28 (m, 2H), 8.15-7.96 (m, 2H), 6.40 (s, 1H), 2.61-2.54 (m, 1H), 1.42-1.35 (m, 2H), 1.32-1.22 (m, 2H), 0.96-0.84 (m, 4H). N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide R85 [00213]  embedded image Method 1a using INTE39 and INTF26, [UPLC Acidic], 491, (1.09) 12.60 (s, 1H), 8.89 (t, J = 1.9 Hz, 1H), 8.74 (d, J = 8.1 Hz, 1H), 8.64 (d, J = 2.7 Hz, 1H), 8.21-8.15 (m, 1H), 8.09-7.98 (m, 2H), 7.98-7.91 (m, 2H), 6.57 (s, 1H), 5.13-5.02 (m, 1H), 3.46-3.34 (m, 2H), 3.23 (s, 3H), 2.62-2.54 (m, 1H), 2.18- 2.10 (m, 1H), 2.07-1.98 (m, 1H), 0.95-0.85 (m, 4H). N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(5-fluoropyridin-3-yl)benzamide R86 [00214]  embedded image Method 1a using INTE39 and INTF39, [UPLC Acidic], 520, (1.24) 12.64 (s, 1H), 9.18 (s, 1H), 8.71 (d, J = 8.2 Hz, 1H), 8.62 (s, 1H), 8.14- 8.05 (m, 2H), 7.87-7.77 (m, 1H), 6.57 (s, 1H), 5.12-5.03 (m, 1H), 3.46-

3.37 (m, 2H), 3.25 (s, 3H), 2.90 (q, J = 7.6 Hz, 2H) 2.63-2.55 (m, 1H), 2.18-2.05 (m, 1H), 2.05-1.91 (m, 1H), 1.33 (t, J = 7.6 Hz, 3H), 0.97-0.83 (m, 4H). N-(1-(2-(cyclopropanesulfon-amido)thiazol-4-yl)-3- methoxypropyl)-4-(6-ethyl- pyrazin-2-yl)-2-fluorobenzamide R87 [00215]  Method 1a using INTE39 and INTF34, [UPLC Acidic], 560, (1.33) 12.65 (s, 1H), 9.73 (s, 1H), 9.24 (s, 1H), 8.78 (d, J = 8.0 Hz, 1H), 8.21- 8.12 (m, 2H), 7.92-7.83 (m, 1H), 6.57 (s, 1H), 5.12-5.03 (m, 1H), 3.49-3.36 (m, 2H), 3.25 (s, 3H), 2.64-2.55 (m, 1H), 2.19-2.07 (m, 1H), 2.05-1.92 (m, 1H), 0.98-0.83 (m, 4H). N-(1-(2-(cyclopropanesulfon- amido)thiazol-4-yl)-3- methoxypropyl)-2-fluoro-4-(6- (trifluoromethyl)pyrazin-2- yl)benzamide R88 [00216]  Method 1a using INTE39 and INTF35, [HPLC Acidic], 536, (2.08) 12.63 (s, 1H), 8.93 (s, 1H), 8.66 (s, 1H), 8.33 (s, 1H), 8.11-8.03 (m, 2H), 7.85-7.73 (m, 1H), 6.52 (s, 1H), 5.13-4.96 (m, 1H), 4.51 (q, J = 7.0 Hz, 2H), 3.47-3.37 (m, 2H), 3.25 (s, 3H), 2.60-2.52 (m, 1H), 2.18-2.08 (m, 1H), 2.02-1.81 (m, 1H), 1.42 (t, J = 7.0 Hz, 3H), 0.99- 0.65 (m, 4H). N-(1-(2-(cyclopropanesulfon- amido)thiazol-4-yl)-3- methoxypropyl)-4-(6- ethoxy-pyrazin-2-yl)-2- fluorobenzamide R89 [00217]  Method 1a using INTE39 and INTF36, [UPLC Acidic], 551, (1.42) 12.64 (s, 1H), 8.91 (s, 1H), 8.71 (d, J = 9.1 Hz, 1H), 8.28 (s, 1H), 8.11- 8.02 (m, 2H), 7.85-7.78 (m, 1H), 6.55 (s, 1H), 5.43 (h, J = 6.2 Hz, 1H), 5.12-5.03 (m, 1H), 3.47-3.38 (m, 2H), 3.25 (s, 3H), 2.63-2.56 (m, 1H), 2.17-2.10 (m, 1H), 2.03 1.93 (m, 1H), 1.40 (d, J = 6.2 Hz, 6H), 0.96-0.85 (m, 4H). N-(1-(2-(cyclopropanesulfon- amido)thiazol-4-yl)-3- methoxypropyl)-2- fluoro-4-(6- isopropoxy-pyrazin-2- yl)benzamide R90 [00218]  Method 1a using INTE39 and INTF37, [UPLC Acidic], 519, (1.27) 12.61 (s, 1H), 8.91 (s, 1H), 8.74 (d, J = 8.1 Hz, 1H), 8.30 (s, 1H), 8.28- 8.22 (m, 2H), 8.07-8.00 (m, 2H), 6.58 (s, 1H), 5.12-5.04 (m, 1H), 4.51 (q, J = 7.0 Hz, 2H), 3.46-3.35 (m, 2H), 3.23 (s, 3H), 2.63-2.55 (m, 1H), 2.18-2.09 (m, 1H), 2.09 1.99 (m, 1H), 1.42 (t, J = 7.0 Hz, 3H), 0.95-0.86 (m, 4H). N-(1-(2-(cyclopropanesulfon- amido)thiazol-4-yl)-3- methoxypropyl)-4-(6-ethoxy- pyrazin-2-yl)benzamide R91 [00219]  Method 1a using INTE23 and INTF35, [HPLC Acidic], 492, (2.02) 12.66 (s, 1H), 8.93 (s, 1H), 8.81 (d, J = 7.7 Hz, 1H), 8.33 (s, 1H), 8.09- 8.01 (m, 2H), 7.84-7.73 (m, 1H), 6.54 (s, 1H), 5.06- 4.96 (m, 1H), 4.51 (q, J = 7.0 Hz, 2H), 2.63-2.53 (m, 1H), 1.46 (d, J = 6.9 Hz, 3H), 1.42 (t, J = 7.0 Hz, 3H), 0.94-0.85 (m, 4H). N-(1-(2-(cyclopropanesulfon- amido) thiazol-4-yl)ethyl)-4-(6- ethoxy-pyrazin-2-yl)-2- fluorobenzamide R92 [00220]  Method 1a using INTE39 and INTF35, Chiral IC1 (17.4), [HPLC Acidic], 536, (2.08) 12.64 (s, 1H), 8.94 (s, 1H), 8.74- 8.67 (m, 1H), 8.33 (s, 1H), 8.15- 7.99 (m, 2H), 7.86-7.72 (m, 1H), 6.58 (s, 1H), 5.16-5.02 (m, 1H), 4.51 (q, J = 7.0 Hz, 2H), 3.49-3.33 (m, 2H), 3.25 (s, 3H), 2.64-2.57 (m, 1H), 2.22-2.05 (m, 1H), 2.05- 1.92 (m, 1H), 1.42 (t, J = 7.0 Hz, 3H), 0.97-0.81 (m, 4H). SINGLE ENANTIOMER- stereochemistry unassigned N-(1-(2-(cyclopropanesulfon- amido)thiazol-4-yl)-3- methoxypropyl)-4-(6- ethoxy-pyrazin-2-yl)-2- fluorobenzamide R93 [00221]  Method 1a using INTE39 and INTF35, Chiral IC1 (22.7), [HPLC Acidic], 536, (2.08) 12.64 (s, 1H), 8.94 (s, 1H), 8.79- 8.67 (m, 1H) 8.33 (s, 1H), 8.18- 8.03 (m, 2H), 7.89-7.73 (m, 1H), 6.57 (s, 1H), 5.16-5.02 (m, 1H),, 4.51 (q, J = 7.0 Hz, 2H), 3.46-3.37 (m, 2H), 3.25 (s, 3H), 2.63-2.56 (m, 1H), 2.21-2.04 (m, 1H), 2.02-1.91 (m, 1H), 1.42 (t, J = 7.0 Hz, 3H), 0.96-0.80 (m, 4H). SINGLE ENANTIOMER- stereochemistry unassigned N-(1-(2-(cyclopropanesulfon- amido)thiazol-4-yl)-3- methoxypropyl)-4-(6- ethoxy-pyrazin-2-yl)-2- fluorobenzamide

Biological Examples

Biological Example 1—Human CTPS1 Enzyme Inhibition

[0567] The enzyme inhibitory activities of compounds invented against the target of interest were determined using the ADP-Glo™ Max assay (Promega, UK). Assays for human CTPS1 were performed in 1x assay buffer containing 50 mM Tris, 10 mM MgCl.sub.2, 0.01% Tween-20, pH to 8.0 accordingly. Finally, immediately before use, L-cysteine was added to the 1× assay buffer to a final concentration of 2 mM. All reagents are from Sigma-Aldrich unless specified otherwise.

Human full length active C-terminal FLAG-Hiss-tag CTPS1 (UniProtKB-P17812, CTPS [1-591]-GGDYKDDDDKGGHHHHHHHH) was obtained from Proteros biostructures GmbH.

Assay Procedure

[0568] 3× human CTPS1 protein was prepared in 1× assay buffer to the final working protein concentration required for the reaction. A 2 uL volume per well of 3× human CTPS1 protein was mixed with 2 uL per well of 3× test compound (compound prepared in 1× assay buffer to an appropriate final 3× compound concentration respective to the concentration response curve designed for the compounds under test) for 10 minutes at 25° C. The enzymatic reaction was then initiated by addition of a 2 uL per well volume of a pre-mixed substrate mix (UltraPure ATP from ADP-Glo™ Max kit (0.31 mM), GTP (0.034 mM), UTP (0.48 mM) and L-glutamine (0.186 mM)) and the mixture was incubated for an appropriate amount of time within the determined linear phase of the reaction at 25° C. under sealed plate conditions with constant agitation at 500 revolutions per minute (rpm). A DP-Glo™ Max reagent was added for 60 minutes (6 uL per well) and subsequently ADP-Glo™ Max development reagent was added for 60 minutes (12 uL per well) prior to signal detection in a microplate reader (EnVision® Multilabel Reader, Perkin Elmer). Following each reagent addition over the course of the assay, assay plates were pulse centrifuged for 30 seconds at 500 rpm.

[0569] In all cases, the enzyme converts ATP to ADP and the ADP-Glo™ Max reagent subsequently depletes any remaining endogenous ATP in the reaction system. The ADP-Glo™ Max detection reagent converts the ADP that has been enzymatically produced back into ATP and using ATP as a substrate together with luciferin for the enzyme luciferase, light is generated which produces a detectable luminescence. The luminescent signal measured is directly proportional to the amount of ADP produced by the enzyme reaction and a reduction in this signal upon compound treatment demonstrates enzyme inhibition. The percentage inhibition produced by each concentration of compound was calculated using the equation shown below:

$$[00001] \% \text{Inhibition} = 1 - \frac{(\text{Mean}_{\text{Min}} - \text{Mean}_{\text{Inh}})}{(\text{Mean}_{\text{Min}} - \text{Mean}_{\text{Max}})} \times 100$$

[0570] Percentage inhibition was then plotted against compound concentration, and the 50% inhibitory concentration (IC.sub.50) was determined from the resultant concentration-response curve.

TABLE-US-00007 TABLE 7 Human CTPS1 Enzyme Inhibition data grouped by potency range (± indicates IC.sub.50 in the range of >10 to 21 micromolar, + indicates IC.sub.50 in the range >1 to 10 micromolar, ++ indicates IC.sub.50 in the range >0.1 to 1 micromolar, +++ indicates IC.sub.50 of ≤0.1 micromolar) R CTPS1 R1 ++ R2 ++ R3 ++ R4 +++ R5 +++ R6 +++ R7 ++ R8 + R9 + R10 +++ R11 +++ R12 +++ R13 +++ R14 +++ R15 +++ R16 ++ R17 ++ R18 ++ R19 +++ R20 +++ R21 +++ R22 ++ R23 ++ R24 ++ R25 ++ R26 ++ R27 ± R28 +++ R29 +++ R30 ++ R31 ++ R32 ++ R33 + R34 + R35 +++ R36 ++ R37 +++ R38 ++ R39 ++ R40 ++ R41 ++ R42 +++ R43 +++ R44 ++ R45 ++ R46 ++ R47 ++ R48 ++ R49 ++ R50 + R51 +++ R52 +++ R53 ++ R54 +++ R55 +++ R56 +++ R57 ++ R58 ++ R59 ++ R60 ++ R61 ++ R62 ++ R63 ++ R64 ++ R65 +++ R66 ++ R67 ++ R68 + R69 +++ R70 ++ R71 +++ R72 + R73 + R74 ++ R75 ++ R76 ++ R77 + R78 ++ R79 ++ R80 +++ R81 ++ R82 +++ R83 +++ R84 +++ R85 ++ R86 ++ R87 ++ R88 ++ R89 +++ R90 +++ R91 +++ R92 +++ R93 +++

Biological Example 2—RapidFire/MS-based Enzyme Selectivity Assays

Human CTPS1 versus CTPS2 Selectivity Assessment by RapidFire/MS Analysis.

[0571] The enzyme inhibitory activities against each target isoform of interest were determined for the compounds of the invention using an optimised RapidFire high-throughput mass spectrometry (RF/MS) assay format. RF/MS assays CTPS1 and for both human CTPS2 were performed in assay buffer consisting of 50 mM HEPES (Merck), 20 mM MgCl.sub.2, 5 mM KCl, 1 mM DTT, 0.01% Tween-20, pH to 8.0 accordingly. All reagents were from Sigma-Aldrich unless specified otherwise. Human full-length active C-terminal FLAG-His-tag CTPS1 (UniProtK B-P17812, CTPS [1-591]-GGDYKDDDDKGGHHHHHHHH) was obtained from Proteros biostructures GmbH. Human full length active C-terminal FLAG-His-A vi tagged CTPS2 (UniProtKB-Q9NRF8, CTPS2 [1-586]-DY KDDDDKHHHHHHHGLNDIFEAQKIEWHE) was obtained from Harker Bio.

Assay Procedure

[0572] Human CTPS (1 or 2) protein was prepared in 1× assay buffer to the final working protein concentration required for the reaction. A 2 uL volume per well of 2× CTPS (1 or 2) protein was mixed with 40nl of compound using acoustic (ECHO) delivery and incubated for 10 minutes at 25° C. Each isoform enzymatic reaction was subsequently initiated by addition of 2 uL per well of a 2× substrate mix in assay buffer. For hCTPS1: ATP (0.3 mM), UTP (0.2 mM), GTP (0.07 mM) and L-glutamine (0.1 mM). For hCTPS2: ATP (0.1 mM), UTP (0.04 mM), GTP (0.03 mM) and L-glutamine (0.1 mM). Each mixture was incubated for an appropriate amount of time per isoform within the determined linear phase of the reaction at 25° C. A 60 uL volume of stop solution (1% formic acid with 0.5 uM .sup.13C.sub.9-.sup.15N.sub.3-CTP in H.sub.2O) was added and the plate immediately heat-sealed and centrifuged for 10 minutes at 4,000 rpm. Following centrifugation, plates were loaded onto the Agilent RapidFire microfluidic solid phase extraction system coupled to an API4000 triple quadrupole mass spectrometer (RF/M S) for analysis.

[0573] In all cases, the enzyme converts UTP to CTP. Highly specific and sensitive multiple reaction monitoring (MRM) MS methods were optimised for the detection of the enzymatic reaction product, CTP, and the stable isotope labelled product standard

.sup.13C.sub.9-.sup.15N.sub.3-CTP. Readout for data analysis was calculated as the ratio between the peak area of the product CTP and the internal standard .sup.13C.sub.9-.sup.15N.sub.3-CTP. For data reporting, the following equation was used:

$$[00002] R = \frac{P}{IS}$$

(R=ratio/readout, P=product signal area, IS=internal standard signal area)

[0574] For each screening plate, the means of the negative (DMSO) and positive control values were used for the calculation of the respective assay window (S/B) and Z' values. The median of the respective control values was used for calculation of percent inhibition according to the following equation:

$$[00003] I = \frac{R_{reg} - R_{sample}}{[R_{reg} - R_{pos}]} \%$$

(I=Inhibition, R.sub.neg=median of negative control readout values, R.sub.pos=median of positive control readout values, R.sub.sample=sample readout value)

[0575] Percentage inhibition was then plotted against compound concentration, and the 50% inhibitory concentration (IC.sub.50) was determined from the resultant concentration-response curve.

[0576] Fold selectivity between CTPS1 and CTPS2 was subsequently calculated according to the following equation:

$$[00004] \text{Foldselectivity} = \frac{\text{CTPS2IC}_{50}}{\text{CTPS1IC}_{50}}$$

[0577] Certain compounds were tested in the assay above. The data for all compounds tested are presented below.

TABLE-US-00008 TABLE 8 Selectivity data split into grouping of 2-30 fold (+), >30-60 fold (+) or >60 fold (+) R Selectivity R5 + R6 ++ R7 ++ R11 ++ R19 ++ R23 ++ R25 ++ R26 +++ R41 ++ R42 ++ R43 ++ R45 ++ R46 + R47 + R48 ++ R51 ++ R52 +++ R54 + R55 +++ R56 +++ R62 +++ R63 + R64 ++ R68 ++ R69 +++ R70 +++ R71 +++ R73 + R74 ++ R75 +++ R76 + R78 ++ R79 + R80 +++ R82 +++ R83 +++ R84 +++ R86 +++ R87 ++ R88 +++ R89 +++ R90 ++ R91 +++ R92 +++ R93 +++

[0578] All compounds of the invention which have been tested were found to demonstrate inhibition of CTPS1 enzyme in this assay. Consequently, these compounds may be expected to have utility in the inhibition of CTPS1.

[0579] All compounds tested in the assay described in Biological Assay 2 were found to have at least 2 fold selectivity for CTPS1 over CTPS2, with many compounds having a selectivity for CTPS1 of over 60 fold.

[0580] In particular, these compounds may be expected to have utility in the treatment of diseases

whereby a selective CTPS1 compound is beneficial.

[0581] The compounds of the invention are also expected to have utility as research tools, for example, for use in CTPS assays.

[0582] Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer, step, group of integers or group of steps but not to the exclusion of any other integer, step, group of integers or group of steps.

[0583] The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the claims which follow.

[0584] All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Clauses of the Invention

[0585] Clause 1. A compound of formula (I):

##STR00222##

wherein [0586] R.sub.1 is C.sub.1-5alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl which cycloalkyl is optionally substituted by CH.sub.3, C.sub.1-3alkyleneOC.sub.1-2alkyl, or CF.sub.3; [0587] R.sub.3 is H, CH.sub.3, halo, OC.sub.1-2alkyl or CF.sub.3; [0588] R.sub.4 and R.sub.5 are each independently H, C.sub.1-6alkyl, C.sub.0-2alkyleneC.sub.3-6cycloalkyl, C.sub.0-2alkyleneC.sub.3-6heterocycloalkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-6alkylOH or C.sub.1-6haloalkyl, or R.sub.4 and R.sub.5 together with the carbon atom to which they are attached form a C.sub.3-6cycloalkyl or C.sub.3-6heterocycloalkyl ring; [0589] R.sub.6 is H or C.sub.1-3alkyl; [0590] Ar1 is a 6-membered aryl or heteroaryl; [0591] Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide; [0592] R.sub.10 is H, halo, C.sub.1-3alkyl, OC.sub.1-2alkyl, C.sub.1-2haloalkyl, OC.sub.1-2haloalkyl or CN; [0593] R.sub.11 is H, F, Cl, CH.sub.3, ethyl, OCH.sub.3, CF.sub.3, OCF.sub.3 or CN; [0594] R.sub.12 is attached to Ar2 in the meta or ortho position relative to Ar1 and R.sub.12 is H, halo, C.sub.1-4alkyl, C.sub.2-4alkynyl, C(=O)C.sub.1-2alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl, OC.sub.1-4alkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-4haloalkyl, OC.sub.1-4haloalkyl, CN, OC.sub.0-2alkyleneC.sub.3-5cycloalkyl, OCH.sub.2CH.sub.2N (CH.sub.3).sub.2, OH, C.sub.1-4alkylOH, NR.sub.23R.sub.24, SO.sub.2CH.sub.3, C(O)N(CH.sub.3).sub.2, NHC(O)C.sub.1-3alkyl, or a C.sub.3-6heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R.sub.12 together with a nitrogen atom to which it is attached forms an N-oxide (N.sup.+—O.sup.—); [0595] R.sub.23 is H or C.sub.1-2alkyl; and [0596] R.sub.24 is H or C.sub.1-2alkyl; [0597] or a salt and/or solvate thereof and/or derivative thereof.

[0598] Clause 2. The compound according to clause 1 which is a compound of formula (I):

##STR00223##

wherein [0599] R.sub.1 is C.sub.1-4alkyl, C.sub.1-2alkyleneOC.sub.1-2alkyl or C.sub.0-1alkyleneC.sub.3-4cycloalkyl which cycloalkyl is optionally substituted by CH.sub.3; [0600] R.sub.3 is H, CH.sub.3, F or Cl; [0601] R.sub.4 and R.sub.5 are each independently H, C.sub.1-4alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-4alkylOH or C.sub.1-4haloalkyl; [0602] R.sub.6 is H or C.sub.1-3alkyl; [0603] Ar1 is a 6-membered aryl or heteroaryl; [0604] Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide; [0605] R.sub.10 is H, halo, C.sub.1-3alkyl, OC.sub.1-2alkyl, C.sub.1-2haloalkyl, OC.sub.1-2haloalkyl or CN; and [0606] R.sub.12 is attached to Ar2 in the meta position relative to Ar1 and R.sub.12 is H, halo, C.sub.1-4alkyl, C.sub.2alkynyl,

C(=O)C.sub.1-2alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl, OC.sub.1-4alkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-4haloalkyl, OC.sub.1-4haloalkyl or CN; [0607] or a salt and/or solvate thereof and/or derivative thereof.

[0608] Clause 3. The compound according to clause 1 which is a compound of formula (I):

##STR00224##

wherein [0609] R.sub.1 is C.sub.0-1alkyleneC.sub.3-4cycloalkyl; [0610] R.sub.3 is H, CH.sub.3 or Cl; [0611] R.sub.4 and R.sub.5 are each independently H, C.sub.1-4alkyl or C.sub.1-3alkyleneOC.sub.1-3alkyl; [0612] or R.sub.4 together with R.sub.5 form a C.sub.3-6cycloalkyl ring [0613] R.sub.6 is H or C.sub.1-3alkyl; [0614] Ar₁ is a 6-membered aryl or heteroaryl; [0615] Ar₂ is a 6-membered aryl or heteroaryl and is attached to Ar₁ in the para position relative to the amide; [0616] R.sub.10 is H, halo, C.sub.1-3alkyl, OC.sub.1-2alkyl or C.sub.1-2haloalkyl; and [0617] R.sub.12 is attached to Ar₂ in the meta position relative to Ar₁ and R.sub.12 is H, halo, C.sub.1-4alkyl, C(=O)C.sub.1-2alkyl, OC.sub.1-4alkyl, C.sub.1-4haloalkyl, OC.sub.1-4haloalkyl or CN; [0618] or a salt and/or solvate thereof and/or derivative thereof.

[0619] Clause 4. The compound according to any one of clauses 1 to 3 wherein R.sub.1 is C.sub.1-5alkyl.

[0620] Clause 5. The compound according to clause 4 wherein R.sub.1 is C.sub.1-4alkyl.

[0621] Clause 6. The compound according to any one of clauses 1 to 3 wherein R.sub.1 is C.sub.1-3alkyleneOC.sub.1-2alkyl.

[0622] Clause 7. The compound according to any one of clauses 1 to 3 wherein R.sub.1 is C.sub.1-2alkyleneOC.sub.1-2alkyl.

[0623] Clause 8. The compound according to any one of clauses 1 to 3 wherein R.sub.1 is C.sub.0-2alkyleneC.sub.3-5cycloalkyl which cycloalkyl is optionally substituted by CH.sub.3.

[0624] Clause 9. The compound according to clause 8 wherein R.sub.1 is C.sub.0-1alkyleneC.sub.3-4cycloalkyl which cycloalkyl is optionally substituted by CH.sub.3.

[0625] Clause 10. The compound according to clause 9 wherein R.sub.1 is C.sub.0-1alkyleneC.sub.3-4cycloalkyl.

[0626] Clause 11. The compound according to any one of clauses 9 or 10 wherein R.sub.1 is C.sub.3-4cycloalkyl.

[0627] Clause 12. The compound according to clause 11 wherein R.sub.1 is cyclopropyl.

[0628] Clause 13. The compound according to clause 9 wherein R.sub.1 is C.sub.0-1alkyleneC.sub.3-4cycloalkyl which cycloalkyl is substituted by CH.sub.3.

[0629] Clause 14. The compound according to any one of clauses 1 to 13 wherein R.sub.3 is H.

[0630] Clause 15. The compound according to any one of clauses 1 to 13 wherein R.sub.3 is Me.

[0631] Clause 16. The compound according to any one of clauses 1 to 13 wherein R.sub.3 is halo.

[0632] Clause 17. The compound according to clause 16 wherein R.sub.3 is F.

[0633] Clause 18. The compound according to clause 16 wherein R.sub.3 is Cl.

[0634] Clause 19. The compound according to any one of clauses 1 to 13 wherein R.sub.3 is OC.sub.1-2alkyl.

[0635] Clause 20. The compound according to any one of clauses 1 to 13 wherein R.sub.3 is OCF.sub.3.

[0636] Clause 21. The compound according to any one of clauses 1 to 13 wherein R.sub.3 is CF.sub.3.

[0637] Clause 22. The compound according to any one of clauses 1 to 21 wherein R.sub.4 is H.

[0638] Clause 23. The compound according to any one of clauses 1 to 21 wherein R.sub.4 is C.sub.1-6alkyl.

[0639] Clause 24. The compound according to clause 23 wherein R.sub.4 is C.sub.1-4alkyl.

[0640] Clause 25. The compound according to clause 24 wherein R.sub.4 is methyl or ethyl.

[0641] Clause 26. The compound according to any one of clauses 1 to 21 wherein R.sub.4 is C.sub.0-2alkyleneC.sub.3-6cycloalkyl.

[0642] Clause 27. The compound according to clause 26 wherein R.sub.4 is C.sub.0-2alkyleneC.sub.3-5cycloalkyl.

[0643] Clause 28. The compound according to any one of clauses 1 to 21 wherein R.sub.4 is C.sub.1-3alkyleneOC.sub.1-3alkyl such as CH.sub.2CH.sub.2OCH.sub.3.

[0644] Clause 29. The compound according to any one of clauses 1 to 21 wherein R.sub.4 is C.sub.0-2alkyleneC.sub.3-6heterocycloalkyl.

[0645] Clause 30. The compound according to any one of clauses 1 to 21 wherein R.sub.4 is C.sub.1-6alkylOH.

[0646] Clause 31. The compound according to clause 30 wherein R.sub.4 is C.sub.1-4alkylOH.

[0647] Clause 32. The compound according to clause 1 to 21 wherein R.sub.4 is C.sub.1-6haloalkyl.

[0648] Clause 33. The compound according to clause 32 wherein R.sub.4 is C.sub.1-4haloalkyl.

[0649] Clause 34. The compound according to any one of clauses 1 to 33 wherein R.sub.5 is H.

[0650] Clause 35. The compound according to any one of clauses 1 to 33 wherein R.sub.5 is C.sub.1-6alkyl.

[0651] Clause 36. The compound according to clause 35 wherein R.sub.5 is C.sub.1-4alkyl.

[0652] Clause 37. The compound according to clause 36 wherein R.sub.5 is methyl or ethyl.

[0653] Clause 38. The compound according to any one of clauses 1 to 33 wherein R.sub.5 is C.sub.0-2alkyleneC.sub.3-6cycloalkyl.

[0654] Clause 39. The compound according to clause 38 wherein R.sub.5 is C.sub.0-2alkyleneC.sub.3-5cycloalkyl.

[0655] Clause 40. The compound according to any one of clauses 1 to 33 wherein R.sub.5 is C.sub.0-2alkyleneC.sub.3-6heterocycloalkyl.

[0656] Clause 41. The compound according to any one of clauses 1 to 33 wherein R.sub.5 is C.sub.1-3alkyleneOC.sub.1-3alkyl such as CH.sub.2CH.sub.2OCH.sub.3.

[0657] Clause 42. The compound according to any one of clauses 1 to 33 wherein R.sub.5 is C.sub.1-6alkylOH.

[0658] Clause 43. The compound according to clause 42 wherein R.sub.5 is C.sub.1-4alkylOH.

[0659] Clause 44. The compound according to any one of clauses 1 to 33 wherein R.sub.5 is C.sub.1-6haloalkyl.

[0660] Clause 45. The compound according to clause 44 wherein R.sub.5 is C.sub.1-4haloalkyl.

[0661] Clause 46. The compound according to any one of clauses 1 to 21 wherein R.sub.4 and R.sub.5 together with the carbon atom to which they are attached form a C.sub.3-6cycloalkyl such as cyclopropyl.

[0662] Clause 47. The compound according to any one of clauses 1 to 21 wherein R.sub.4 and R.sub.5 together with the carbon atom to which they are attached form a C.sub.3-6heterocycloalkyl such as tetrahydropyranyl or piperidiny.

[0663] Clause 48. The compound according to any one of clauses 1 to 47 wherein at least one, such as one, nitrogen atom of a C.sub.3-6heterocycloalkyl ring is substituted, for example by C.sub.1-4alkyl, C(O)H, C(O)C.sub.1-4alkyl, C(O)OC.sub.1-4alkyl, C(O)OC.sub.1-4alkylaryl such as C(O)OBz, C(O)NHC.sub.1-4alkyl, C(O)NHC.sub.1-4alkylaryl such as C(O)NHBz, an Fmoc group, C(O)C.sub.1-4haloalkyl, C(O)OC.sub.1-4haloalkyl or C(O)NHC.sub.1-4haloalkyl such as C(O)OtBu.

[0664] Clause 49. The compound according to any one of clauses 1 to 47 wherein any nitrogen atom in the C.sub.3-6heterocycloalkyl ring is not substituted.

[0665] Clause 50. The compound according to any one of clauses 1 to 49 wherein at least one, such as one, sulphur atom of a C.sub.3-6heterocycloalkyl ring is substituted, for example by one oxygen atom to form S=O or by two oxygen atoms to form S(O).sub.2.

[0666] Clause 51. The compound according to any one of clauses 1 to 49 wherein any sulphur atom in the C.sub.3-6heterocycloalkyl ring is not substituted.

[0667] Clause 52. The compound according to any one of clauses 1 to 34 wherein R.sub.4 and R.sub.5 are both H.

[0668] Clause 53. The compound according to any one of clauses 1 to 37 wherein R.sub.4 and R.sub.5 are both methyl.

[0669] Clause 54. The compound according to any one of clauses 1 to 37 wherein R.sub.4 and R.sub.5 are both ethyl.

[0670] Clause 55. The compound according to any one of clauses 1 to 34 wherein R.sub.4 is ethyl and R.sub.5 is H.

[0671] Clause 56. The compound according to clause 55 wherein R.sub.4 and R.sub.5 are arranged in an S configuration.

[0672] Clause 57. The compound according to any one of clauses 1 to 56 wherein R.sub.6 is H.

[0673] Clause 58. The compound according to any one of clauses 1 to 56 wherein R.sub.6 is C.sub.1-3alkyl.

[0674] Clause 59. The compound according to clause 58 wherein R.sub.6 is methyl.

[0675] Clause 60. The compound according to any one of clauses 1 to 59 wherein Ar₁ is phenyl.

[0676] Clause 61. The compound according to any one of clauses 1 to 59 wherein Ar₁ is 2-pyridyl.

[0677] Clause 62. The compound according to any one of clauses 1 to 61 wherein Ar₂ is 3-pyridyl.

[0678] Clause 63. The compound according to any one of clauses 1 to 61 wherein Ar₂ is 2,5-pyrazinyl.

[0679] Clause 64. The compound according to any one of clauses 1 to 63 wherein R.sub.10 is H.

[0680] Clause 65. The compound according to any one of clauses 1 to 63 wherein R.sub.10 is halo such as F.

[0681] Clause 66. The compound according to any one of clauses 1 to 63 wherein R.sub.10 is C.sub.1-3alkyl such as methyl.

[0682] Clause 67. The compound according to any one of clauses 1 to 63 wherein R.sub.10 is OC.sub.1-2alkyl such as OCH.sub.3.

[0683] Clause 68. The compound according to any one of clauses 1 to 63 wherein R.sub.10 is C.sub.1-2haloalkyl such as CF.sub.3.

[0684] Clause 69. The compound according to any one of clauses 1 to 63 wherein R.sub.10 is OC.sub.1-2haloalkyl.

[0685] Clause 70. The compound according to any one of clauses 1 to 63 wherein R.sub.10 is CN.

[0686] Clause 71. The compound according to any one of clauses 65 to 70 wherein R.sub.10 ortho to the amide.

[0687] Clause 72. The compound according to any one of clauses 1 to 71 wherein R.sub.11 is H.

[0688] Clause 73. The compound according to any one of clauses 1 to 71 wherein R.sub.11 is F.

[0689] Clause 74. The compound according to any one of clauses 1 to 71 wherein R.sub.11 is Cl.

[0690] Clause 75. The compound according to any one of clauses 1 to 71 wherein R.sub.11 is CH.sub.3.

[0691] Clause 76. The compound according to any one of clauses 1 to 71 wherein R_n is ethyl.

[0692] Clause 77. The compound according to any one of clauses 1 to 71 wherein R.sub.11 is OCH.sub.3.

[0693] Clause 78. The compound according to any one of clauses 1 to 71 wherein R_n is CF.sub.3.

[0694] Clause 79. The compound according to any one of clauses 1 to 71 wherein R.sub.11 is OCF.sub.3.

[0695] Clause 80. The compound according to any one of clauses 1 to 71 wherein R.sub.11 is CN.

[0696] Clause 81. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is H.

[0697] Clause 82. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is halo such as fluoro or chloro.

[0698] Clause 83. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is C.sub.1-4alkyl such as

[0699] CH.sub.3 or ethyl.

[0700] Clause 84. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is C.sub.2-4alkynyl.

[0701] Clause 85. The compound according to clause 84 wherein R.sub.12 is C.sub.2alkynyl.

[0702] Clause 86. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is C(=O)C.sub.1-2alkyl such as C(=O)CH.sub.3.

[0703] Clause 87. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is C.sub.0-2alkyleneC.sub.3-5cycloalkyl.

[0704] Clause 88. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is OC.sub.1-4alkyl such as OCH.sub.3, OEt or OiPr.

[0705] Clause 89. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is C.sub.1-3alkyleneOC.sub.1-3alkyl.

[0706] Clause 90. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is C.sub.1-4haloalkyl such as CF.sub.3.

[0707] Clause 91. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is OC.sub.1-4haloalkyl such as OCH.sub.2CF.sub.3.

[0708] Clause 92. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is CN.

[0709] Clause 93. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is OC.sub.0-2alkyleneC.sub.3-5cycloalkyl.

[0710] Clause 94. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is OCH.sub.2CH.sub.2N(CH.sub.3).sub.2.

[0711] Clause 95. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is OH.

[0712] Clause 96. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is C.sub.1-4alkylOH.

[0713] Clause 97. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is NR.sub.23R.sub.24.

[0714] Clause 98. The compound according to clause 97 wherein R.sub.23 is H.

[0715] Clause 99. The compound according to clause 97 wherein R.sub.23 is C.sub.1-2alkyl such as CH.sub.3.

[0716] Clause 100. The compound according to any one of clauses 97 to 99 wherein R.sub.24 is H.

[0717] Clause 101. The compound according to any one of clauses 97 to 99 wherein R.sub.24 is C.sub.1-2alkyl such as CH.sub.3.

[0718] Clause 102. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is SO.sub.2CH.sub.3.

[0719] Clause 103. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is C(O)N(CH.sub.3).sub.2.

[0720] Clause 104. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is NHC(O)C.sub.1-3alkyl.

[0721] Clause 105. The compound according to any one of clauses 1 to 80 wherein R.sub.12 is a C.sub.3-6heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar².

[0722] Clause 106. The compound according to any one of clauses 1 to 80 wherein R.sub.12 together with a nitrogen atom to which it is attached forms an N-oxide (N.sup.+—O.sup.-).

[0723] Clause 107. The compound according to any one of clauses 82 to 106 wherein R.sub.12 is attached at the meta position of Ar².

[0724] Clause 108. The compound according to any one of clauses 82 to 106 wherein R.sub.12 is attached at the ortho position of Ar².

[0725] Clause 109. A compound of the examples R1 to R71.

[0726] Clause 110. A compound of the examples R72 to R93.

[0727] Clause 111. A compound of INTE1 to INTE20 or INTF1 to INTF53.

[0728] Clause 112. A compound of INTE21 to INTE 39.

[0729] Clause 113. A compound of formula (II):

##STR00225##

wherein R.sub.1, R.sub.3, R.sub.4 and R.sub.5 are as defined in any one of clauses 1 to 3.

[0730] Clause 114. A compound of formula (III):

##STR00226##

wherein R.sub.10, R.sub.12, Ar.sub.1 and Ar.sub.2 are as defined in any one of clauses 1 to 3.

[0731] Clause 115. A compound of formula (III-A):

##STR00227##

wherein R.sub.10, R.sub.1, R.sub.12, Ar.sub.1 and Ar.sub.2 are as defined in any one of clauses 1 to 3.

[0732] Clause 116. A compound of formula (VIII):

##STR00228##

wherein R.sub.1, R.sub.3 and R.sub.4 are as defined in any one of clauses 1 to 3.

[0733] Clause 117. A compound according to any one of clauses 113 to 116 which is in the form of a salt.

[0734] Clause 118. A compound according to any one of clauses 1 to 110, for use as a medicament.

[0735] Clause 119. The compound according to clause 118, for use in the inhibition of CTPS1 in a subject.

[0736] Clause 120. The compound according to clause 118, for use in the reduction of T-cell and/or B-cell proliferation in a subject.

[0737] Clause 121. The compound according to clause 118, for use in the treatment or prophylaxis of: inflammatory skin diseases such as psoriasis or lichen planus; acute and/or chronic GVHD such as steroid resistant acute GVHD; acute lymphoproliferative syndrome (ALPS); systemic lupus erythematosus, lupus nephritis or cutaneous lupus; or transplantation.

[0738] Clause 122. The compound according to clause 118, for use in the treatment or prophylaxis of myasthenia gravis, multiple sclerosis or scleroderma/systemic sclerosis.

[0739] Clause 123. A compound according to clause 118, for use in the treatment of cancer.

[0740] Clause 124. A method for treating cancer in a subject, by administering to a subject in need thereof a compound according to any one of clauses 1 to 110.

[0741] Clause 125. Use of a compound according to any one of clauses 1 to 110, in the manufacture of a medicament for the treatment of cancer in a subject.

[0742] Clause 126. The compound according to clause 123, the method according to clause 124 or the use according to clause 125 wherein the cancer is a haematological cancer.

[0743] Clause 127. The compound, method or use according to clause 126 wherein the haematological cancer is selected from the group consisting of A cute myeloid leukemia, Angioimmunoblastic T-cell lymphoma, B-cell acute lymphoblastic leukemia, Sweet Syndrome, T-cell Non-Hodgkins lymphoma (including natural killer/T-cell lymphoma, adult T-cell leukaemia/lymphoma, enteropathy type T-cell lymphoma, hepatosplenic T-cell lymphoma and cutaneous T-cell lymphoma), T-cell acute lymphoblastic leukemia, B-cell Non-Hodgkins lymphoma (including Burkitt lymphoma, diffuse large B-cell lymphoma, Follicular lymphoma, Mantle cell lymphoma, Marginal Zone lymphoma), Hairy Cell Leukemia, Hodgkin lymphoma, Lymphoblastic lymphoma, Lymphoplasmacytic lymphoma, Mucosa-associated lymphoid tissue lymphoma, Multiple myeloma, Myelodysplastic syndrome, Plasma cell myeloma, Primary mediastinal large B-cell lymphoma, chronic myeloproliferative disorders (such as chronic myeloid leukemia, primary myelofibrosis, essential thrombocytemia, polycytemia vera) and chronic lymphocytic leukemia.

[0744] Clause 128. The compound according to clause 123, the method according to clause 124 or the use according to clause 125 wherein the cancer is a non-haematological cancer such as bladder cancer, breast cancer, melanoma, neuroblastoma, malignant pleural mesothelioma and sarcoma, such as breast cancer and melanoma.

- [0745] Clause 129. The compound according to clause 118, for use in enhancing recovery from vascular injury or surgery and reducing morbidity and mortality associated with neointima and restenosis in a subject.
- [0746] Clause 130. A method for enhancing recovery from vascular injury or surgery and reducing morbidity and mortality associated with neointima and restenosis in a subject, by administering to a subject in need thereof a compound according to any one of clauses 1 to 110.
- [0747] Clause 131. Use of a compound according to any one of clauses 1 to 110, in the manufacture of a medicament for enhancing recovery from vascular injury or surgery and reducing morbidity and mortality associated with neointima and restenosis in a subject.
- [0748] Clause 132. A method for the inhibition of CTPS1 in a subject, which comprises administering to the subject an effective amount of a compound according to any one of clauses 1 to 110.
- [0749] Clause 133. Use of a compound according to any one of clauses 1 to 110, in the manufacture of a medicament for the inhibition of CTPS1 in a subject.
- [0750] Clause 134. A pharmaceutical composition comprising a compound according to any one of clauses 1 to 110.
- [0751] Clause 135. The compound, method or use according to any one of clauses 118 to 133, for administration to a human subject.
- [0752] Clause 136. The compound, method, use or composition according to any one of clauses 118 to 135, for administration in conjunction with a further pharmaceutically acceptable active ingredient or ingredients.
- [0753] Clause 137. The compound, method, use or composition according to any one of clauses 118 to 136, for topical administration to the skin, eye or gut.
- [0754] Clause 138. The compound according to any one of clauses 1 to 137, which is in natural isotopic form.

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Claims

1. A compound of formula (I): ##STR00229## wherein R.sub.1 is C.sub.1-5alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl which cycloalkyl is optionally substituted by CH.sub.3, C.sub.1-3alkyleneOC.sub.1-2alkyl, or CF.sub.3; R.sub.3 is H, CH.sub.3, halo, OC.sub.1-2alkyl or CF.sub.3; R.sub.4 and R.sub.5 are each independently H, C.sub.1-6alkyl, C.sub.0-2alkyleneC.sub.3-6cycloalkyl, C.sub.0-2alkyleneC.sub.3-6heterocycloalkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-6alkylOH or C.sub.1-6haloalkyl, or R.sub.4 and R.sub.5 together with the carbon atom to which they are attached form a C.sub.3-6cycloalkyl or C.sub.3-6heterocycloalkyl ring; R.sub.6 is H or C.sub.1-3alkyl; Ar1 is a 6-membered aryl or heteroaryl; Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide; R.sub.10 is H, halo, C.sub.1-3alkyl, OC.sub.1-2alkyl, C.sub.1-2haloalkyl, OC.sub.1-2haloalkyl or CN; R.sub.11 is H, F, Cl, CH.sub.3, ethyl, OCH.sub.3, CF.sub.3, OCF.sub.3 or CN; R.sub.12 is attached to Ar2 in the meta or ortho position relative to Ar1 and R.sub.12 is H, halo, C.sub.1-4alkyl, C.sub.2-4alkynyl, C(=O)C.sub.1-2alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl, OC.sub.1-4alkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-4haloalkyl, OC.sub.1-4haloalkyl, CN, OC.sub.0-2alkyleneC.sub.3-5cycloalkyl, OCH.sub.2CH.sub.2N(CH.sub.3).sub.2, OH, C.sub.1-4alkylOH, NR.sub.23R.sub.24, SO.sub.2CH.sub.3, C(O)N (CH.sub.3).sub.2, NHC(O)C.sub.1-3alkyl, or a C.sub.3-6heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R.sub.12 together with a nitrogen atom to which it is attached forms an N-oxide (N⁺—O⁻); R.sub.23 is H or C.sub.1-2alkyl; R.sub.24 is H or C.sub.1-2alkyl; or a salt and/or solvate thereof and/or derivative thereof.

2. The compound according to claim 1 wherein: R.sub.1 is C.sub.1-4alkyl, C.sub.1-2alkyleneOC.sub.1-2alkyl or C.sub.0-1alkyleneC.sub.3-4cycloalkyl which cycloalkyl is optionally substituted by CH.sub.3; R.sub.3 is H, CH.sub.3, F or Cl; R.sub.4 and R.sub.5 are each independently H, C.sub.1-4alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-4alkylOH or C.sub.1-4haloalkyl; R.sub.6 is H or C.sub.1-3alkyl; Ar1 is a 6-membered aryl or heteroaryl; Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide; R.sub.10 is H, halo, C.sub.1-3alkyl, OC.sub.1-2alkyl, C.sub.1-2haloalkyl, OC.sub.1-2haloalkyl or CN; R.sub.11 is H; and R.sub.12 is attached to Ar2 in the meta position relative to Ar1 and R.sub.12 is H, halo, C.sub.1-4alkyl, C.sub.2alkynyl, C(=O)C.sub.1-2alkyl, C.sub.0-2alkyleneC.sub.3-5cycloalkyl, OC.sub.1-4alkyl, C.sub.1-3alkyleneOC.sub.1-3alkyl, C.sub.1-4haloalkyl, OC.sub.1-4haloalkyl or CN; or a salt and/or solvate thereof and/or derivative thereof.

3. The compound according to claim 1 wherein: R.sub.1 is C.sub.0-1alkyleneC.sub.3-4cycloalkyl; R.sub.3 is H, CH.sub.3 or Cl; R.sub.4 and R.sub.5 are each independently H, C.sub.1-4alkyl or C.sub.1-3alkyleneOC.sub.1-3alkyl; or R.sub.4 together with R.sub.5 form a C.sub.3-6cycloalkyl ring R.sub.6 is H or C.sub.1-3alkyl; Ar1 is a 6-membered aryl or heteroaryl; Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide; R.sub.10 is H, halo, C.sub.1-3alkyl, OC.sub.1-2alkyl or C.sub.1-2haloalkyl; and R.sub.12 is attached to Ar2 in the meta position relative to Ar1 and R.sub.12 is H, halo, C.sub.1-4alkyl, C(=O)C.sub.1-2alkyl, OC.sub.1-4alkyl, C.sub.1-4haloalkyl, OC.sub.1-4haloalkyl or CN; or a salt and/or solvate thereof and/or derivative thereof.
4. The compound according to any one of claims 1 to 3 wherein R.sub.1 is C.sub.3-4cycloalkyl such as cyclopropyl.
5. The compound according to any one of claims 1 to 4 wherein R.sub.3 is H.
6. The compound according to any one of claims 1 to 5 wherein R.sub.4 is H or C.sub.1-4alkyl such as methyl or ethyl.
7. The compound according to any one of claims 1 to 6 wherein R.sub.5 is H or C.sub.1-4alkyl such as methyl or ethyl.
8. The compound according to any one of claims 1 to 7 wherein R.sub.4 and R.sub.5 are both H, or R.sub.4 and R.sub.5 are both methyl, or R.sub.4 and R.sub.5 are both ethyl.
9. The compound according to any one of claims 1 to 5 wherein R.sub.4 is CH.sub.2CH.sub.2OCH.sub.3 and R.sub.5 is H.
10. The compound according to any one of claims 1 to 5 wherein R.sub.4 and R.sub.5 together with the carbon atom to which they are attached form a C.sub.3-6cycloalkyl or C.sub.3-6heterocycloalkyl ring;
11. The compound according to any one of claims 1 to 10 wherein R.sub.6 is H or methyl e.g. H.
12. The compound according to any one of claims 1 to 11 wherein Ar1 is phenyl or 2-pyridyl such as phenyl.
13. The compound according to any one of claims 1 to 12 wherein Ar2 is 3-pyridyl or 2,5-pyrazinyl such as 2,5-pyrazinyl.
14. The compound according to any one of claims 1 to 13 wherein R.sub.10 is H, halo, C.sub.1-3alkyl, OC.sub.1-2alkyl or C.sub.1-2haloalkyl such as H, fluoro, CH.sub.3, OCH.sub.3 or CF.sub.3 e.g. H or fluoro.
15. The compound according to any one of claims 1 to 14 wherein R.sub.11 is H.
16. The compound according to any one of claims 1 to 15 wherein R.sub.12 is H, halo, C.sub.1-4alkyl, C(=O)C.sub.1-2alkyl, OC.sub.1-4alkyl, C.sub.1-4haloalkyl or OC.sub.1-4haloalkyl such as H, fluoro, chloro, CH.sub.3, Et, OCH.sub.3, OEt, OiPr, CF.sub.3 or OCH.sub.2CF.sub.3, in particular fluoro, chloro, CH.sub.3, OCH.sub.3, OEt, OiPr or CF.sub.3, such as chloro, OEt, OiPr, CF.sub.3, e.g. chloro, OEt, CF.sub.3.
17. A compound which is selected from the group consisting of: a compound of formula (II): ##STR00230## a compound of formula (III): ##STR00231## and a compound of formula (VIII): ##STR00232## wherein R.sub.1, R.sub.3, R.sub.4, R.sub.5, R.sub.10, R.sub.12, Ar1 and Ar2 are as defined in claim 1.
18. A compound of formula (III-A): ##STR00233## or a salt thereof, wherein R.sub.10, R.sub.11, R.sub.12, Ar.sub.1 and Ar.sub.2 are as defined in any one of claims 1 to 3.
19. A compound according to any one of claims 1 to 16, for use as a medicament.
20. The compound according to claim 19, for use in the inhibition of CTPS1 in a subject.
21. The compound according to claim 19, for use in the reduction of T-cell and/or B-cell proliferation in a subject.
22. The compound according to claim 19, for use in the treatment or prophylaxis of: inflammatory skin diseases such as psoriasis or lichen planus; acute and/or chronic GVHD such as steroid resistant acute GVHD; acute lymphoproliferative syndrome (ALPS); systemic lupus

erythematosus, lupus nephritis or cutaneous lupus; or transplantation.

23. The compound according to claim 19, for use in the treatment or prophylaxis of myasthenia gravis, multiple sclerosis, or scleroderma/systemic sclerosis.

24. A compound according to claim 19, for use in the treatment of cancer.

25. The compound according to claim 24 wherein the cancer is a haematological cancer.

26. The compound, method or use according to claim 25 wherein the haematological cancer is selected from the group consisting of Acute myeloid leukemia, Angioimmunoblastic T-cell lymphoma, B-cell acute lymphoblastic leukemia, Sweet Syndrome, T-cell Non-Hodgkins lymphoma (including natural killer/T-cell lymphoma, adult T-cell leukaemia/lymphoma, enteropathy type T-cell lymphoma, hepatosplenic T-cell lymphoma and cutaneous T-cell lymphoma), T-cell acute lymphoblastic leukemia, B-cell Non-Hodgkins lymphoma (including Burkitt lymphoma, diffuse large B-cell lymphoma, Follicular lymphoma, Mantle cell lymphoma, Marginal Zone lymphoma), Hairy Cell Leukemia, Hodgkin lymphoma, Lymphoblastic lymphoma, Lymphoplasmacytic lymphoma, Mucosa-associated lymphoid tissue lymphoma, Multiple myeloma, Myelodysplastic syndrome, Plasma cell myeloma, Primary mediastinal large B-cell lymphoma, chronic myeloproliferative disorders (such as chronic myeloid leukemia, primary myelofibrosis, essential thrombocytemia, polycythemia vera) and chronic lymphocytic leukemia.

27. A compound according to claim 19, for use in enhancing recovery from vascular injury or surgery and reducing morbidity and mortality associated with neointima and restenosis in a subject.

28. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16.

29. The compound or composition according to any one of claims 19 to 28, for administration in conjunction with a further pharmaceutically acceptable active ingredient or ingredients.

30. The compound or composition according to any one of claims 19 to 29, for topical administration to the skin, eye or gut.
