ANTAGONIST COMPOUNDS

INTRODUCTION

[0001] The present invention relates to certain compounds that function as antagonists of the adenosine A2a receptor. Additionally, some of the compounds are also antagonists of both A2a and the A2b receptor. The present invention also relates to processes for the preparation of these compounds, to pharmaceutical compositions comprising them, and to their use in the treatment of diseases or conditions in which adenosine A2a and/or A2b receptor activity is implicated, such as, for example, cancer.

BACKGROUND OF THE INVENTION

[0002] A number of immunosuppressive pathways are active in the tumour microenvironment which enable tumour cells to evade elimination by cytotoxic T cells and can diminish the clinical response of patients to immunotherapy with anti-checkpoint antibodies. The anti-PD-1 antibodies pembrolizumab and nivolumab and anti-PD-L1 antibodies durvalumab, avelumab and atezolizumab are approved for the treatment of number of solid tumours including non-small cell lung cancer, head and neck squamous cancer and urothelial cancer. However, only 20-30% of patients respond to checkpoint blockade and the side effects of such treatments are significant (Sukari et al, 2016). Consequently, other approaches to enhance the cytotoxic potential of the tumour microenvironment are actively being investigated. This includes agents that could be used as monotherapies or, more likely, used in combination with checkpoint inhibitors and cytotoxic agents to enhance their efficacy.

[0003] One approach that has attracted attention is to interfere with the production and/or action of adenosine in the tumour microenvironment (Vijayan et al, 2017). Adenosine has immunosuppressive properties and is present in the tumour microenvironment at high concentrations. Recent studies estimate the concentration of adenosine to be about 10μM in human tumours compared to <1 μM in normal tissue (Houthuys et al 2017). Adenosine is formed at both intracellular and extracellular sites by two distinct pathways that involve two different substrates. Intracellular adenosine is derived from AMP and S-adenosyl homocysteine whilst the high extracellular adenosine concentrations observed during metabolic stress are associated with the release and degradation of precursor adenine nucleotides (ATP, ADP and AMP) by the concerted action of CD39 and CD73 (Vijayan et al, 2017).

[0004] CD39 and CD73 are upregulated in the tumour microenvironment in response to hypoxia. CD73 represents a putative patient stratification method for adenosine antagonists as its expression on tumour cells is also associated with poor overall prognosis in many different cancer types suggesting that adenosine production contributes to the undesirable

immunosuppressive phenotype of the tumour microenvironment (Gao et al 2014; Loi et al, 2013;). CD73 expression by tumour-infiltrating immune cells is also important in promoting tumour immune suppression as CD73 negative Treg cells fail to suppress effector T cell functions (Deaglio et al, 2007; Reinhardt et al, (2017). Furthermore, patients resistant to anti-PD1 treatment have elevated levels of CD73 (Reinhardt et al, 2017).

[0005] Adenosine regulates cell function via occupancy of specific GPCRs on the cell surface of the P1 purinoceptor subtypes. The P1 receptor family is further subdivided into A1, A2a, A2b and A3.

[0006] A2 receptors are subdivided into A2a and A2b, based on high and low affinity for adenosine, respectively. A2a is expressed by lymphocytes and activation of A2a leads to suppression of cytokine production and other effector functions. Tumour growth is inhibited by genetic ablation of A2a in syngeneic mouse models and this effect has been demonstrated to be due to enhanced lymphocyte activation and cytotoxic function (Ohta et al, 2006; Waickman et al 2012; Beavis et al, 2013; Mittal et al, 2014; Cekic et al, 2014). A2a-/- mice show an increased response to inhibition of checkpoint pathways such as PD-1, with an improvement in both tumour free survival and overall survival. Adenosine-mediated A2a activation also limits the efficacy of ant-CTLA4 treatment (Iannone et al, 2014).

[0007] The effects of genetic deficiency of A2a in mouse models is mimicked by pharmacological blockade of A2a. A2a antagonists have been shown to enhance the cytotoxic CD8+T cells and to enhance the ability of NK cells prevent metastasis of CD73-expressing tumours (Beavis et al, 2013). Importantly, A2a antagonists enhance the efficacy of anti-PD1 antibodies (Beavis et al, 2015).

[0008] These findings have prompted the development of selective A2a antagonists for use in cancer immunotherapy and clinical trials are ongoing with CPI-444, the first selective A2a antagonist to be evaluated in cancer, being used as both as a monotherapy and in combination with the anti-PDL1 antibody atezolizumab. The preliminary data indicated that the compound was well tolerated and showed early indications of reducing tumour size and enhancing CD8+T infiltration into tumour tissue.

[0009] The adenosine A2b receptor also plays a key role in cancer progression through modulation of the tumour microenvironment. A2b is expressed by cells of myeloid origin and the high concentrations of adenosine found within the tumour microenvironment can modify the behaviour of tumour associated macrophages, myeloid-derived suppressor cells and dendritic cells. Activation of A2b leads to polarisation of immunosuppressive M2 macrophages (Csoka et al, 2012), formation of myeloid-derived suppressive cells (Rhyzov et al, 2011) and promotes the immunosuppressive and pro-angiogenic phenotype of dendritic cells (Novitskiy et al, 2008; Wilson et al, 2009). Blockade of A2b has been shown to reduce tumour size in a number of mouse cancer models (Cekic et al, 2012; Sorrentino et al, 2015; Iannone et al,

2013), an effect associated with diminished infiltration of MDSCs and production of VEGF (Sorrentino et al, 2015; Iannone et al, 2013).

[0010] Consequently, dual inhibition of both A2a and A2b is an attractive approach to reduce immunosuppression within the tumour microenvironment to inhibit growth.

SUMMARY OF THE INVENTION

[0011] According to a first aspect of the present invention, there is provided a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein.

[0012] According to a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in admixture with a pharmaceutically acceptable diluent or carrier.

[0013] According to a further aspect of the present invention, there is provided a method of antagonising adenosine A2a receptors, or A2a and A2b receptors, *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein.

[0014] According to a further aspect of the present invention, there is provided a method of selectively antagonising adenosine A2a receptors, or A2a and A2b receptors *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein.

[0015] According to a further aspect of the present invention, there is provided a method of inhibiting cell proliferation, *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional antiproliferative agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[0016] According to a further aspect of the present invention, there is provided a method of treating a disease or disorder associated with adenosine A2a and/or A2b receptor activity in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein.

[0017] According to a further aspect of the present invention, there is provided a method of treating a proliferative disorder in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional antiproliferative agents

(e.g. checkpoint inhibitors and/or cytotoxic agents).

[0018] According to a further aspect of the present invention, there is provided a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional anticancer agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[0019] According to a further aspect of the present invention, there is provided a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein for use in therapy.

[0020] According to a further aspect of the present invention, there is provided a compound or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein, for use in the treatment of a proliferative condition. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional antiproliferative agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[0021] According to a further aspect of the present invention, there is provided a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein for use in the treatment of cancer. In a particular embodiment, the cancer is human cancer. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional anticancer agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[0022] According to a further aspect of the present invention, there is provided a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein for use as an adenosine A2a and/or A2b antagonist. In an embodiment, the compounds of the invention are selective adenosine A2a and A2b antagonists.

[0023] According to a further aspect of the present invention, there is provided a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein for use in the treatment of a disease or disorder in which adenosine A2a and/or A2b is implicated.

[0024] According to a further aspect of the present invention, there is provided the use of a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in the manufacture of a medicament for the treatment of a proliferative condition. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional antiproliferative agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[0025] According to a further aspect of the present invention, there is provide the use of a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein

in the manufacture of a medicament for the treatment of cancer. Suitably, the cancer is a human cancer. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional anticancer agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[0026] According to a further aspect of the present invention, there is provided a use of a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in the manufacture of a medicament for use as an adenosine A2a and/or A2b antagonist.

[0027] According to a further aspect of the present invention, there is provided a use of a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in the manufacture of a medicament for the treatment of a disease or disorder in which adenosine A2a is implicated.

[0028] According to a further aspect of the present invention, there is provided a process for preparing a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein.

[0029] According to a further aspect of the present invention, there is provided a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, obtainable by, or obtained by, or directly obtained by a process of preparing a compound as defined herein.

[0030] According to a further aspect of the present invention, there are provided novel intermediates as defined herein which are suitable for use in any one of the synthetic methods set out herein.

[0031] Features, including optional, suitable, and preferred features in relation to one aspect of the invention may also be features, including optional, suitable and preferred features in relation to any other aspect of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0032] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0033] It is to be appreciated that references to “treating” or “treatment” include prophylaxis as well as the alleviation of established symptoms of a condition. “Treating” or “treatment” of a state, disorder or condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, i.e., causing regression of the

state, disorder or condition or at least one of its clinical or subclinical symptoms.

[0034] A “therapeutically effective amount” means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0035] In this specification the term “alkyl” includes both straight and branched chain alkyl groups. References to individual alkyl groups such as “propyl” are specific for the straight chain version only and references to individual branched chain alkyl groups such as “isopropyl” are specific for the branched chain version only. For Example, “(1-6C)alkyl” includes (1-4C)alkyl, (1-3C)alkyl, propyl, isopropyl and *t*-butyl. A similar convention applies to other radicals, for example “phenyl(1-6C)alkyl” includes phenyl(1-4C)alkyl, benzyl, 1-phenylethyl and 2-phenylethyl.

[0036] The term "(m-nC)" or "(m-nC) group" used alone or as a prefix, refers to any group having m to n carbon atoms.

[0037] An “alkylene,” “alkenylene,” or “alkynylene” group is an alkyl, alkenyl, or alkynyl group that is positioned between and serves to connect two other chemical groups. Thus, “(1-6C)alkylene” means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, for example, methylene, ethylene, propylene, 2-methylpropylene, pentylene, and the like.

[0038] “(2-6C)alkenylene” means a linear divalent hydrocarbon radical of two to six carbon atoms or a branched divalent hydrocarbon radical of three to six carbon atoms, containing at least one double bond, for example, as in ethenylene, 2,4-pentadienylene, and the like.

[0039] “(2-6C)alkynylene” means a linear divalent hydrocarbon radical of two to six carbon atoms or a branched divalent hydrocarbon radical of three to six carbon atoms, containing at least one triple bond, for example, as in ethynylene, propynylene, and butynylene and the like.

[0040] “(3-8C)cycloalkyl” means a hydrocarbon ring containing from 3 to 8 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl.

[0041] “(3-8C)cycloalkenyl” means a hydrocarbon ring containing at least one double bond, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl, such as 3-cyclohexen-1-yl, or cyclooctenyl.

[0042] “(3-8C)cycloalkyl-(1-6C)alkylene” means a (3-8C)cycloalkyl group covalently attached to a (1-6C)alkylene group, both of which are defined herein.

[0043] The term “halo” or “halogeno” refers to fluoro, chloro, bromo and iodo.

[0044] The term "heterocyclyl", "heterocyclic" or "heterocycle" means a non-aromatic saturated or partially saturated monocyclic, fused, bridged, or spiro bicyclic heterocyclic ring system(s). Monocyclic heterocyclic rings contain from about 3 to 12 (suitably from 3 to 7) ring atoms, with from 1 to 5 (suitably 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur in the ring. Bicyclic heterocycles contain from 7 to 17 member atoms, suitably 7 to 12 member atoms, in the ring. Bicyclic heterocyclic(s) rings may be fused, spiro, or bridged ring systems. Examples of heterocyclic groups include cyclic ethers such as oxiranyl, oxetanyl, tetrahydrofuranyl, dioxanyl, and substituted cyclic ethers. Heterocycles containing nitrogen include, for example, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrotriazinyl, tetrahydropyrazolyl, and the like. Typical sulfur containing heterocycles include tetrahydrothienyl, dihydro-1,3-dithiol, tetrahydro-2*H*-thiopyran, and hexahydrothiepine. Other heterocycles include dihydrooxathiolyl, tetrahydrooxazolyl, tetrahydro-oxadiazolyl, tetrahydrodioxazolyl, tetrahydrooxathiazolyl, hexahydrotriazinyl, tetrahydrooxazinyl, morpholinyl, thiomorpholinyl, tetrahydropyrimidinyl, dioxolinyl, octahydrobenzofuranyl, octahydrobenzimidazolyl, and octahydrobenzothiazolyl. For heterocycles containing sulfur, the oxidized sulfur heterocycles containing SO or SO_2 groups are also included. Examples include the sulfoxide and sulfone forms of tetrahydrothienyl and thiomorpholinyl such as tetrahydrothiene 1,1-dioxide and thiomorpholinyl 1,1-dioxide. A suitable value for a heterocyclyl group which bears 1 or 2 oxo (=O) or thioxo (=S) substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl. Particular heterocyclyl groups are saturated monocyclic 3 to 7 membered heterocyclyls containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur, for example azetidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, thiomorpholinyl, thiomorpholinyl 1,1-dioxide, piperidinyl, homopiperidinyl, piperazinyl or homopiperazinyl. As the skilled person would appreciate, any heterocycle may be linked to another group via any suitable atom, such as via a carbon or nitrogen atom. However, reference herein to piperidino or morpholino refers to a piperidin-1-yl or morpholin-4-yl ring that is linked via the ring nitrogen.

[0045] By "bridged ring systems" is meant ring systems in which two rings share more than two atoms, see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages 131-133, 1992. Examples of bridged heterocyclyl ring systems include, aza-bicyclo[2.2.1]heptane, 2-oxa-5-azabicyclo[2.2.1]heptane, aza-bicyclo[2.2.2]octane, aza-bicyclo[3.2.1]octane and quinuclidine.

[0046] By "spiro bicyclic ring systems" we mean that the two ring systems share one common spiro carbon atom, i.e. the heterocyclic ring is linked to a further carbocyclic or heterocyclic

ring through a single common spiro carbon atom. Examples of spiro ring systems include 6-azaspiro[3.4]octane, 2-oxa-6-azaspiro[3.4]octane, 2-azaspiro[3.3]heptanes, 2-oxa-6-azaspiro[3.3]heptanes, 7-oxa-2-azaspiro[3.5]nonane, 6-oxa-2-azaspiro[3.4]octane, 2-oxa-7-azaspiro[3.5]nonane and 2-oxa-6-azaspiro[3.5]nonane.

[0047] "Heterocyclyl(1-6C)alkyl" means a heterocyclyl group covalently attached to a (1-6C)alkylene group, both of which are defined herein.

[0048] The term "heteroaryl" or "heteroaromatic" means an aromatic mono-, bi-, or polycyclic ring incorporating one or more (for example 14, particularly 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur. The term heteroaryl includes both monovalent species and divalent species. Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring, for example a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulfur and oxygen. Typically, the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general, the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

[0049] Examples of heteroaryl include furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, isoindolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzothiazolyl, indazolyl, purinyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl, pteridinyl, naphthyridinyl, carbazolyl, phenazinyl, benzisoquinolinyl, pyridopyrazinyl, thieno[2,3b]-furanyl-, 2H-furo[3,2b]-pyranyl-, 5H-pyrido[2,3-d]-ooxazinyl-, 1H-pyrazolo[4,3-d]-oxazolyl, 4H-imidazo[4,5d]thiazolyl, pyrazino[2,3d]pyridazinyl, -imidazo[2,1b]thiazolyl, -imidazo[1,2b][1,2,4]-triazinyl. "Heteroaryl" also covers partially aromatic bi- or polycyclic ring systems wherein at least one ring is an aromatic ring and one or more of the other ring(s) is a nonaromatic, saturated or partially saturated ring, provided at least one ring contains one or more heteroatoms selected from nitrogen, oxygen or -sulfur-. Examples of partially aromatic heteroaryl groups include for example, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 2-oxo-1,2,3,4-tetrahydroquinolinyl, dihydrobenzthienyl, dihydrobenzfuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,3]dioxolyl,

2,2-dioxo-1,3-dihydro-2-benzothienyl, 4,5,6,7-tetrahydrobenzofuranyl, indolinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazinyl, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl and 6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazinyl.

[0050] Examples of five membered heteroaryl groups include but are not limited to pyrrolyl, furanyl, thienyl, imidazolyl, furazanyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl and tetrazolyl groups.

[0051] Examples of six membered heteroaryl groups include but are not limited to pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl and triazinyl.

[0052] A bicyclic heteroaryl group may be, for example, a group selected from:

a benzene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a pyridine ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a pyrimidine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

a pyrrole ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a pyrazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

a pyrazine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

an imidazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

an oxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

an isoxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

a thiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

an isothiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

a thiophene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a furan ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a cyclohexyl ring fused to a 5- or 6-membered heteroaromatic ring containing 1, 2 or 3 ring heteroatoms; and

a cyclopentyl ring fused to a 5- or 6-membered heteroaromatic ring containing 1, 2 or 3 ring heteroatoms.

[0053] Particular Examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzfuranyl, benzthiophenyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, benzisothiazolyl, isobenzofuranyl, indolyl, isoindolyl, indolizinyl, indolinyl, isoindolinyl, purinyl (e.g., adeninyl, guaninyl), indazolyl, benzodioxolyl and pyrazolopyridinyl groups.

[0054] Particular Examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinolinyl, isoquinolinyl, chromanyl, thiochromanyl,

chromenyl, isochromenyl, chromanyl, isochromanyl, benzodioxanyl, quinolizinyl, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl groups.

[0055] "Heteroaryl(1-6C)alkyl" means a heteroaryl group covalently attached to a (1-6C)alkylene group, both of which are defined herein. Examples of heteroaralkyl groups include pyridin-3-ylmethyl, 3-(benzofuran-2-yl)propyl, and the like.

[0056] The term "aryl" means a cyclic or polycyclic aromatic ring having from 5 to 12 carbon atoms. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. In particular embodiment, an aryl is phenyl.

[0057] The term "aryl(1-6C)alkyl" means an aryl group covalently attached to a (1-6C)alkylene group, both of which are defined herein. Examples of aryl-(1-6C)alkyl groups include benzyl, phenylethyl, and the like.

[0058] This specification also makes use of several composite terms to describe groups comprising more than one functionality. Such terms will be understood by a person skilled in the art. For Example heterocyclyl(m-nC)alkyl comprises (m-nC)alkyl substituted by heterocyclyl.

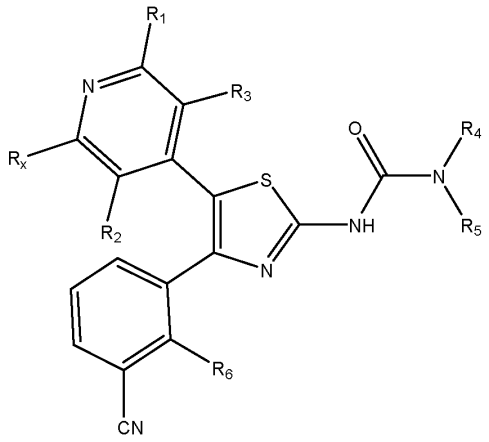
[0059] The term "optionally substituted" refers to either groups, structures, or molecules that are substituted and those that are not substituted. The term "wherein a/any CH, CH_2, CH_3 group or heteroatom (i.e. NH) within a R^1 group is optionally substituted" suitably means that (any) one of the hydrogen radicals of the R^1 group is substituted by a relevant stipulated group.

[0060] Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

[0061] The phrase "compound of the invention" means those compounds which are disclosed herein, both generically and specifically.

Compounds of the invention

[0062] In a first aspect, the present invention relates to compounds, or pharmaceutically acceptable salts, hydrates or solvates thereof, having the structural formula I shown below:



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wherein:

R_x is selected from methyl, CD_3, chloro and CF_3;

R_1 is selected from (1-3C)alkyl, halo, (1-3C)haloalkyl, (1-3C)haloalkoxy, (1-3C)hydroxyalkyl, cyano, cyclopropyl, oxetan-3-yl, $-(CR_{1C}R_{1D})_{q1}-OR_{1A}$, $-(CR_{1C}R_{1D})_{q1}-C(O)R_{1A}$, $-(CR_{1C}R_{1D})_{q1}-C(O)OR_{1A}$, $-(CR_{1C}R_{1D})_{q1}-OC(O)R_{1A}$, $-(CR_{1C}R_{1D})_{q1}-C(O)N(R_{1B})R_{1A}$, $-(CR_{1C}R_{1D})_{q1}-N(R_{1B})C(O)R_{1A}$, $-(CR_{1C}R_{1D})_{q1}-S(O)_pR_{1A}$ (where p is 0, 1 or 2), $-(CR_{1C}R_{1D})_{q1}-SO_2N(R_{1B})R_{1A}$, or $-(CR_{1C}R_{1D})_{q1}-N(R_{1B})SO_2R_{1A}$,

wherein q1 is 0, 1, or 2; and

wherein R_{1A} and R_{1B} are each independently selected from hydrogen, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkyl(1-2C)alkyl;

wherein R_{1C} and R_{1D} are each independently selected from hydrogen or (1-2C)alkyl;

R_2 and R_3 are both hydrogen or one of R_2 and R_3 is hydrogen and the other is selected from fluoro, methyl or methoxy;

R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups,

wherein R_{10C} is selected from oxo, thioxo, halo, or cyano substituents, or a group of the formula:

$$-[CR_{7a}R_{7b}]_n-L-Z$$

wherein

n is 0 to 6;

R_{7a} and R_{7b} are each independently selected from hydrogen, fluoro or (1-2C)alkyl;

L is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_a)-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_a)-$, $-N(R_a)C(O)-$, $-N(R_a)C(O)N(R_b)-$, $-C(S)N(R_a)-$, $-N(R_a)C(S)-$,

-$N(R_a)C(S)N(R_b)$-, -$S(O)_2N(R_a)$-, or -$N(R_a)SO_2$-, wherein R_a and R_b are each independently selected from hydrogen or (1-2C)alkyl; and

Z is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, aryl, aryl(1-2C)alkyl, heterocyclyl, heterocyclyl(1-2C)alkyl, heteroaryl or heteroaryl(1-2C)alkyl; and wherein Z is optionally substituted by one or more substituents selected from (1-6C)alkyl, halo, (1-6C)haloalkyl, (1-6C)haloalkoxy, cyano, nitro, -NR_cR_d, -OR_c, -$C(O)R_c$, -$C(O)OR_c$, -$OC(O)R_c$, -$C(O)N(R_c)R_d$, -$N(R_c)C(O)R_d$, -$S(O)_yR_c$ (where y is 0, 1 or 2), -$SO_2N(R_c)R_d$, -$N(R_c)SO_2R_d$, -$(CH_2)_zNR_cR_d$ (where z is 1, 2 or 3) or oxo,

wherein any alkyl moiety in a substituent group on Z is optionally further substituted by cyano, halo, hydroxy, amino, oxo, (1-2C)alkyl or (1-2C)alkoxy and R_c and R_d are each independently selected from hydrogen, (1-6C)alkyl, (1-6C)haloalkyl or (3-6C)cycloalkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N},

wherein R_{10N} is -$S(O)_2NH_2$ or selected from:

(i) –Z_1;

(ii) –L_{1a}–Z_1; or

(iii) –$[CR_{8a}R_{8b}]_{1-6}$–L_{1b}–Z_1;

wherein

R_{2a} and R_{2b} are each independently selected from hydrogen, fluoro or (1-2C)alkyl;

L_{1a} is selected from -C(O)-, -$S(O)_2$-, -C(O)O-, -$C(O)N(R_{a1})$-, -$S(O)_2N(R_{a1})$- or -$N(R_{a1})$-, wherein R_{a1} is selected from hydrogen or (1-2C)alkyl;

L_{1b} is absent or selected from -O-, -S-, -SO-, -SO_2-, -$N(R_{a2})$-, -C(O)-, -C(O)O-, -OC(O)-, -$C(O)N(R_{a2})$-, -$N(R_{a2})C(O)$-, -$N(R_{a2})C(O)N(R_{b2})$-, -$C(S)N(R_{a2})$-, -$N(R_{a2})C(S)$-, -$N(R_{a2})C(S)N(R_{b2})$-, -$S(O)_2N(R_{a2})$-, or -$N(R_{a2})SO_2$, wherein R_{a2} and R_{b2} are each independently selected from hydrogen or (1-2C)alkyl; and

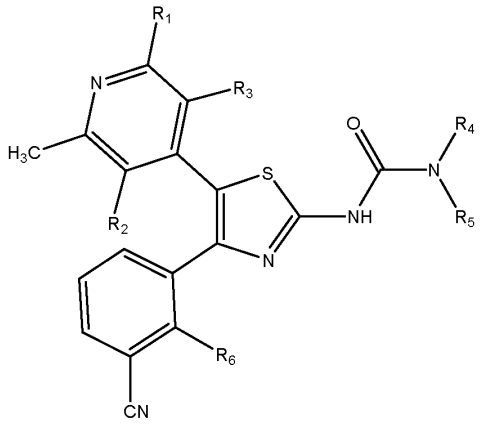
Z_1 is selected from (1-6C)alkyl, (3-6C)cycloalkyl, aryl, heterocyclyl, heteroaryl, (3-6C)cycloalkyl(1-2C)alkyl, aryl(1-2C)alkyl, heterocyclyl(1-2C)alkyl or heteroaryl(1-2C)alkyl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-6C)alkyl, halo, (1-6C)haloalkoxy, cyano, nitro, -NR_eR_f, -OR_e, -$C(O)R_e$, -$C(O)OR_e$, -$OC(O)R_e$, -$C(O)N(R_e)R_f$, -$N(R_e)C(O)R_f$, -$S(O)_yR_e$ (where y is 0, 1 or 2), -$SO_2N(R_e)R_f$, -$N(R_e)SO_2R_f$, -$(CH_2)_zNR_eR_f$ (where z is 1, 2 or 3)

or oxo, and wherein R_e and R_f are each independently selected from hydrogen, (1-6C)alkyl, (1-6C)haloalkyl or (3-6C)cycloalkyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, (1-3C)alkyl or (2-3C)alkanoyl; and

R_6 is selected from hydrogen, halo, methyl, methoxy and trifluoromethyl.

[0063] In a second aspect, the present invention relates to compounds, or pharmaceutically acceptable salts, hydrates or solvates thereof, having the structural formula I' (a sub definition of Formula I) shown below:



I'

wherein:

R_1 is selected from (1-2C)alkyl, halo, (1-2C)haloalkyl, (1-2C)haloalkoxy, cyano, $-(CH_2)_{q1}-OR_{1A}$, $-(CH_2)_{q1}-C(O)R_{1A}$, $-(CH_2)_{q1}-C(O)OR_{1A}$, $-(CH_2)_{q1}-OC(O)R_{1A}$, $-(CH_2)_{q1}-C(O)N(R_{1B})R_{1A}$, $-(CH_2)_{q1}-N(R_{1B})C(O)R_{1A}$, $-(CH_2)_{q1}-S(O)_pR_{1A}$ (where p is 0, 1 or 2), $-(CH_2)_{q1}-SO_2N(R_{1B})R_{1A}$, or $-(CH_2)_{q1}-N(R_{1B})SO_2R_{1A}$,

wherein q1 is 0, 1, or 2; and

wherein R_{1A} and R_{1B} are each independently selected from hydrogen, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkyl(1-2C)alkyl;

R_2 and R_3 are both hydrogen or one of R_2 and R_3 is hydrogen and the other is selected from fluoro, methyl or methoxy;

R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups,

wherein R_{10C} is selected from oxo, thioxo, halo, or cyano substituents, or a group of the formula:

$-[CR_{7a}R_{7b}]_n-L-Z$

wherein

n is 0 to 6;

R_{7a} and R_{7b} are each independently selected from hydrogen, fluoro or (1-2C)alkyl;

L is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_a)-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_a)-$, $-N(R_a)C(O)-$, $-N(R_a)C(O)N(R_b)-$, $-C(S)N(R_a)-$, $-N(R_a)C(S)-$, $-N(R_a)C(S)N(R_b)-$, $-S(O)_2N(R_a)-$, or $-N(R_a)SO_2-$, wherein R_a and R_b are each independently selected from hydrogen or (1-2C)alkyl; and

Z is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, aryl, aryl(1-2C)alkyl, heterocyclyl, heterocyclyl(1-2C)alkyl, heteroaryl or heteroaryl(1-2C)alkyl; and wherein Z is optionally substituted by one or more substituents selected from (1-6C)alkyl, halo, (1-6C)haloalkyl, (1-6C)haloalkoxy, cyano, nitro, $-NR_cR_d$, $-OR_c$, $-C(O)R_c$, $-C(O)OR_c$, $-OC(O)R_c$, $-C(O)N(R_c)R_d$, $-N(R_c)C(O)R_d$, $-S(O)_yR_c$ (where y is 0, 1 or 2), $-SO_2N(R_c)R_d$, $-N(R_c)SO_2R_d$, $-(CH_2)_zNR_cR_d$ (where z is 1, 2 or 3) or oxo,

wherein any alkyl moiety in a substituent group on Z is optionally further substituted by cyano, halo, hydroxy, amino, oxo, (1-2C)alkyl or (1-2C)alkoxy and R_c and R_d are each independently selected from hydrogen, (1-6C)alkyl, (1-6C)haloalkyl or (3-6C)cycloalkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N},

wherein R_{10N} is $-S(O)_2NH_2$ or selected from:

(i) $-Z_1$;

(ii) $-L_{1a}-Z_1$; or

(iii) $-[CR_{8a}R_{8b}]_{1-6}-L_{1b}-Z_1$;

wherein

R_{2a} and R_{2b} are each independently selected from hydrogen, fluoro or (1-2C)alkyl;

L_{1a} is selected from -C(O)-, $-S(O)_2-$, -C(O)O-, $-C(O)N(R_{a1})-$, $-S(O)_2N(R_{a1})-$ or $-N(R_{a1})-$, wherein R_{a1} is selected from hydrogen or (1-2C)alkyl;

L_{1b} is absent or selected from -O-, -S-, -SO-, $-SO_{2-}$, $-N(R_{a2})-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_{a2})-$, $-N(R_{a2})C(O)-$, $-N(R_{a2})C(O)N(R_{b2})-$, $-C(S)N(R_{a2})-$, $-N(R_{a2})C(S)-$, $-N(R_{a2})C(S)N(R_{b2})-$, $-S(O)_2N(R_{a2})-$, or $-N(R_{a2})SO_2$, wherein R_{a2} and R_{b2} are each independently selected from hydrogen or (1-2C)alkyl; and

Z_1 is selected from (1-6C)alkyl, (3-6C)cycloalkyl, aryl, heterocyclyl, heteroaryl, (3-6C)cycloalkyl(1-2C)alkyl, aryl(1-2C)alkyl, heterocyclyl(1-2C)alkyl or heteroaryl(1-

2C)alkyl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-6C)alkyl, halo, (1-6C)haloalkoxy, cyano, nitro, $-NR_eR_f$, $-OR_e$, $-C(O)R_e$, $-C(O)OR_e$, $-OC(O)R_e$, $-C(O)N(R_e)R_f$, $-N(R_e)C(O)R_f$, $-S(O)_yR_e$ (where y is 0, 1 or 2), $-SO_2N(R_e)R_f$, $-N(R_e)SO_2R_f$, $-(CH_2)_zNR_eR_f$ (where z is 1, 2 or 3) or oxo, and wherein R_e and R_f are each independently selected from hydrogen, (1-6C)alkyl, (1-6C)haloalkyl or (3-6C)cycloalkyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, (1-3C)alkyl or (2-3C)alkanoyl; and

R_6 is selected from hydrogen, halo, methyl, methoxy and trifluoromethyl.

[0064] Particular compounds of the invention include, for example, compounds of the formula I, or pharmaceutically acceptable salts, hydrates and/or solvates thereof, wherein, unless otherwise stated, each of R_x, R_1, R_2, R_3, R_4, R_5 and R_6 have any of the meanings defined hereinbefore or in any of paragraphs (1) to (32) hereinafter:-

(1) R_1 is selected from (1-2C)alkyl, halo, (1-2C)haloalkyl, (1-2C)haloalkoxy, cyano, $-(CH_2)_{q1}-OR_{1A}$ and $-(CH_2)_{q1}-C(O)R_{1A}$;
wherein q1 is 0 or 1; and
wherein R_{1A} is selected from hydrogen or (1-2C)alkyl;

(1a) R_1 is selected from (1-3C)alkyl, halo, (1-3C)haloalkyl, (1-3C)haloalkoxy, (1-3C)hydroxyalkyl, cyano, cyclopropyl, oxetan-3-yl, $-(CH_2)_{q1}-OR_{1A}$ and $-(CH_2)_{q1}-C(O)R_{1A}$;
wherein q1 is 0 or 1; and
wherein R_{1A} is selected from hydrogen or (1-2C)alkyl;

(2) R_1 is selected from (1-2C)alkyl, halo, (1-2C)haloalkyl and $-C(O)R_{1A}$;
wherein R_{1A} is selected from hydrogen or methyl;

(2a) R_1 is selected from (1-3C)alkyl, halo, (1-3C)haloalkyl, (1-3C)haloalkoxy, (1-3C)hydroxyalkyl, cyano, cyclopropyl, oxetan-3-yl and $-OR_{1A}$;

(3) R_1 is selected from methyl, halo and $-CF_3$;

(3a) R_1 is selected from methyl, CD_3, isopropyl, halo, (1-3C)hydroxyalkyl, cyano, cyclopropyl, oxetan-3-yl, -OMe, $-CH_2F$, $-CHF_2$ and $-CF_3$;

(3b) R_1 is selected from methyl, CD_3, isopropyl, halo, (1-3C)hydroxyalkyl, cyano, cyclopropyl, oxetan-3-yl, -OMe, CHF_2 and $-CF_3$;

(4) R_1 is selected from methyl and halo;

(4a) R_1 is selected from methyl, CD_3, isopropyl, hydroxymethyl, 2-hydroxyisopropyl, cyclopropyl, oxetan-3-yl, and halo;

(5) R_1 is selected from methyl, fluoro or chloro;

(6) R_1 is selected from methyl or chloro;

(7) R_1 is methyl;

(7a) R_1 is methyl or CD_3;

(8) R_1 is chloro;

(8a) R_1 is CD_3;

(8b) R_1 is isopropyl;

(8c) R_1 is hydroxymethyl;

(8d) R_1 is 2-hydroxyisopropyl;

(8e) R_1 is cyclopropyl;

(8f) R_1 is oxetan-3-yl

(9) R_2 and R_3 are both hydrogen or one of R_2 and R_3 is hydrogen and the other is fluoro or methyl;

(10) R_2 and R_3 are both hydrogen;

(11) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups, wherein R_{10C} is selected from oxo, thioxo, halo, or cyano substituents, or a group of the formula:

$$–[CH_2]_n–L–Z$$

wherein

n is 0 to 4;

L is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_a)-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_a)-$, $-N(R_a)C(O)-$, $-N(R_a)C(O)N(R_b)-$, $-S(O)_2N(R_a)-$, or $-N(R_a)SO_2-$, wherein R_a and R_b are each independently selected from hydrogen or (1-2C)alkyl; and

Z is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, aryl, aryl(1-2C)alkyl, heterocyclyl, heterocyclyl(1-2C)alkyl, heteroaryl or heteroaryl(1-2C)alkyl; and wherein Z is optionally substituted by one or more substituents selected from (1-4C)alkyl, halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, cyano, nitro, $-NR_cR_d$, $-OR_c$, $-C(O)R_c$, $-C(O)OR_c$, $-OC(O)R_c$, $-C(O)N(R_c)R_d$, $-N(R_c)C(O)R_d$, $-S(O)_yR_c$ (where y is 0, 1 or 2), $-SO_2N(R_c)R_d$, $-N(R_c)SO_2R_d$, $-(CH_2)_zNR_cR_d$ (where z is 1, 2 or 3) or oxo,

wherein any alkyl moiety in a substituent group on Z is optionally further substituted by cyano, halo, hydroxy, amino, oxo, (1-2C)alkyl or (1-2C)alkoxy

and R_c and R_d are each independently selected from hydrogen, (1-4C)alkyl, (1-4C)haloalkyl or (3-6C)cycloalkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is $-S(O)_2NH_2$ or selected from:

(i) $–Z_1$;

(ii) $–L_{1a}–Z_1$; or

(iii) $–[CR_{8a}R_{8b}]_{1-4}–L_{1b}–Z_1$;

wherein

R_{2a} and R_{2b} are both hydrogen;

L_{1a} is selected from $-C(O)-$, $-S(O)_2-$, $-C(O)O-$, $-C(O)N(R_{a1})-$ or $-S(O)_2N(R_{a1})-$, wherein R_{a1} is hydrogen or methyl;

L_{1b} is absent or selected from $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-N(R_{a2})-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-C(O)N(R_{a2})-$, $-N(R_{a2})C(O)-$, $-N(R_{a2})C(O)N(R_{b2})-$, $-C(S)N(R_{a2})-$, $-N(R_{a2})C(S)-$, $-N(R_{a2})C(S)N(R_{b2})-$, $-S(O)_2N(R_{a2})-$, or $-N(R_{a2})SO_2$, wherein R_{a2} and R_{b2} are each independently selected from hydrogen or methyl; and

Z_1 is selected from (1-6C)alkyl, (3-6C)cycloalkyl, aryl, heterocyclyl, heteroaryl, (3-6C)cycloalkyl(1-2C)alkyl, aryl(1-2C)alkyl, heterocyclyl(1-2C)alkyl or heteroaryl(1-2C)alkyl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-4C)alkyl, halo, (1-4C)haloalkoxy, cyano, nitro, $-NR_eR_f$, $-OR_e$, $-C(O)R_e$, $-C(O)OR_e$, $-OC(O)R_e$, $-C(O)N(R_e)R_f$, $-N(R_e)C(O)R_f$, $-S(O)_yR_e$ (where y is 0, 1 or 2), $-SO_2N(R_e)R_f$, $-N(R_e)SO_2R_f$, $-(CH_2)_zNR_eR_f$ (where z is 1, 2 or 3) or oxo, and wherein R_e and R_f are each independently selected from hydrogen, (1-4C)alkyl, (1-4C)haloalkyl or (3-6C)cycloalkyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as $S(=O)$, $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen,(1-3C)alkyl or (2-3C)alkanoyl;

(12) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups, wherein R_{10C} is selected from oxo, halo, or cyano substituents, or a group of the formula:

$$–[CH_2]_n–L–Z$$

wherein

n is 0 to 2;

L is absent or selected from -O-, -S-, -SO-, -SO_2-, -N(R_{a2})-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{a2})-, -N(R_{a2})C(O)-, -N(R_{a2})C(O)N(R_{b2})-, -$S(O)_2$N(R_{a2})-, or -N(R_{a2})SO_2-, wherein R_{a2} and R_{b2} are each independently selected from hydrogen or methyl; and

Z is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, aryl, heterocyclyl or heteroaryl; and wherein Z is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkyl, (1-2C)haloalkoxy, cyano, -NR_cR_d, -OR_c, -C(O)R_c, -C(O)OR_c, -OC(O)R_c, -C(O)N(R_c)R_d, -N(R_c)C(O)R_d, -$S(O)_yR_c$ (where y is 0, 1 or 2), -SO_2N(R_c)R_d, -N(R_c)SO_2R_d, -$(CH_2)_z$NR_cR_d (where z is 1 or 2) or oxo;

wherein any alkyl moiety in a substituent group on Z_1 is optionally further substituted by cyano, halo, hydroxy, amino, oxo, (1-2C)alkyl or (1-2C)alkoxy and R_c and R_d are each independently selected from hydrogen, (1-2C)alkyl, (1-2C)haloalkyl or (3-6C)cycloalkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is -$S(O)_2NH_2$ or selected from:

(i) –Z_1;

(ii) –L_{1a}–Z_1; or

(iii) –[$CR_{8a}R_{8b}$]$_{1-2}$–L_{1b}–Z_1;

wherein

R_{2a} and R_{2b} are both hydrogen;

L_{1a} is selected from -C(O)-, -$S(O)_2$- or -$S(O)_2$N(R_{a1})-, wherein R_{a1} is hydrogen or methyl;

L_{1b} is absent or selected from -O-, -S-, -SO-, -SO_2-, -N(R_{a2})-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{a2})-, -N(R_{a2})C(O)-, -N(R_{a2})C(O)N(R_{b2})-, -$S(O)_2$N(R_{a2})-, or -N(R_{a2})SO_2, wherein R_{a2} and R_{b2} are each independently selected from hydrogen or methyl; and

Z_1 is selected from (1-6C)alkyl, (3-6C)cycloalkyl, aryl, heterocyclyl, heteroaryl, (3-6C)cycloalkyl(1-2C)alkyl or aryl(1-2C)alkyl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkoxy, cyano, nitro, -NR_eR_f, -OR_e, -C(O)R_e, -C(O)OR_e, -OC(O)R_e, -C(O)N(R_e)R_f, -N(R_e)C(O)R_f,

$-S(O)_yR_e$ (where y is 0, 1 or 2), $-SO_2N(R_e)R_f$, $-N(R_e)SO_2R_f$, $-(CH_2)_zNR_eR_f$ (where z is 1, 2 or 3) or oxo, and wherein R_e and R_f are each independently selected from hydrogen or (1-2C)alkyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen,(1-3C)alkyl or (2-3C)alkanoyl;

(13) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups, wherein R_{10C} is selected from oxo, halo, or cyano substituents, or a group of the formula:

$$–[CH_2]_n–L–Z$$

wherein

n is 0 to 2;

L is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_a)-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_a)-$, $-N(R_a)C(O)-$, $-N(R_a)C(O)N(R_b)-$, $-S(O)_2N(R_a)-$, or $-N(R_a)SO_2-$, wherein R_a and R_b are hydrogen; and

Z is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, aryl, heterocyclyl or heteroaryl; and wherein Z is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkyl, (1-2C)haloalkoxy, cyano, $-NR_cR_d$, $-OR_c$, $-C(O)R_c$, $-C(O)OR_c$, $-OC(O)R_c$, $-C(O)N(R_c)R_d$, $-N(R_c)C(O)R_d$, $-S(O)_yR_c$ (where y is 0, 1 or 2), $-SO_2N(R_c)R_d$, $-N(R_c)SO_2R_d$, $-(CH_2)_zNR_cR_d$ (where z is 1 or 2) or oxo;

wherein R_c and R_d are each independently selected from hydrogen, (1-2C)alkyl or (1-2C)haloalkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is $-S(O)_2NH_2$ or selected from:

(i) $–Z_1$;

(ii) $–L_{1a}–Z_1$; or

(iii) $–[CR_{8a}R_{8b}]_{1-2}–L_{1b}–Z_1$;

wherein

R_{2a} and R_{2b} are both hydrogen;

L_{1a} is selected from -C(O)-, $-S(O)_2-$ or $-S(O)_2N(R_{a1})-$, wherein R_{a1} is hydrogen;

L_{1b} is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_{a2})-$, $-C(O)N(R_{a2})-$, $-N(R_{a2})C(O)-$, $-S(O)_2N(R_{a2})-$ or $-N(R_{a2})SO_2$, wherein R_{a2} is hydrogen; and

Z_1 is selected from (1-6C)alkyl, (3-6C)cycloalkyl, aryl, heterocyclyl, heteroaryl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkoxy, cyano, $-NR_eR_f$, $-OR_e$, $-C(O)R_e$, $-C(O)OR_e$, $-OC(O)R_e$, $-C(O)N(R_e)R_f$, $-N(R_e)C(O)R_f$, $-S(O)_yR_e$ (where y is 0, 1 or 2), $-SO_2N(R_e)R_f$, $-N(R_e)SO_2R_f$, $-(CH_2)_zNR_cR_d$ (where z is 1 or 2); and wherein R_e and R_f are each independently selected from hydrogen or methyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, (1-2C)alkyl or (2C)alkanoyl;

(14) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups,

wherein R_{10C} is selected from oxo, halo, or cyano, or a group of the formula:

$$–[CH_2]_n–L–Z$$

wherein

n is 0 to 2;

L is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_a)-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_a)-$, $-N(R_a)C(O)-$, $-S(O)_2N(R_a)-$, or $-N(R_a)SO_2-$, wherein R_a and R_b are hydrogen; and

Z is selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, phenyl, a 4-7 membered heterocyclyl or a 5 or 6-membered heteroaryl; and wherein Z is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkyl, (1-2C)haloalkoxy, cyano, $-NR_cR_d$, $-OR_c$, $-C(O)R_c$, $-C(O)OR_c$, $-OC(O)R_c$, $-C(O)N(R_c)R_d$, $-N(R_c)C(O)R_d$, $-S(O)_yR_c$ (where y is 0, 1 or 2), $-SO_2N(R_c)R_d$, $-N(R_c)SO_2R_d$, $-(CH_2)_zNR_cR_d$ (where z is 1 or 2) or oxo;

wherein R_c and R_d are each independently selected from hydrogen or (1-2C)alkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is $-S(O)_2NH_2$ or selected from:

(i) $–Z_1$;

(ii) $–L_{1a}–Z_1$; or

(iii) $–[CR_{8a}R_{8b}]_{1-2}–L_{1b}–Z_1$;

wherein

R_{2a} and R_{2b} are both hydrogen;

L_{1a} is selected from -C(O)-, -$S(O)_2$- or -$S(O)_2N(R_{a1})$-, wherein R_{a1} is hydrogen;

L_{1b} is absent or selected from -O-, -S-, -SO-, -SO_2-, -$N(R_{a2})$-, -$C(O)N(R_{a2})$-, -$N(R_{a2})C(O)$-, -$S(O)_2N(R_{a2})$- or -$N(R_{a2})SO_2$, wherein R_{a2} is hydrogen; and

Z_1 is selected from (1-4C)alkyl, phenyl, a 4-7 membered heterocyclyl or a 5 or 6-membered heteroaryl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkoxy, cyano, -NR_eR_f, -OR_e, -$C(O)R_e$, -$C(O)OR_e$, -$OC(O)R_e$, -$C(O)N(R_e)R_f$, -$N(R_e)C(O)R_f$, -$S(O)_yR_e$ (where y is 0, 1 or 2), -$SO_2N(R_e)R_f$, -$N(R_e)SO_2R_f$, -$(CH_2)_zNR_cR_d$ (where z is 1 or 2); and wherein R_e and R_f are each independently selected from hydrogen or methyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, (1-2C)alkyl or (2C)alkanoyl;

(15) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups, wherein R_{10C} is selected from oxo, halo, or cyano substituents, or a group of the formula:

$$–[CH_2]_n–L–Z$$

wherein

n is 0 to 2;

L is absent or selected from -O-, -S-, -SO-, -SO_2-, -$N(R_a)$-, -C(O)-, -C(O)O-, -$OC(O)$-, -$C(O)N(R_a)$-, -$N(R_a)C(O)$-, -$S(O)_2N(R_a)$-, or -$N(R_a)SO_2$-, wherein R_a and R_b are hydrogen; and

Z is selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, phenyl, a 4-7 membered heterocyclyl or a 5 or 6-membered heteroaryl; and wherein Z is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkyl, (1-2C)haloalkoxy, cyano, -NR_cR_d, -OR_c, -$C(O)R_c$, -$C(O)N(R_c)R_d$, -$N(R_c)C(O)R_d$ or -$S(O)_yR_c$ (where y is 0, 1 or 2) or oxo;

wherein R_c and R_d are each independently selected from hydrogen or (1-2C)alkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is -$S(O)_2NH_2$ or selected from:

(i) –Z_1;

(ii) $-L_{1a}-Z_1$; or

(iii) $-[CR_{8a}R_{8b}]_{1-2}-L_{1b}-Z_1$;

wherein

R_{2a} and R_{2b} are both hydrogen;

L_{1a} is selected from -C(O)-, $-S(O)_2-$ or $-S(O)_2N(R_{a1})-$, wherein R_{a1} is hydrogen;

L_{1b} is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_{a2})-$, $-C(O)N(R_{a2})-$, $-N(R_{a2})C(O)-$, $-S(O)_2N(R_{a2})-$ or $-N(R_{a2})SO_2$, wherein R_{a2} is hydrogen; and

Z_1 is selected from (1-4C)alkyl, phenyl, a 4-7 membered heterocyclyl or a 5 or 6-membered heteroaryl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkoxy, cyano, $-NR_eR_f$, $-OR_e$, $-C(O)R_e$, $-C(O)N(R_e)R_f$, $-N(R_e)C(O)R_f$, $-S(O)_yR_e$ (where y is 0, 1 or 2); and wherein R_e and R_f are each independently selected from hydrogen or methyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, methyl or (2C)alkanoyl;

(15a) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups, wherein R_{10C} is selected from oxo, halo, or cyano substituents, or a group of the formula:

$$-[CH_2]_n-L-Z$$

wherein

n is 0 to 2;

L is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_a)-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_a)-$, $-N(R_a)C(O)-$, $-S(O)_2N(R_a)-$, or $-N(R_a)SO_2-$, wherein R_a and R_b are hydrogen; and

Z is selected from hydrogen, (1-4C)alkyl or (3-6C)cycloalkyl; and wherein Z is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkyl, (1-2C)haloalkoxy, cyano, $-NR_cR_d$, $-OR_c$, $-C(O)R_c$, $-C(O)N(R_c)R_d$, $-N(R_c)C(O)R_d$ or $-S(O)_yR_c$ (where y is 0, 1 or 2) or oxo;

wherein R_c and R_d are each independently selected from hydrogen or (1-2C)alkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is $-S(O)_2NH_2$ or selected from:

(i) $-Z_1$;

(ii) $-L_{1a}-Z_1$; or

(iii) $-[CR_{8a}R_{8b}]_{1-2}-L_{1b}-Z_1$;

wherein

R_{2a} and R_{2b} are both hydrogen;

L_{1a} is selected from -C(O)-, $-S(O)_2-$ or $-S(O)_2N(R_{a1})-$, wherein R_{a1} is hydrogen;

L_{1b} is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_{a2})-$, $-C(O)N(R_{a2})-$, $-N(R_{a2})C(O)-$, $-S(O)_2N(R_{a2})-$ or $-N(R_{a2})SO_2$, wherein R_{a2} is hydrogen; and

Z_1 is selected from (1-4C)alkyl, wherein Z_1 is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkoxy, cyano, $-NR_eR_f$, $-OR_e$, $-C(O)R_e$, $-C(O)N(R_e)R_f$, $-N(R_e)C(O)R_f$, $-S(O)_yR_e$ (where y is 0, 1 or 2); and wherein R_e and R_f are each independently selected from hydrogen or methyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, methyl or (2C)alkanoyl;

(15b) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups, wherein R_{10C} is selected from oxo, halo, or cyano substituents, or a group of the formula:

$$-L-Z$$

wherein

L is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_a)-$, -C(O)-, -C(O)O-, $-OC(O)-$, $-C(O)N(R_a)-$, $-N(R_a)C(O)-$, $-S(O)_2N(R_a)-$, or $-N(R_a)SO_2-$, wherein R_a and R_b are hydrogen; and

Z is selected from hydrogen, (1-4C)alkyl or (3-6C)cycloalkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is $-S(O)_2NH_2$ or (1-4C)alkyl,

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, methyl or (2C)alkanoyl;

(15c) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups, wherein R_{10C} is selected from oxo, halo, cyano, (1-4C)alkyl or (3-6C)cycloalkyl;
and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is $-S(O)_2NH_2$ or (1-4C)alkyl, and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, methyl or (2C)alkanoyl;

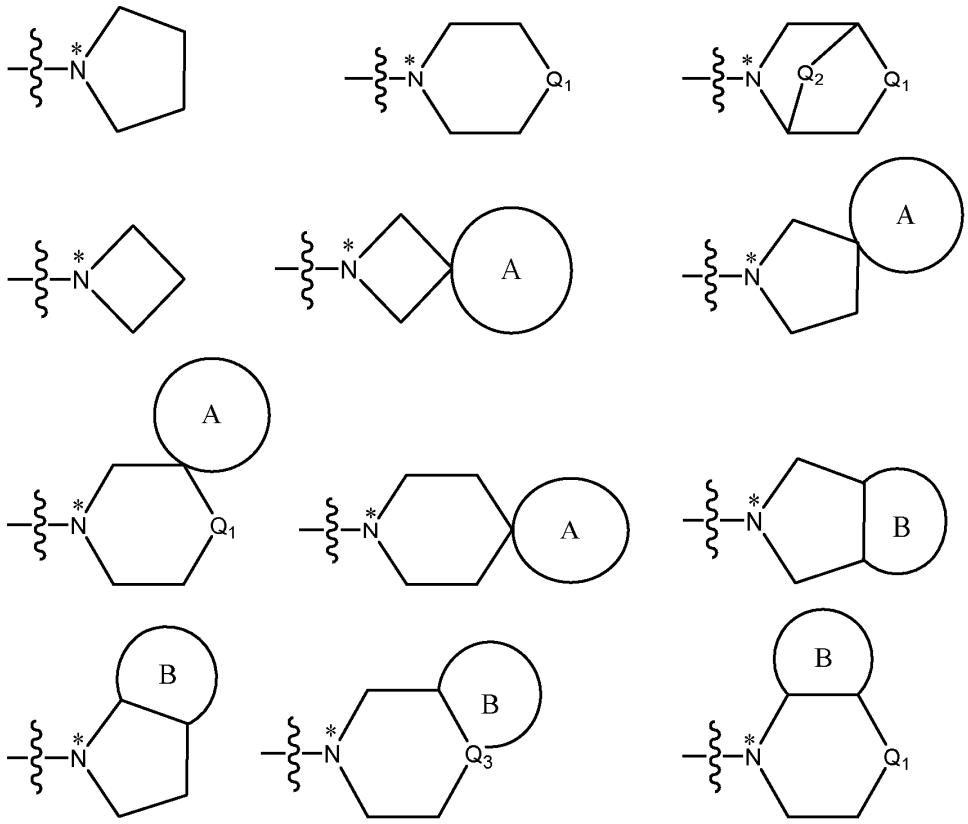
(16) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a 4 to 12 membered heterocyclic ring and wherein the heterocyclic ring is optionally substituted with one or more R_{10C} or R_{10N} substituent groups, wherein R_{10c} and R_{10N} are as defined in any one of paragraphs (11) to (15c) above;

(17) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a 4 to 8 membered monocyclic or bridged heterocyclic ring or a 7 to 12-membered bicyclic or spiro bicyclic heterocyclic ring, and wherein the heterocyclic ring is optionally substituted with one or more R_{10C} or R_{10N} substituent groups, wherein R_{10c} and R_{10N} are as defined in any one of paragraphs (11) to (15c) above;

(18) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a 4 to 7 membered monocyclic or bridged heterocyclic ring or a 7 to 11-membered bicyclic or spiro bicyclic heterocyclic ring, and wherein the heterocyclic ring is optionally substituted with one or more R_{10C} or R_{10N} substituent groups, wherein R_{10c} and R_{10N} are as defined in any one of paragraphs (11) to (15c) above;

(19) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a 5 or 6 membered monocyclic heterocyclic ring or a 7 to 10-membered bicyclic or spiro bicyclic heterocyclic ring, and wherein the heterocyclic ring is optionally substituted with one or more R_{10C} or R_{10N} substituent groups, wherein R_{10c} and R_{10N} are as defined in any one of paragraphs (11) to (15c) above;

(20) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



wherein * denotes the N atom to which R_4 and R_5 are attached;

Q_1 is O, NH, S, S(O), $S(O)_2$, $S(O)(=NR_e)$, N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_2 is -CH_2-, -CHR_{10C}-, -$C(R_{10c})_2$-, -CHR_{10C}-CH_2-, -CH_2-CHR_{10C}-, -CHR_{10C}-CHR_{10C}-, -$C(R_{10c})_2$-CH_2-, or -CH_2-$C(R_{10c})_2$-;

Q_3 is CH, CR_{10C} or N;

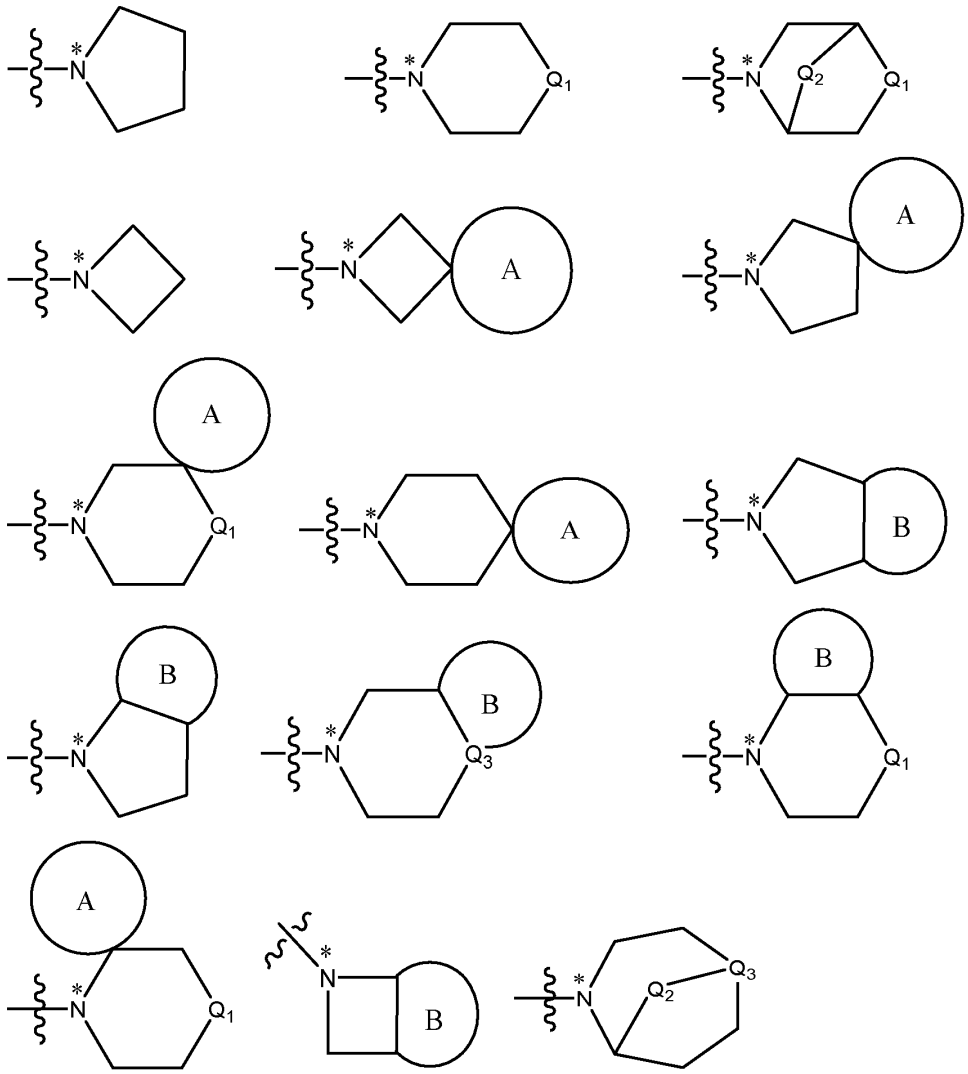
Ring A is a spiro-fused 4, 5 or 6 membered carbocyclic or heterocyclic ring;

Ring B is a fused 4, 5 or 6 membered carbocyclic or heterocyclic ring;

wherein R_e is selected from hydrogen or methyl;

and wherein each of the heterocyclic ring systems is optionally substituted with one or more R_{10c} or R_{10N} substituent groups as defined in any one of paragraphs (11) to (15c) above;

(20a) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



wherein * denotes the N atom to which R_4 and R_5 are attached;

Q_1 is O, NH, S, S(O), $S(O)_2$, $S(O)(=NR_e)$, N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_2 is -CH_2-, -CHR_{10C}-, -$C(R_{10c})_2$-, -CHR_{10C}-CH_2-, -CH_2-CHR_{10C}-, -CHR_{10C}-CHR_{10C}-, -$C(R_{10c})_2$-CH_2-, or -CH_2-$C(R_{10c})_2$-;

Q_3 is CH, CR_{10C} or N;

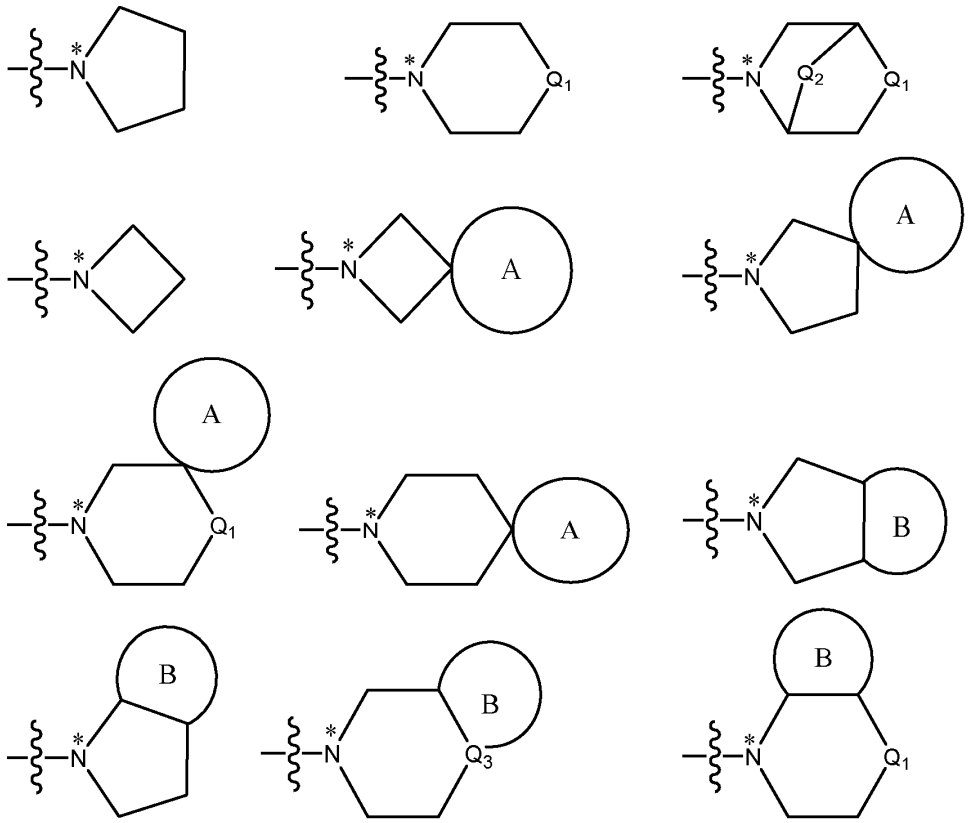
Ring A is a spiro-fused 4, 5 or 6 membered carbocyclic or heterocyclic ring;

Ring B is a fused 4, 5 or 6 membered carbocyclic or heterocyclic ring;

wherein R_e is selected from hydrogen or methyl;

and wherein each of the heterocyclic ring systems is optionally substituted with one or more R_{10c} or R_{10N} substituent groups as defined in any one of paragraphs (11) to (15c) above;

(21) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



wherein * denotes the N atom to which R_4 and R_5 are attached;

Q_1 is O, NH, S, S(O), $S(O)_2$, S(O)(=NR_e), N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_2 is -CH_2-, -CHR_{10C}-, or -$C(R_{10c})_2$-;

Q_3 is CH, CR_{10C} or N;

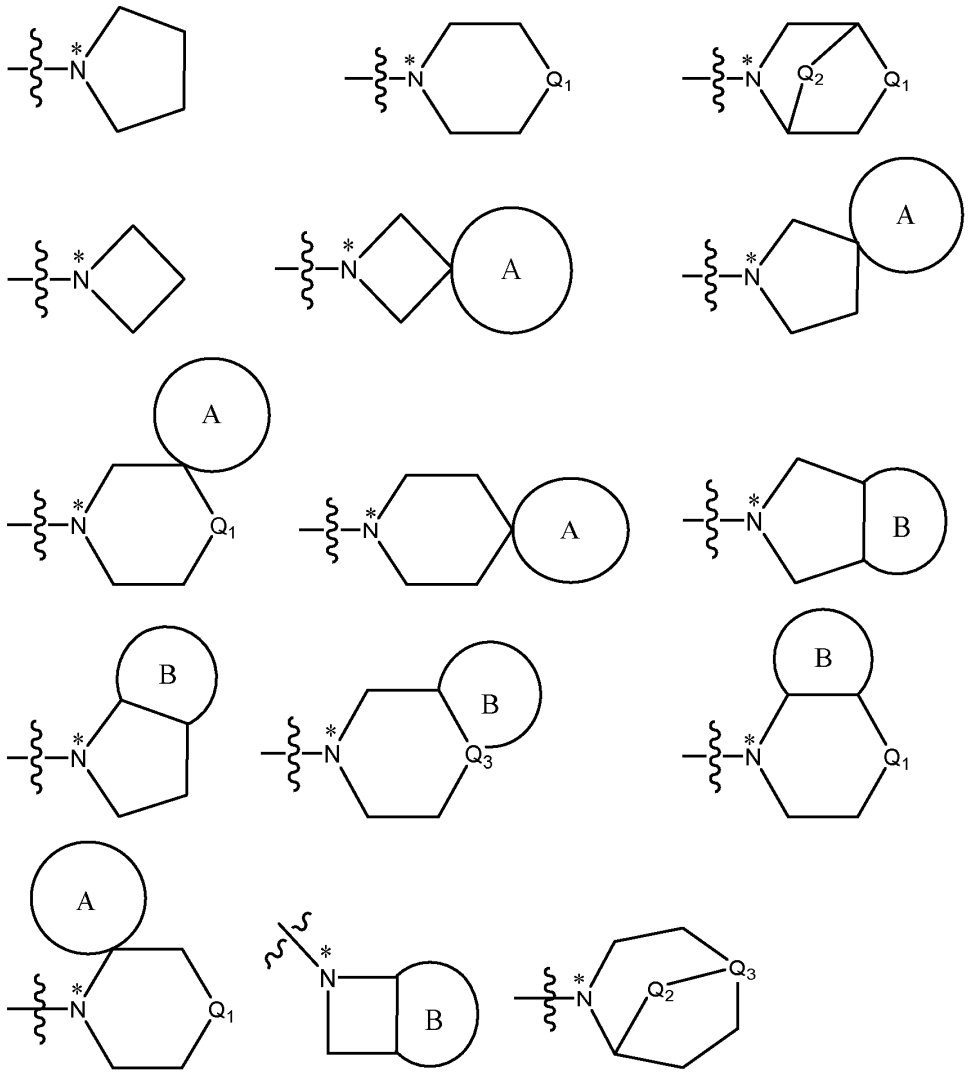
Ring A is a spiro-fused 4, 5 or 6 membered carbocyclic or heterocyclic ring;

Ring B is a fused 4, 5 or 6 membered carbocyclic or heterocyclic ring;

wherein R_e is selected from hydrogen, (1-3C)alkyl or (2-3C)alkanoyl;

and wherein each of the heterocyclic ring systems is optionally substituted with one or more R_{10c} or R_{10N} substituent groups as defined in any one of paragraphs (11) to (15c) above;

(21a) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



wherein * denotes the N atom to which R_4 and R_5 are attached;

Q_1 is O, NH, S, S(O), $S(O)_2$, $S(O)(=NR_e)$, N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_2 is -CH_2-, -CHR_{10C}-, or -$C(R_{10c})_2$-;

Q_3 is CH, CR_{10C} or N;

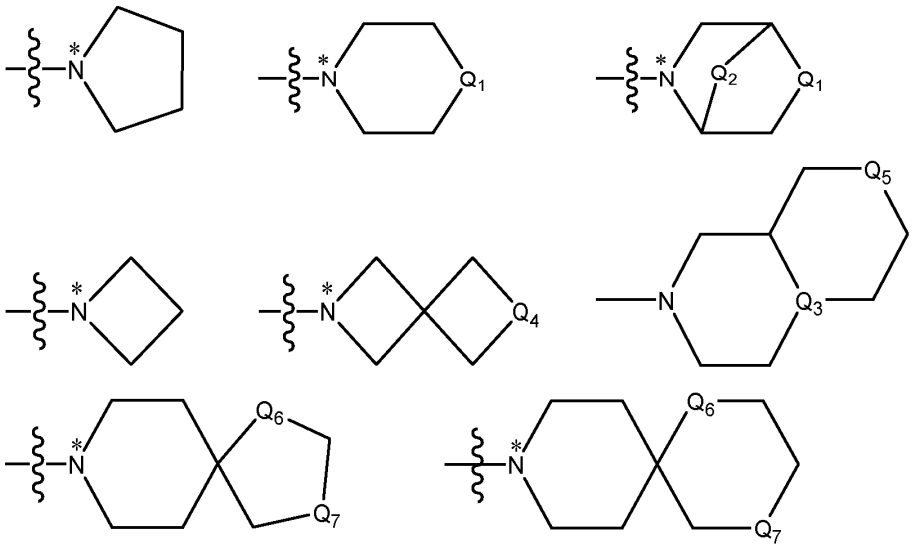
Ring A is a spiro-fused 4, 5 or 6 membered carbocyclic or heterocyclic ring;

Ring B is a fused 4, 5 or 6 membered carbocyclic or heterocyclic ring;

wherein R_e is selected from hydrogen, (1-3C)alkyl or (2-3C)alkanoyl;

and wherein each of the heterocyclic ring systems is optionally substituted with one or more R_{10c} or R_{10N} substituent groups as defined in any one of paragraphs (11) to (15c) above;

(21b) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



wherein * denotes the N atom to which R_4 and R_5 are attached;

Q_1 is O, NH, S, S(O), $S(O)_2$, $S(O)(=NR_e)$, N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_2 is -CH_2-;

Q_3 is CH, CR_{10C} or N;

Q_4 is O, NH, S, S(O), $S(O)_2$, $S(O)(=NR_e)$, N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_5 is O, NH, S, S(O), $S(O)_2$, $S(O)(=NR_e)$, N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

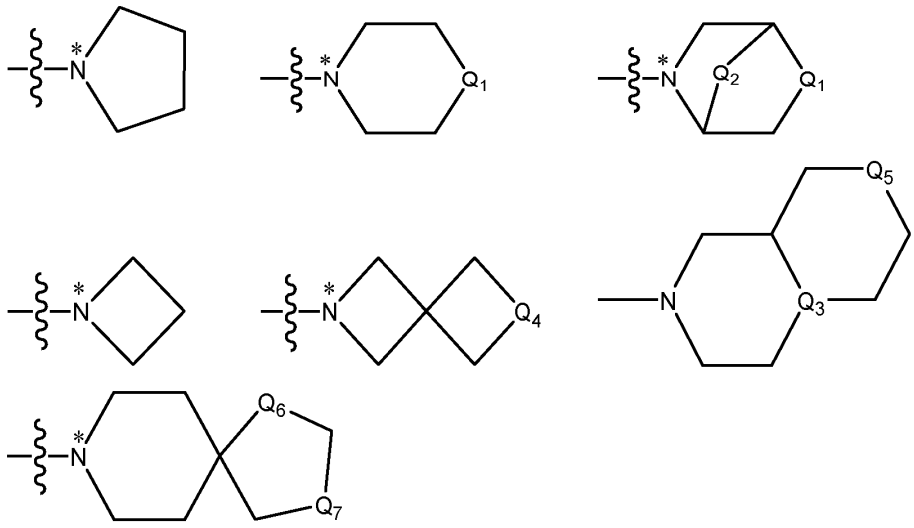
Q_6 is O, NH, S, S(O), $S(O)_2$, $S(O)(=NR_e)$, N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_7 is O, NH, S, S(O), $S(O)_2$, $S(O)(=NR_e)$, N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

wherein R_e is selected from hydrogen, (1-2C)alkyl or (2C)alkanoyl;

and wherein each of the heterocyclic ring systems is optionally substituted with one or more R_{10c} or R_{10N} substituent groups as defined in any one of paragraphs (11) to (15c) above;

(22) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



wherein * denotes the N atom to which R_4 and R_5 are attached;

Q_1 is O, NH, S, S(O), $S(O)_2$, S(O)(=NR_e), N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_2 is -CH_2-;

Q_3 is CH, CR_{10C} or N;

Q_4 is O, NH, S, S(O), $S(O)_2$, S(O)(=NR_e), N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_5 is O, NH, S, S(O), $S(O)_2$, S(O)(=NR_e), N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

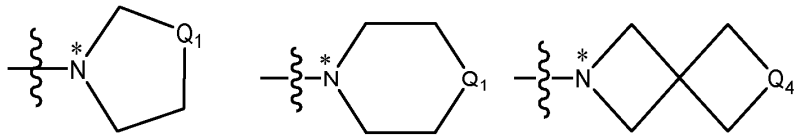
Q_6 is O, NH, S, S(O), $S(O)_2$, S(O)(=NR_e), N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_7 is O, NH, S, S(O), $S(O)_2$, S(O)(=NR_e), N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

wherein R_e is selected from hydrogen, (1-2C)alkyl or (2C)alkanoyl;

and wherein each of the heterocyclic ring systems is optionally substituted with one or more R_{10c} or R_{10N} substituent groups as defined in any one of paragraphs (11) to (15c) above;

(22a) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



wherein * denotes the N atom to which R_4 and R_5 are attached;

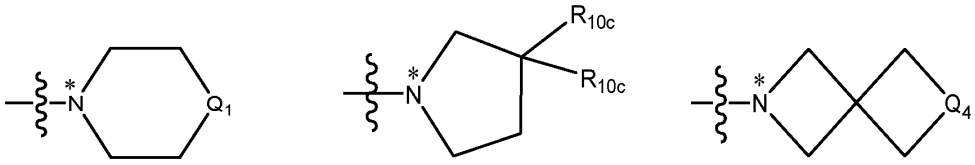
Q_1 is O, NH, S, S(O), $S(O)_2$, S(O)(=NR_e), N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_4 is O, NH, S, S(O), $S(O)_2$, S(O)(=NR_e), N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

wherein R_e is selected from hydrogen, (1-2C)alkyl or (2C)alkanoyl;

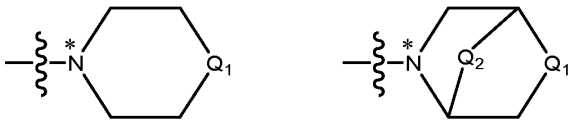
and wherein each of the heterocyclic ring systems is optionally substituted with one or more R_{10c} or R_{10N} substituent groups as defined in any one of paragraphs (11) to (15c) above;

(22b) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



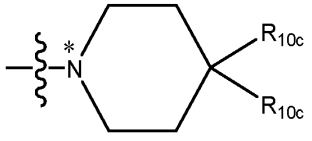
wherein * denotes the N atom to which R_4 and R_5 are attached;
Q_1 is O, NH, N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;
Q_4 is O, NH, N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;
wherein R_e is selected from hydrogen, methyl or (2C)alkanoyl;
and R_{10c} or R_{10N} are as defined in any one of paragraphs (11) to (15c) above;

(23) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



wherein * denotes the N atom to which R_4 and R_5 are attached;
Q_1 is O, NH, S, S(O), $S(O)_2$, S(O)(=NR_e), N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;
Q_2 is -CH_2-;
wherein R_e is selected from hydrogen, methyl or (2C)alkanoyl;
and R_{10c} or R_{10N} are as defined in any one of paragraphs (11) to (15c) above;

(24) R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring of the structure:



wherein * denotes the N atom to which R_4 and R_5 are attached;

and each R_{10c} is independently selected from the options defined in any one of paragraphs (11) to (15c) above;

(25) R_6 is selected from hydrogen, halo or methyl;

(26) R_6 is selected from hydrogen or methyl;

(27) R_6 is hydrogen;

(28) R_x is selected from methyl, CD_3 or chloro;

(29) R_x is selected from methyl or CD_3;

(30) R_x is methyl;

(31) R_x is CD_3

(32) R_x is chloro;

[0065] Suitably, a heteroaryl or heterocyclyl group as defined herein is a monocyclic heteroaryl or mono, bicyclic, spiro bicyclic or bridged heterocyclyl group comprising one, two or three heteroatoms selected from N, O or S.

[0066] Suitably, a heteroaryl is a 5- or 6-membered heteroaryl ring comprising one, two or three heteroatoms selected from N, O or S.

[0067] Suitably, a heterocyclyl group is a 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl ring comprising one, two or three heteroatoms selected from N, O or S. Most suitably, a heterocyclyl group is a 5-, 6- or 7-membered ring comprising one, two or three heteroatoms selected from N, O or S [e.g. morpholinyl (e.g. 4-morpholinyl), pyridinyl, piperazinyl, homopiperazinyl or pyrrolidinonyl] or a 7-, 8-, 9- or 10-membered spiro bicyclic ring system comprising one, two or three heteroatoms selected from N, O or S.

[0068] Suitably, an aryl group is phenyl.

[0069] Suitably, R_1 is as defined in paragraphs (1) to (8) above. In an embodiment, R_1 is as defined in paragraph (6) above.

[0070] Suitably, R_1 is as defined in paragraphs (1) to (8f) above. More suitably, R_1 is as defined in paragraphs (1a), (2a), (3a), (3b), (4a), (7a), (8a), (8b), (8c), (8d), (8e) or (8f) above. In an embodiment, R_1 is as defined in paragraph (4a) or (7a) above.

[0071] Suitably, R_2 and R_3 are as defined in any one of paragraphs (9) or (10) above. Most suitably, R_2 and R_3 are as defined in paragraph (10) above.

[0072] Suitably, R_4 and R_5 are as defined in any one of paragraphs (11) to (24) above. More suitably, R_4 and R_5 are as defined in paragraph (15), (15a), (15b) or (15c), (20a), (21a), (21b), (22a) or (22b) above. In certain groups of compounds of the invention, R_4 and R_5 are as

defined in paragraph (16), (17), (18), (20), (21), (22) (23), (24), (20a), (21a), (21b), (22a) or (22b) above.

[0073] Suitably, R_4 and R_5 are as defined in any one of paragraphs (11) to (24) above. More suitably, R_4 and R_5 are as defined in paragraph (15) above. Even more suitably, R_4 and R_5 are as defined in paragraph (16), (17) or (18) above. In certain groups of compounds of the invention, R_4 and R_5 are as defined in paragraph (20), (21), (22) (23) or (24) above.

[0074] Suitably, R_x is as defined in any one of paragraphs (28) to (31) above. Most suitably, R_x is as defined in paragraph (29) above.

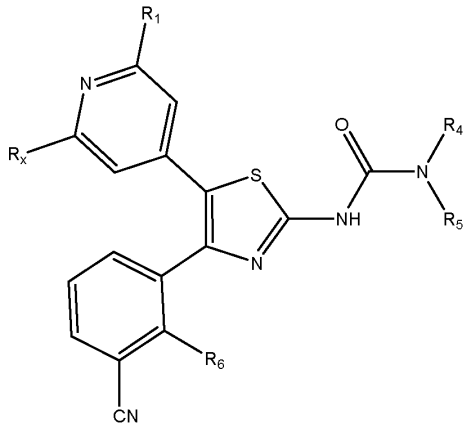
[0075] Suitably, R_{10c} and R_{10N} are as defined in any one of paragraphs (11) to (15c) above. More suitably, R_{10c} and R_{10N} are as defined in any one of paragraphs (15) to (15c) above. Even more suitably, R_{10c} and R_{10N} are as defined in any one of paragraphs (15a), (15b) or (15c) above.

[0076] Suitably, R_6 is as defined in any one of paragraphs (25) to (27) above. More suitably, R_6 is as defined in paragraph (27) above.

[0077] In a particular group of compounds of Formula I above, R_1 is as defined in any one of paragraphs (1), (2), (3), (4), (5), (6), (7) or (8) and R_2, R_3, R_4, R_5 and R_6 each have any one of the definitions set out herein.

[0078] In a particular group of compounds of Formula I above, R_1 is as defined in any one of paragraphs (1a), (2a), (3a), (3b), (4a), (7a), (8a), (8b), (8c), (8d), (8e), (8f) above, and R_z R_2, R_3, R_4, R_5 and R_6 each have any one of the definitions set out herein.

[0079] In a particular group of compounds of Formula I above, R_2 and R_3 are hydrogen, i.e. the compounds have the structural formula IA (a sub-formula of Formula I) shown below:



IA

wherein R_x, R_1, R_4, R_5, R_6 and R_x each have any one of the definitions set out herein.

[0080] In an embodiment of the compounds of formula IA:

R_x is as defined in any one of paragraphs (28) to (31) above

R_1 is as defined in any one of paragraph (1) to (8f) above;

R_4 and R_5 are as defined in any one of paragraphs (11) to (24) above; and

R_6 is as defined in any one of paragraphs (25) to (27) above;

[0081] In another embodiment of the compounds of formula IA:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraphs (1a), (2a), (3a), (3b), (4a), (7a), (8a), (8b), (8c), (8d), (8e) or (8f) above;

R_4 and R_5 are as defined in paragraph (12) above; and

R_6 is as defined in paragraphs (25) above.

[0082] In another embodiment of the compounds of formula IA:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_4 and R_5 are as defined in paragraph (15), (15a), (15b), (15c) or (16) above; and

R_6 is as defined in paragraphs (27) above.

[0083] In another embodiment of the compounds of formula IA:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_4 and R_5 are as defined in paragraph (16) above; and

R_6 is as defined in paragraphs (27) above.

[0084] In another embodiment of the compounds of formula IA':

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_4 and R_5 are as defined in paragraph (17) above; and

R_6 is as defined in paragraphs (27) above.

[0085] In another embodiment of the compounds of formula IA:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_4 and R_5 are as defined in paragraph (18) above; and

R_6 is as defined in paragraphs (27) above.

[0086] In another embodiment of the compounds of formula IA:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_4 and R_5 are as defined in paragraph (19) above; and

R_6 is as defined in paragraphs (27) above.

[0087] In another embodiment of the compounds of formula IA:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_4 and R_5 are as defined in paragraph (20) above; and

R_6 is as defined in paragraphs (27) above.

[0088] In another embodiment of the compounds of formula IA:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_4 and R_5 are as defined in paragraph (21) above; and

R_6 is as defined in paragraphs (27) above.

[0089] In another embodiment of the compounds of formula IA:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_4 and R_5 are as defined in paragraph (22) above; and

R_6 is as defined in paragraphs (27) above.

[0090] In another embodiment of the compounds of formula IA:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (6) above;

R_4 and R_5 are as defined in paragraph (23) above; and

R_6 is as defined in paragraphs (27) above.

[0091] In another embodiment of the compounds of formula IA:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_4 and R_5 are as defined in paragraph (24) above; and

R_6 is as defined in paragraphs (27) above.

[0092] In another embodiment of the compounds of formula IA:

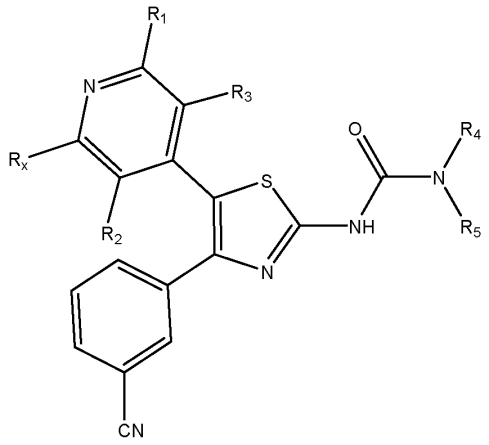
R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_4 and R_5 are as defined in paragraph (20a), (21a), (21b), (22a) or (22b) above; and

R_6 is as defined in paragraphs (27) above.

[0093] In a particular group of compounds of Formula I above, R_6 is hydrogen, i.e. the compounds have the structural formula IB (a sub-formula of Formula I') shown below:



IB

wherein R_x, R_1, R_2, R_3, R_4 and R_5 each have any one of the definitions set out herein.

[0094] In an embodiment of the compounds of formula IB:

R_x is as defined in any one of paragraphs (28) to (31) above

R_1 is as defined in any one of paragraph (1) to (8f) above;

R_2 and R_3 are as defined in paragraph (9) or (10); and

R_4 and R_5 are as defined in any one of paragraphs (11) to (24) above.

[0095] In another embodiment of the compounds of formula IB:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraphs (1a), (2a), (3a), (3b), (4a), (7a), (8a), (8b), (8c), (8d), (8e) or (8f) above;

R_2 and R_3 are as defined in paragraph (9); and

R_4 and R_5 are as defined in paragraph (12) above.

[0096] In another embodiment of the compounds of formula IB:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (15), (15a), (15b) or (15c) above.

[0097] In another embodiment of the compounds of formula IB:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (16) above.

[0098] In another embodiment of the compounds of formula IB:

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (17) above.

[0099] In another embodiment of the compounds of formula IB:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (18) above.

[00100] In another embodiment of the compounds of formula IB:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (19) above.

[00101] In another embodiment of the compounds of formula IB:

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (20) above.

[00102] In another embodiment of the compounds of formula IB:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (21) above.

[00103] In another embodiment of the compounds of formula IB:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (22) above.

[00104] In another embodiment of the compounds of formula IB:

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (23) above.

[00105] In another embodiment of the compounds of formula IB:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (24) above.

[00106] In another embodiment of the compounds of formula IB:

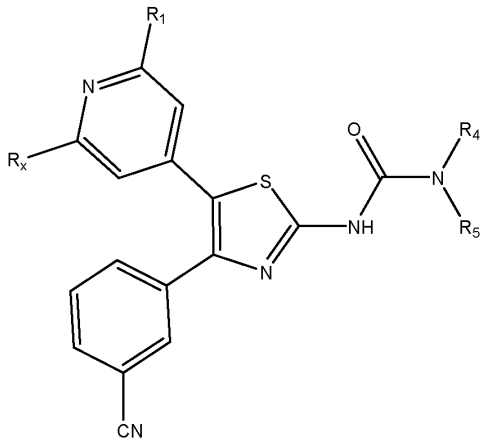
R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (20a), (21a), (21b), (22a) or (22b) above.

[00107] In a particular group of compounds of Formula I above, R_2, R_3 and R_6 are hydrogen, i.e. the compounds have the structural formula IC (a sub-formula of Formula I) shown below:



IC

wherein R_x, R_1, R_4 and R_5 each have any one of the definitions set out herein.

[00108] In an embodiment of the compounds of formula IC:

R_x is as defined in any one of paragraphs (28) to (31) above

R_1 is as defined in any one of paragraph (1) to (8f) above; and

R_4 and R_5 are as defined in any one of paragraphs (11) to (24) above.

[00109] In another embodiment of the compounds of formula IC:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraphs (1a), (2a), (3a), (3b), (4a), (7a), (8a), (8b), (8c), (8d), (8e) or (8f) above; and

R_4 and R_5 are as defined in paragraph (12) above.

[00110] In another embodiment of the compounds of formula IC:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above; and

R_4 and R_5 are as defined in paragraph (15), (15a), (15b) or (15c) above.

[00111] In another embodiment of the compounds of formula IC:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above; and

R_4 and R_5 are as defined in paragraph (16) above.

[00112] In another embodiment of the compounds of formula IC:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above; and

R_4 and R_5 are as defined in paragraph (17) above.

[00113] In another embodiment of the compounds of formula IC:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above; and

R_4 and R_5 are as defined in paragraph (18) above.

[00114] In another embodiment of the compounds of formula IC:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above; and

R_4 and R_5 are as defined in paragraph (19) above.

[00115] In another embodiment of the compounds of formula IC:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above; and

R_4 and R_5 are as defined in paragraph (20) above.

[00116] In another embodiment of the compounds of formula IC:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above; and

R_4 and R_5 are as defined in paragraph (21) above.

[00117] In another embodiment of the compounds of formula IC:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above; and

R_4 and R_5 are as defined in paragraph (22) above.

[00118] In another embodiment of the compounds of formula IC':

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above; and

R_4 and R_5 are as defined in paragraph (23) above.

[00119] In another embodiment of the compounds of formula IC:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above; and

R_4 and R_5 are as defined in paragraph (24) above.

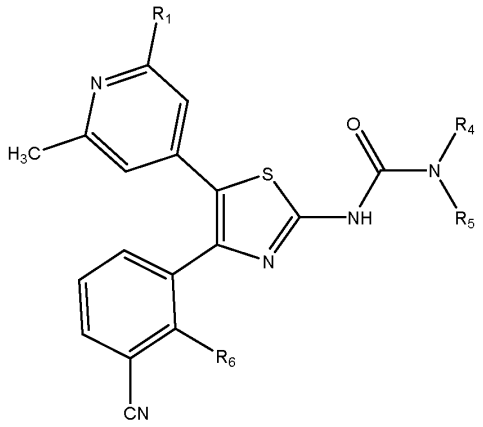
[00120] In another embodiment of the compounds of formula IC:

R_x is as defined in paragraph (29) above;

R_1 is as defined in paragraph (4a) above; and

R_4 and R_5 are as defined in paragraph (20a), (21a), (21b), (22a) or (22b) above; and

[00121] In a particular group of compounds of Formula I above, R_2 and R_3 are hydrogen, i.e. the compounds have the structural formula IA' (a sub-formula of Formula I) shown below:



IA'

wherein R_1, R_4, R_5 and R_6 each have any one of the definitions set out herein.

[00122] In an embodiment of the compounds of formula IA':

R_1 is as defined in any one of paragraph (1) to (8) above;

R_4 and R_5 are as defined in any one of paragraphs (11) to (24) above; and

R_6 is as defined in any one of paragraphs (25) to (27) above.

[00123] In another embodiment of the compounds of formula IA':

R_1 is as defined in paragraph (2) above;

R_4 and R_5 are as defined in paragraph (12) above; and

R_6 is as defined in paragraphs (25) above.

[00124] In another embodiment of the compounds of formula IA':

R_1 is as defined in paragraph (6) above;

R_4 and R_5 are as defined in paragraph (15), (15a), (15b) or (15c) above; and

R_6 is as defined in paragraphs (27) above.

[00125] In another embodiment of the compounds of formula IA':

R_1 is as defined in paragraph (6) above;

R_4 and R_5 are as defined in paragraph (16) above; and

R_6 is as defined in paragraphs (27) above.

[00126] In another embodiment of the compounds of formula IA':

R_1 is as defined in paragraph (6) above;

R_4 and R_5 are as defined in paragraph (17) above; and

R_6 is as defined in paragraphs (27) above.

[00127] In another embodiment of the compounds of formula IA':

R_1 is as defined in paragraph (6) above;

R_4 and R_5 are as defined in paragraph (18) above; and

R_6 is as defined in paragraphs (27) above.

[00128] In another embodiment of the compounds of formula IA':

R_1 is as defined in paragraph (6) above;

R_4 and R_5 are as defined in paragraph (19) above; and

R_6 is as defined in paragraphs (27) above.

[00129] In another embodiment of the compounds of formula IA':

R_1 is as defined in paragraph (6) above;

R_4 and R_5 are as defined in paragraph (20) above; and

R_6 is as defined in paragraphs (27) above.

[00130] In another embodiment of the compounds of formula IA':

R_1 is as defined in paragraph (6) above;

R_4 and R_5 are as defined in paragraph (21) above; and

R_6 is as defined in paragraphs (27) above.

[00131] In another embodiment of the compounds of formula IA':

R_1 is as defined in paragraph (6) above;

R_4 and R_5 are as defined in paragraph (22) above; and

R_6 is as defined in paragraphs (27) above.

[00132] In another embodiment of the compounds of formula IA':

R_1 is as defined in paragraph (6) above;

R_4 and R_5 are as defined in paragraph (23) above; and

R_6 is as defined in paragraphs (27) above.

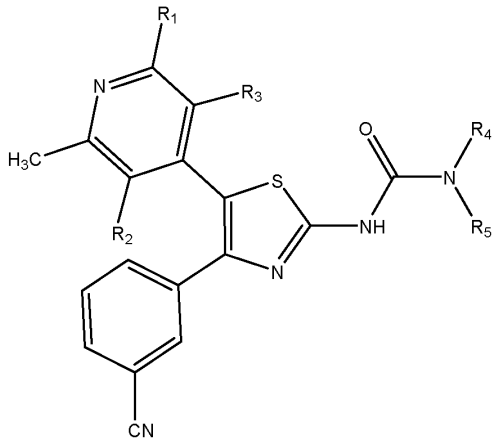
[00133] In another embodiment of the compounds of formula IA':

R_1 is as defined in paragraph (6) above;

R_4 and R_5 are as defined in paragraph (24) above; and

R_6 is as defined in paragraphs (27) above.

[00134] In a particular group of compounds of Formula I above, R_6 is hydrogen, i.e. the compounds have the structural formula IB' (a sub-formula of Formula I) shown below:



IB'

wherein R_1, R_2, R_3, R_4 and R_5 each have any one of the definitions set out herein.

[00135] In an embodiment of the compounds of formula IB':

R_1 is as defined in any one of paragraph (1) to (8) above;

R_2 and R_3 are as defined in paragraph (9) or (10); and

R_4 and R_5 are as defined in any one of paragraphs (11) to (24) above.

[00136] In another embodiment of the compounds of formula IB':

R_1 is as defined in paragraph (2) above;

R_2 and R_3 are as defined in paragraph (9); and

R_4 and R_5 are as defined in paragraph (12) above.

[00137] In another embodiment of the compounds of formula IB':

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (15), (15a), (15b) or (15c) above.

[00138] In another embodiment of the compounds of formula IB':

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (16) above.

[00139] In another embodiment of the compounds of formula IB':

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (17) above.

[00140] In another embodiment of the compounds of formula IB':

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (18) above.

[00141] In another embodiment of the compounds of formula IB':

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (19) above.

[00142] In another embodiment of the compounds of formula IB':

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (20) above.

[00143] In another embodiment of the compounds of formula IB':

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (21) above.

[00144] In another embodiment of the compounds of formula IB':

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (22) above.

[00145] In another embodiment of the compounds of formula IB':

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (23) above.

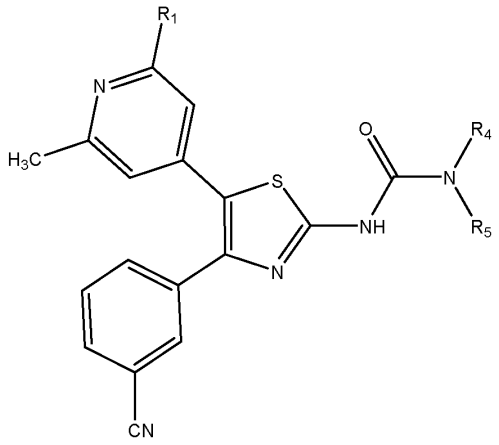
[00146] In another embodiment of the compounds of formula IB':

R_1 is as defined in paragraph (6) above;

R_2 and R_3 are as defined in paragraph (10); and

R_4 and R_5 are as defined in paragraph (24) above.

[00147] In a particular group of compounds of Formula I above, R_2, R_3 and R_6 are hydrogen, i.e. the compounds have the structural formula IC' (a sub-formula of Formula I) shown below:



IC'

wherein R_1, R_4 and R_5 each have any one of the definitions set out herein.

[00148] In an embodiment of the compounds of formula IC':

R_1 is as defined in any one of paragraph (1) to (8) above; and

R_4 and R_5 are as defined in any one of paragraphs (11) to (24) above.

[00149] In another embodiment of the compounds of formula IC':

R_1 is as defined in paragraph (2) above; and

R_4 and R_5 are as defined in paragraph (12) above.

[00150] In another embodiment of the compounds of formula IC':

R_1 is as defined in paragraph (6) above; and

R_4 and R_5 are as defined in paragraph (15), (15a), (15b) or (15c) above.

[00151] In another embodiment of the compounds of formula IC':

R_1 is as defined in paragraph (6) above; and

R_4 and R_5 are as defined in paragraph (16) above.

[00152] In another embodiment of the compounds of formula IC':

R_1 is as defined in paragraph (6) above; and

R_4 and R_5 are as defined in paragraph (17) above.

[00153] In another embodiment of the compounds of formula IC':

R_1 is as defined in paragraph (6) above; and

R_4 and R_5 are as defined in paragraph (18) above.

[00154] In another embodiment of the compounds of formula IC':

R_1 is as defined in paragraph (6) above; and

R_4 and R_5 are as defined in paragraph (19) above.

[00155] In another embodiment of the compounds of formula IC':

R_1 is as defined in paragraph (6) above; and

R_4 and R_5 are as defined in paragraph (20) above.

[00156] In another embodiment of the compounds of formula IC':

R_1 is as defined in paragraph (6) above; and

R_4 and R_5 are as defined in paragraph (21) above.

[00157] In another embodiment of the compounds of formula IC':

R_1 is as defined in paragraph (6) above; and

R_4 and R_5 are as defined in paragraph (22) above.

[00158] In another embodiment of the compounds of formula IC':

R_1 is as defined in paragraph (6) above; and

R_4 and R_5 are as defined in paragraph (23) above.

[00159] In another embodiment of the compounds of formula IC':

R_1 is as defined in paragraph (6) above; and

R_4 and R_5 are as defined in paragraph (24) above.

[00160] Particular compounds of the present invention include any of the compounds described in the example section of the present application, or a pharmaceutically acceptable salt or solvate thereof, and, in particular, any of the following:

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]morpholine-4-carboxamide

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide

(2R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1-carboxamide

(3R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]pyrrolidine-1-carboxamide

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-(2-hydroxy-2-methyl-propyl)pyrrolidine-1-carboxamide

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)morpholine-4-carboxamide

(2S)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-methyl-piperazine-1-carboxamide

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-hydroxy-4-methyl-piperidine-1-carboxamide
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-cyano-4-methyl-piperidine-1-carboxamide
(3S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperazine-1-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide
(3R)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-piperazine-1-carboxamide
N4-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]morpholine-2,4-dicarboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-3-oxo-piperazine-1-carboxamide
(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)morpholine-4-carboxamide
4-acetyl-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methylsulfonyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-sulfamoyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)morpholine-4-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methoxy-piperidine-1-carboxamide

4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(hydroxymethyl)piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)azetidine-1-carboxamide
3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,1-dioxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3-dimethyl-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
N1-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1,4-dicarboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxyethyl)piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxyethyl)-3-oxo-piperazine-1-carboxamide
4,4-dicyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxy-2-methyl-propyl)piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-methyl-1,7-diazaspiro[3.4]octane-7-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxy-1,1-dimethyl-ethyl)piperazine-1-carboxamide
(8aS)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxamide
(8aR)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide
(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-pyrrolidine-1-carboxamide

4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(methoxymethyl)piperidine-1-carboxamide

4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-fluoro-piperidine-1-carboxamide

(3S)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-3-methyl-azetidine-1-carboxamide

(2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid

methyl (2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylate

(3S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(hydroxymethyl)piperazine-1-carboxamide

(3R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(hydroxymethyl)piperazine-1-carboxamide

(3S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide

(3R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide

(1S,4S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide

(3R)-N1-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1,3-dicarboxamide

(3S)-N1-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1,3-dicarboxamide

4-amino-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide

4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide

(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methylsulfonyl-pyrrolidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-7-azaspiro[3.5]nonane-7-carboxamide

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

(1R,4R)-5-acetyl-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide
(1S,4S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
N-[5-[2,6-bis(trideuteriomethyl)-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
(4aS,7aR)-N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-9-methyl-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxamide
(4aS,7aS)-N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
3-cyano-N-[4-(3-cyanophenyl)-5-[2-methyl-6-(oxetan-3-yl)-4-pyridyl]thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-[2-methyl-6-(oxetan-3-yl)-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-morpholino-azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-tetrahydropyran-4-yl-piperazine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-pyrrolidin-1-yl-azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(dimethylamino)azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(morpholinomethyl)piperidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane-8-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-3,6-diazabicyclo[3.2.0]heptane-6-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,4-diazabicyclo[3.2.1]octane-4-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-5,6,8,8a-tetrahydro-1H-oxazolo[3,4-a]pyrazine-7-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,2-dioxo-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]thiazine-8-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-oxo-3,6,7,8,9,9a-hexahydro-1H-pyrido[1,2-a]pyrazine-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-9-oxo-3,4,6,7,8,9a-hexahydro-1H-pyrazino[1,2-a]pyrazine-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-1,3,4,8,9,9a-hexahydropyrazino[1,2-c][1,3]oxazine-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-1,3,4,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-2-carboxamide

N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-sulfamoyl-pyrrolidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-2,7-diazaspiro[3.5]nonane-7-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-pyrazol-1-yl-piperidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(1,2,4-oxadiazol-3-yl)piperidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3-dioxo-5,6,8,8a-tetrahydroimidazo[1,5-a]pyrazine-7-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-2,8-diazaspiro[4.5]decane-8-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(1H-imidazol-2-yl)piperidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-10-oxo-3,9-diazaspiro[5.5]undecane-3-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxamide

N1-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-N4-methyl-piperidine-1,4-dicarboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide

(3S)-N1-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1,3-dicarboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-oxoimidazolidin-1-yl)piperidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-methylimino-1-oxo-1,4-thiazinane-4-carboxamide

N1-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-N4-(2-hydroxyethyl)piperidine-1,4-dicarboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-7-oxa-2,5-diazaspiro[3.5]nonane-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6,9-dioxo-1,3,4,7,8,9a-hexahydropyrazino[1,2-a]pyrazine-2-carboxamide

(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-oxo-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-3-oxo-2,8-diazaspiro[4.5]decane-8-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-8-methyl-6,9-dioxo-3,4,7,9a-tetrahydro-1H-pyrazino[1,2-a]pyrazine-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-2,8-diazaspiro[4.5]decane-8-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-2,9-diazaspiro[5.5]undecane-9-carboxamide

4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(1-hydroxy-1-methyl-ethyl)piperidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-3,4,7,8,9,9a-hexahydro-1H-pyrazino[1,2-c]pyrimidine-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-3,4,7,8,9,9a-hexahydro-1H-pyrido[1,2-a]pyrazine-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-hydroxy-6-methyl-2-azaspiro[3.3]heptane-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-1,8-diazaspiro[4.5]decane-8-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,2-dioxo-2λ^{6}-thia-6-azaspiro[3.3]heptane-6-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)morpholine-4-carboxamide

(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide

(3aR,6aS)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrole-5-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-3-oxa-1,9-diazaspiro[5.5]undecane-9-carboxamide

(1S,5S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-methyl-3,6-diazabicyclo[3.2.2]nonane-3-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-methyl-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide

(3aS,6aS)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxa-2-azaspiro[3.4]octane-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-7-oxa-2-azaspiro[3.5]nonane-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-2,7-diazaspiro[3.4]octane-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane-8-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-2,5,7-triazaspiro[3.4]octane-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-1,9-diazaspiro[5.5]undecane-9-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5-oxo-2,6-diazaspiro[3.4]octane-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-ethyl-piperazine-1-carboxamide

N-[4-(3-cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide

1-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]piperidine-4-carboxylic acid

(3S)-1-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]pyrrolidine-3-carboxylic acid

3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)azetidine-1-carboxamide

(3R)-1-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]pyrrolidine-3-carboxylic acid

4-cyano-N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-3-methyl-azetidine-1-carboxamide

3-cyano-N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-azetidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-2,7-diazaspiro[3.5]nonane-7-carboxamide

3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-azetidine-1-carboxamide

1-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]azetidine-3-carboxylic acid

(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)pyrrolidine-1-carboxamide

(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-azetidine-1-carboxamide

(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)azetidine-1-carboxamide

(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-morpholine-4-carboxamide

(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide

(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)morpholine-4-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-1-oxo-2,8-diazaspiro[4.5]decane-8-carboxamide

(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-azetidine-1-carboxamide

N-[4-(3-cyano-2-methyl-phenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

(3R)-N1-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1,3-dicarboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-7-azaspiro[3.4]octane-7-carboxamide

(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)azetidine-1-carboxamide

(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)azetidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-morpholino-pyrrolidine-1-carboxamide

(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-5-oxo-piperazine-1-carboxamide

(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-morpholine-4-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxa-1-azaspiro[3.3]heptane-1-carboxamide

(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)morpholine-4-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3-dimethyl-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide

(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methylsulfonyl-pyrrolidine-1-carboxamide

(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-5-oxo-piperazine-1-carboxamide

(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)azetidine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-methyl-5-oxo-2,6-diazaspiro[3.4]octane-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-methyl-2-oxo-1,8-diazaspiro[4.5]decane-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methylsulfonyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-hydroxy-4-methyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
(4aR,7aS)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5,8-diazaspiro[3.5]nonane-5-carboxamide
trans-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-dimethyl-piperazine-1-carboxamide
4-amino-4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,6-diazabicyclo[3.1.1]heptane-6-carboxamide
(1R,4R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide
cis-(2S,5S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-dimethyl-piperazine-1-carboxamide
(2R,6R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,6-dimethyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,2-dimethyl-piperazine-1-carboxamide

1-acetylimino-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3-oxo-2,7-diazaspiro[3.5]nonane-7-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-1,3-dimethyl-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]piperidine-1-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-(hydroxymethyl)piperidine-1-carboxamide
4,4-dicyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]piperidine-1-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methoxy-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
1-cyanoimino-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-[2-(1-hydroxy-1-methyl-ethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(1-hydroxy-1-methyl-ethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-6-oxa-2-azaspiro[3.4]octane-2-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(1-hydroxy-1-methyl-ethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(1-hydroxyethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
rac-(3S,5R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,5-dimethyl-piperazine-1-carboxamide

(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(trifluoromethyl)piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(trifluoromethyl)piperazine-1-carboxamide
(3S)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide
(3R)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4,7-diazaspiro[2.5]octane-7-carboxamide
(3S,5S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,5-dimethyl-piperazine-1-carboxamide
(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-piperazine-1-carboxamide
(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)piperazine-1-carboxamide
(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxamide
(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-9-oxa-2,6-diazaspiro[4.5]decane-2-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-3-methyl-piperazine-1-carboxamide
(4aS,7aS)-N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxamide
(4aS,7aR)-N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxamide

rac-(4aS,7aS)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-cyclopropyl-piperazine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(cyclopropylmethyl)piperazine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,3-dimethyl-piperazine-1-carboxamide

N-[4-(3-cyanophenyl)-5-(2-methoxy-6-methyl-4-pyridyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide

N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dichloro-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

N-[4-(3-cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide

N-[4-(3-cyanophenyl)-5-(2-methoxy-6-methyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide

N-[4-(3-cyanophenyl)-5-[2-methyl-6-(oxetan-3-yl)-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

N-[5-(2-cyano-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide

N-[4-(3-cyanophenyl)-5-[2-(fluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

N-[4-(3-cyanophenyl)-5-(2-cyclopropyl-6-methyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

N-[4-(3-cyanophenyl)-5-(2-isopropyl-6-methyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

N-[4-(3-cyanophenyl)-5-(2-ethyl-6-methyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-1-oxido-pyridin-1-ium-4-yl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

4-cyano-N-[4-(3-cyano-2-methyl-phenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide

N-[5-(2-acetamido-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

N-[5-[2-(acetamidomethyl)-6-methyl-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(methoxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(1-methoxyethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[5-[2-chloro-6-(1-hydroxy-1-methyl-ethyl)-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide
N-[5-[2,6-bis(trideuteriomethyl)-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-4-cyano-4-methyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-[2-[(1R)-1-hydroxyethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-[(1S)-1-hydroxyethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
(3R)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide
(3S)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide.

[00161] Particular compounds of the present invention include any of the compounds described in the example section of the present application, or a pharmaceutically acceptable salt or solvate thereof, and, in particular, any of the following:
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]morpholine-4-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide;
(2R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]pyrrolidine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-(2-hydroxy-2-methyl-propyl)pyrrolidine-1-carboxamide;

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)morpholine-4-carboxamide;
(2S)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-methyl-piperazine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-hydroxy-4-methyl-piperidine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-cyano-4-methyl-piperidine-1-carboxamide;
(3S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide formate;
(3R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide formate
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperazine-1-carboxamide;
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxyethyl)piperazine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide;
(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-pyrrolidine-1-carboxamide;
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(methoxymethyl)piperidine-1-carboxamide;
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-fluoro-piperidine-1-carboxamide;
(3S)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1-carboxamide;

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-3-methyl-azetidine-1-carboxamide;
(3R)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-piperazine-1-carboxamide
N4-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]morpholine-2,4-dicarboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-3-oxo-piperazine-1-carboxamide;
(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)morpholine-4-carboxamide;
4-acetyl-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methylsulfonyl-piperazine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-sulfamoyl-piperazine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide;
(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)morpholine-4-carboxamide;
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methoxy-piperidine-1-carboxamide;
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(hydroxymethyl)piperidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)azetidine-1-carboxamide;
3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]azetidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,1-dioxo-1,4-thiazinane-4-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3-dimethyl-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
N1-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1,4-dicarboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxyethyl)-3-oxo-piperazine-1-carboxamide;
4,4-Dicyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)azetidine-1-carboxamide;
(2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid;
methyl (2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylate;
(3S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(hydroxymethyl)piperazine-1-carboxamide;
(3R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(hydroxymethyl)piperazine-1-carboxamide;
(3S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide;
(3R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide;
(1S,4S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide;
(3R)-N1-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1,3-dicarboxamide;
(3S)-N1-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1,3-dicarboxamide;
4-Amino-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide;
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide;
(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide;

4-Amino-4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide; and
1-acetylimino-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide.

[00162] The various functional groups and substituents making up the compounds of the formula (I) are typically chosen such that the molecular weight of the compound of the formula (I) does not exceed 1000. More usually, the molecular weight of the compound will be less than 900, for example less than 800, or less than 750, or less than 700, or less than 650. More preferably, the molecular weight is less than 600 and, for example, is 550 or less.

[00163] A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acidaddition salt of a compound of the invention which is sufficiently basic, for example, an acidaddition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulfuric, phosphoric, trifluoroacetic, formic, citric methane sulfonate or maleic acid. In addition, a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a pharmaceutically acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris(2hydroxyethyl)amine.

[00164] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are nonsuperimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center-, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R and Ssequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or -levorotatory- (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[00165] The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R) or (S)stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the

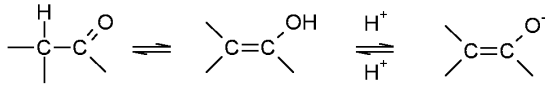
specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are wellknown in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 2001), for example by synthesis from optically active starting materials or by resolution of a racemic form. Some of the compounds of the invention may have geometric isomeric centres (E and Z isomers). It is to be understood that the present invention encompasses all optical, diastereoisomers and geometric isomers and mixtures thereof that possess antiproliferative activity.

[00166] The present invention also encompasses compounds of the invention as defined herein which comprise one or more isotopic substitutions. For Example, H may be in any isotopic form, including 1H, 2H(D), and 3H (T); C may be in any isotopic form, including 12C, 13C, and 14C; and O may be in any isotopic form, including 16O and18O; and the like.

[00167] It is also to be understood that certain compounds of the formula (I) may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms that possess antiproliferative activity.

[00168] It is also to be understood that certain compounds of the formula I may exhibit polymorphism, and that the invention encompasses all such forms that possess antiproliferative activity.

[00169] Compounds of the formula I may exist in a number of different tautomeric forms and references to compounds of the formula I include all such forms. For the avoidance of doubt, where a compound can exist in one of several tautomeric forms, and only one is specifically described or shown, all others are nevertheless embraced by formula I. Examples of tautomeric forms include keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



keto enol enolate

[00170] Compounds of the formula I containing an amine function may also form N-oxides. A reference herein to a compound of the formula I that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular Examples of N-oxides are

the N-oxides of a *tertiary* amine or a nitrogen atom of a nitrogen-containing heterocycle. N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (Syn. Comm. 1977, 7, 509-514) in which the amine compound is reacted with m-chloroperoxybenzoic acid (mCPBA), for example, in an inert solvent such as dichloromethane.

[00171] The compounds of formula (I) may be administered in the form of a prodrug which is broken down in the human or animal body to release a compound of the invention. A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed when the compound of the invention contains a suitable group or substituent to which a property-modifying group can be attached. Examples of pro-drugs include *in vivo* cleavable ester derivatives that may be formed at a carboxy group or a hydroxy group in a compound of the formula (I) and in-vivo cleavable amide derivatives that may be formed at a carboxy group or an amino group in a compound of the formula (I).

[00172] Accordingly, the present invention includes those compounds of the formula (I) as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of the formula I that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the formula (I) may be a synthetically-produced compound or a metabolically-produced compound.

[00173] A suitable pharmaceutically acceptable pro-drug of a compound of the formula (I) is one that is based on reasonable medical judgement as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

[00174] Various forms of pro-drug have been described, for example in the following documents :-

a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);

c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988);

f) N. Kakeya, et al., Chem. Pharm. Bull., 32, 692 (1984);

g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and

h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

[00175] A suitable pharmaceutically acceptable pro-drug of a compound of the formula I that possesses a carboxy group is, for example, an *in vivo* cleavable ester thereof. An *in vivo* cleavable ester of a compound of the formula I containing a carboxy group is, for example, a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically acceptable esters for carboxy include C1-6alkyl esters such as methyl, ethyl and *tert*-butyl, C1-6alkoxymethyl esters such as methoxymethyl esters, C1-6alkanoyloxymethyl esters such as pivaloyloxymethyl esters, 3-phthalidyl esters, C3-8cycloalkylcarbonyloxy- C1-6alkyl esters such as cyclopentylcarbonyloxymethyl and 1-cyclohexylcarbonyloxyethyl esters, 2-oxo-1,3-dioxolenylmethyl esters such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl esters and C1-6alkoxycarbonyloxy- C1-6alkyl esters such as methoxycarbonyloxymethyl and 1-methoxycarbonyloxyethyl esters.

[00176] A suitable pharmaceutically acceptable pro-drug of a compound of the Formula (I) that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof. An *in vivo* cleavable ester or ether of a compound of the formula I containing a hydroxy group is, for example, a pharmaceutically acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically acceptable ester forming groups for a hydroxy group include C1-10alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C1-10alkoxycarbonyl groups such as ethoxycarbonyl, N,N –(C1-6)2carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C1-4alkyl)piperazin-1-

ylmethyl. Suitable pharmaceutically acceptable ether forming groups for a hydroxy group include α-acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

[00177] A suitable pharmaceutically acceptable pro-drug of a compound of the formula (I) that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a C1-4alkylamine such as methylamine, a (C1-4alkyl)2amine such as dimethylamine, N-ethyl-N-methylamine or diethylamine, a C1-4alkoxy- C2-4alkylamine such as 2-methoxyethylamine, a phenyl-C1-4alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

[00178] A suitable pharmaceutically acceptable pro-drug of a compound of the formula I that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically acceptable amides from an amino group include, for example an amide formed with C1-10alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C1-4alkyl)piperazin-1-ylmethyl.

[00179] The *in vivo* effects of a compound of the formula (I) may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the formula (I). As stated hereinbefore, the *in vivo* effects of a compound of the formula (I) may also be exerted by way of metabolism of a precursor compound (a pro-drug).

[00180] Though the present invention may relate to any compound or particular group of compounds defined herein by way of optional, preferred or suitable features or otherwise in terms of particular embodiments, the present invention may also relate to any compound or particular group of compounds that specifically excludes said optional, preferred or suitable features or particular embodiments.

[00181] Suitably, the present invention excludes any individual compounds not possessing the biological activity defined herein.

Synthesis

[00182] The compounds of the present invention can be prepared by any suitable technique known in the art. Particular methods for forming compounds of formula I defined herein are shown in the accompanying examples.

[00183] In the description of the synthetic methods described herein and in any referenced synthetic methods that are used to prepare the starting materials, it is to be

understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be selected by a person skilled in the art.

[00184] It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reaction conditions utilised.

[00185] It will be appreciated that during the synthesis of the compounds of the invention in the processes defined herein, or during the synthesis of certain starting materials, it may be desirable to protect certain substituent groups to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed.

[00186] For Examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with the minimum disturbance of groups elsewhere in the molecule.

[00187] Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

[00188] By way of Example, a suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or tbutoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed by, for example, hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladiumoncarbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

[00189] A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium, sodium hydroxide or ammonia. Alternatively, an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladiumoncarbon.

[00190] A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tbutyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladiumoncarbon.

[00191] Resins may also be used as a protecting group.

[00192] The methodology employed to synthesise a compound of formula (I) will vary depending on the nature of R_1, R_2, R_3, R_4, R_5 and R_6 and any substituent groups associated therewith. Suitable processes for their preparation are described further in the accompanying Examples.

[00193] Once a compound of formula (I) has been synthesised by any one of the processes defined herein, the processes may then further comprise one or more of the additional steps of:

(i) removing any protecting groups present;

(ii) converting the compound formula (I) into another compound of formula (I);

(iii) forming a pharmaceutically acceptable salt, hydrate or solvate of the compound of formula I; and/or

(iv) forming a prodrug of the compound of formula I.

[00194] An Example of (ii) above is when a compound of formula (I) is synthesised and then one or more of the groups of R_1, R_2, R_3, R_4, R_5 and R_6 may be further reacted to change the nature of the group and provide an alternative compound of formula (I).

[00195] The resultant compounds of formula (I) can be isolated and purified using techniques well known in the art.

Biological Activity

[00196] The biological assays described in the example section (Biological Examples 1 to 3) may be used to measure the pharmacological effects of the compounds of the present invention.

[00197] Although the pharmacological properties of the compounds of formula I vary with structural change, as expected, the compounds of the invention were found to be active in the assays described in Biological Examples 1, 2 andd 3.

[00198] In general, in terms of adenosine A2a antagonism, the compounds of the invention demonstrate an IC_{50} of 1 μM or less in the assay described in Biological Example 1, with preferred compounds of the invention demonstrating an IC_{50} of 200 nM or less and the most preferred compounds of the invention demonstrating an IC_{50} of 50 nM or less.

[00199] In general, in terms of adenosine A2b antagonism, the compounds of the invention demonstrate an IC_{50} of 1 μM or less in the assay described in Biological Example 1, with preferred compounds of the invention demonstrating an IC_{50} of 200 nM or less and the most preferred compounds of the invention demonstrating an IC_{50} of 50 nM or less.

[00200] Suitably the IC_{50} at the adenosine A1 or A3 receptors of the compounds of the invention in the assay described in Biological Example 1 is at least two-fold higher than the IC_{50} at the adenosine A2a receptor, and more suitably it is at least 5-fold higher, and even more suitably it is at least 10-fold higher.

Pharmaceutical Compositions

[00201] According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in association with a pharmaceutically acceptable diluent or carrier.

[00202] The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

[00203] The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

[00204] An effective amount of a compound of the present invention for use in therapy is an amount sufficient to treat or prevent a proliferative condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

[00205] The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the individual treated and the particular route of administration. For Example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

[00206] The size of the dose for therapeutic or prophylactic purposes of a compound of the formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

[00207] In using a compound of the invention for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous or intraperitoneal administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration may also be suitable, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

Therapeutic Uses and Applications

[00208] The present invention provides compounds that function as antagonists of adenosine A2 receptors, especially adenosine A2a receptors.

[00209] According to a further aspect of the present invention, there is provided a method of antagonising adenosine A2a receptors *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein.

[00210] According to a further aspect of the present invention, there is provided a method of selectively antagonising adenosine A2a receptros *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein.

[00211] According to a further aspect of the present invention, there is provided a

method of inhibiting cell proliferation, *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional antiproliferative agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[00212] According to a further aspect of the present invention, there is provided a method of treating a disease or disorder in which adenosine A2a receptor activity is implicated in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein.

[00213] According to a further aspect of the present invention, there is provided a method of treating a proliferative disorder in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional antiproliferative agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[00214] According to a further aspect of the present invention, there is provided a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional anticancer agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[00215] According to a further aspect of the present invention, there is provided a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein for use in therapy.

[00216] According to a further aspect of the present invention, there is provided a compound or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein, for use in the treatment of a proliferative condition. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional antiproliferative agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[00217] According to a further aspect of the present invention, there is provided a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein for use in the treatment of cancer. In a particular embodiment, the cancer is human cancer. Suitably, the compound or

pharmaceutical composition is administered in combination with one or more additional anticancer agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[00218] According to a further aspect of the present invention, there is provided a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein for use as an adenosine A2a antagonist. In an embodiment, the compounds of the invention are selective adenosine A2a antagonists. In an alternative embodiment, certain compounds of the invention are selective adenosine A2a and adenosine A2b antagonists.

[00219] According to a further aspect of the present invention, there is provided a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein for use in the treatment of a disease or disorder in which adenosine A2a is implicated.

[00220] According to a further aspect of the present invention, there is provided the use of a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in the manufacture of a medicament for the treatment of a proliferative condition. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional antiproliferative agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[00221] According to a further aspect of the present invention, there is provide the use of a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in the manufacture of a medicament for the treatment of cancer. Suitably, the cancer is a human cancer. Suitably, the compound or pharmaceutical composition is administered in combination with one or more additional anticancer agents (e.g. checkpoint inhibitors and/or cytotoxic agents).

[00222] According to a further aspect of the present invention, there is provided a use of a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in the manufacture of a medicament for use as an adenosine A2a antagonist.

[00223] According to a further aspect of the present invention, there is provided a use of a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in the manufacture of a medicament for use as an adenosine A2a antagonist.

[00224] According to a further aspect of the present invention, there is provided a use of a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in the manufacture of a medicament for the treatment of a disease or disorder in which adenosine A2a receptor activity is implicated.

[00225] The term "proliferative disorder" are used interchangeably herein and pertain to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as, neoplastic or hyperplastic growth, whether *in vitro* or *in vivo*. Examples of proliferative conditions include, but are not limited to, pre-malignant and malignant cellular

proliferation, including but not limited to, malignant neoplasms and tumours, cancers, leukemias, psoriasis, bone diseases, fibroproliferative disorders (e.g., of connective tissues), and atherosclerosis. Any type of cell may be treated, including but not limited to, lung, colon, breast, ovarian, prostate, liver, pancreas, brain, and skin.

[00226] The anti-proliferative effects of the compounds of the present invention have particular application in the treatment of human cancers (by virtue of their adenosine A2a antagonist activity).

[00227] More specifically, there is provided a compound of general formula (I) for use in the treatment of cancer, particularly solid tumours, for example non-small cell or small cell lung cancer, head and neck squamous cancer and urothelial cancer.

[00228] More specifically, there is provided a compound of general formula (I) for use in the treatment of cancer, for example, lung cancer, such as as small cell lung cancer or non-small cell lung cancer.

[00229] There is also provided the use of a compound of general formula (I) in the manufacture of a medicament for the treatment of cancer, particularly solid tumours, for example non-small cell or small cell lung cancer, head and neck squamous cancer and urothelial cancer.

[00230] The invention further provides a method for the treatment of cancer, particularly solid tumours, for example non-small cell or small cell lung cancer, head and neck squamous cancer and urothelial cancer, the method comprising administering to a patient in need of such treatment an effective amount of a compound of general formula (I).

[00231] The patient to be treated is suitably a mammal and more suitably a human.

Routes of Administration

[00232] The compounds of the invention or pharmaceutical compositions comprising these compounds may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or topically (i.e., at the site of desired action).

[00233] Routes of administration include, but are not limited to, oral (e.g, by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, intrasternal, and intratumoural; by implant of a depot or reservoir, for example, subcutaneously

or intramuscularly.

[00234] The compounds of the invention or pharmaceutical compositions comprising these compounds may be administered by intratumoural delivery.

Combination Therapies

[00235] The compounds of formula I are useful for the treatment and/or prophylaxis of proliferative disorders, such as, for example, cancer. A compound of formula I defined herein may be used in combination with one or more additional antiproliferative/anticancer therapies, such as, for example, chemotherapy with one or more additional antiproliferative/anticancer agents, radiotherapy and/or conventional surgery.

[00236] An additional antiproliferative/anticancer agent may be included in the pharmaceutical composition with a compound of formula (I) as defined herein or, alternatively, it may be administered separately, either at the same time as the compound of formula (I) or at an earlier or later time.

[00237] Therefore, in a further aspect of the present invention there is provided a product comprising a compound of general formula (I) and an additional agent useful in the treatment or prevention of cancer as a combined preparation for simultaneous, sequential or separate use in the treatment of cancer.

[00238] The present invention also provides a compound of general formula (I) in combination with one or more additional antiproliferative/anticancer agents for use in the treatment of cancer as a combined preparation for simultaneous, sequential or separate use in the treatment of treatment of cancer.

[00239] In particular, the combination therapy defined herein is suitable for the treatment of solid tumours for example non-small cell or small cell lung cancer, head and neck squamous cancer and urothelial cancer.

[00240] Suitable additional antiproliferative/anti-cancer agents that may be used in combination with a compound of formula I defined herein [either separately or as part of a combined pharmaceutical composition or a combined preparation with the compounds of general formula (I)] include:

1) other forms of cancer immunotherapy and anti-cancer chemotherapeutic agents;
2) adenosine pathway modulators, including, but not limited to A2b antagonists, CD73 inhibitors and CD39 inhibitors;
3) anti-PD-1 and PDL-1 antibodies including, but not limited to, cetrelimab pembrolizumab, nivolumab, durvalumab, avelumab and atezolizumab; and
4) anti-CTLA4 antibodies including, but not limited to, ipilimumab.

[00241] The compounds of of formula I defined herein are particulalrly suited to use in

combination with anti-PD-1 and PDL-1 antibodies including, but not limited to, Cetrelimab, pembrolizumab, nivolumab, durvalumab, avelumab and atezolizumab.

Suitably, the anti-PD1 antibody is one of the antibodies disclosed in U.S. Publication No. 2019/0225689 or U.S. Publication No. 2017/0121409 (incorporated herein by reference in their entireties), such as cetrelimab. Cetrelimab (JNJ-63723283, CET) is a fully human immunoglobulin (Ig) G4 kappa monoclonal antibody that binds to programmed death receptor-1 (PD-1) with high affinity and specificity. Cetrelimab has shown activity in solid tumors. Rutkowski P, et al. Journal of Clinical Oncology. 2019;37(8):31.

[00242] The compounds of of formula I defined herein are particulalrly suited to use in combination with adenosine pathway modulators, including, but not limited to A2b antagonists, CD73 inhibitors and CD39 inhibitors.

[00243] The A2a antagonists of general formula (I) can also be used in combination with cell-based immunotherapy and cancer vaccines that include, but are not limited to CAR-T cell therapy.

[00244] Examples of the additional antiproliferative/anticancer chemotherapeutic agents include, but are not limited to, any one or more of the following:

MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901,selumetinib/ AZD6244, GSK1 120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD3 18088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (e.g., 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), etc.), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, etc.), topoisomerase inhibitors (e.g., irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, etc.), antitumor antibiotics (e.g., doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, etc.), platinum-based compounds or platinum containing agents (e.g. cisplatin, oxaloplatin, arboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-

asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-l, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein- 1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cisporphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fiudarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin;

ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatinA; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone;miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; 06-benzyl guanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-basedimmune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; proteintyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAPinhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction

modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stemcell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin 2 (including recombinant interleukin 2, or rlL.sub.2), interferon alfa-2a; interferon alfa-2b;
interferon alfa-nl; interferon alfa-n3; interferon beta- la; interferon gamma-lb; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate;

melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS- 10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-3 10705), 21- hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), , Vincristine sulfate, Cryptophycin 52 (i.e. LY-355703), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), Oncocidin Al (i.e. BTO-956 and DF E), Fijianolide B, Laulimalide, Narcosine (also known as NSC-5366), Nascapine, Hemiasterlin, Vanadocene acetylacetonate, Monsatrol, Inanocine (i.e. NSC-698666), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and ZEleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, Diazonamide A, Taccalonolide A, Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), Myoseverin B, Resverastatin phosphate sodium, steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone),

progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guerin (BCG), levamisole, interleukin-2, alpha-interferon, etc.), monoclonal antibodies (e.g., anti-CD20, anti-F£ER2, anti-CD52, anti- ULA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, etc.), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to In, 0Y, or I, etc.), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa ™), erlotinib (Tarceva ™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035,BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, hormonal therapies, or the like.

[00245] As indicated above, the combination therapy of the present invention may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

[00246] According to this aspect of the invention there is provided a combination for use in the treatment of a cancer (for example a cancer involving a solid tumour) comprising a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and one or more additional antiproliferative/anticancer agents.

[00247] According to this aspect of the invention there is also provided a combination for use in the treatment of a proliferative condition, such as cancer (for example a cancer involving a solid tumour), comprising a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and one or more additional antiproliferative/anticancer agents selected from those listed above.

[00248] In a further aspect of the invention there is provided a compound of the invention or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use in the treatment of cancer in combination with another anti-tumour agent, optionally selected from one listed herein above.

[00249] Herein, where the term “combination” is used it is to be understood that this refers to

simultaneous, separate or sequential administration. In one aspect of the invention "combination" refers to simultaneous administration. In another aspect of the invention "combination" refers to separate administration. In a further aspect of the invention "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

[00250] According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the invention, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in combination with an anti-tumour agent (optionally selected from one listed herein above), in association with a pharmaceutically acceptable diluent or carrier.

EXAMPLES

General Conditions:

[00251] Mass spectra were run on LC-MS systems using electrospray ionization. These were run using either a Waters Acquity H-Class UPLC with PDA and QDa mass detection, a Waters Acquity Classic UPLC with PDA and SQ mass detection, an Acquity LC (binary pump/PDA detector) + ZQ Mass Spectrometer or Acquity i-Class (quaternary pump/PDA detector) + Quattro Micro Mass Spectrometer, a Waters Acquity LC system with Waters PDA and ELS detectors or a Shimadzu LCMS-2010EV system. [M+H]+ refers to mono-isotopic molecular weights.

[00252] NMR spectra were run on either a Bruker Ultrashield 500 MHz NMR spectrometer, a Bruker Avance III HD 400 MHz NMR spectrometer or a Bruker Avance III HD 500 MHz. Spectra were recorded at 298K and were referenced using the solvent peak.

[00253] The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade. If not mentioned otherwise, all evaporations are performed *in vacuo*, preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, and NMR. Abbreviations used are those conventional in the art. If not defined, the terms have their generally accepted meanings.

Abbreviations

app	apparent

br	broad
CDI	1,1′-carbonyldiimidazole
d	doublet
dd	doublet of doublets
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMA	Dimethylacetamide
EtOAc	ethyl acetate
HPLC	high pressure liquid chromatography
LC-MS	liquid chromatography and mass spectrometry
MeOH	MeOH
MeCN	acetonitrile
MS	mass spectrometry
m	multiplet
mins	minute(s)
mL	milliliter(s)
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
ppm	parts per million
Rt	retention time
s	singlet
t	triplet
TBAF	tetra-n-butylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran

[00254] Referring to the examples that follow, compounds of the preferred embodiments were synthesized using the methods described herein, or other methods, which are known in the art.

[00255] The various starting materials, intermediates, and compounds of the preferred embodiments may be isolated and purified, where appropriate, using conventional techniques such as precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Unless otherwise stated, all starting materials are obtained from commercial suppliers and used without further purification. Salts may be prepared from compounds by known salt-forming procedures.

[00256] If not indicated otherwise, the analytical HPLC conditions are as follows:

Method 2A

Column:	Kinetex Core-Shell C18 2.1 x 50 mm 5 µm
Column Temp	40 °C
Eluents:	A: H_2O+0.1% formic acid, B: MeCN+ 0.1% formic acid
Flow Rate:	1.2 mL/min
Gradient:	0-1.83 min 5-100 B, 1.83- 2.25 min 100% B, 2.25-2.26 min 100-5% B

Method 2.5B

Column:	Phenomenex Gemini-NX C18 2 x 50 mm 3 µm
Column Temp:	40 °C
Eluents:	A: 2 mM ammonium bicarbonate, buffered to pH10, B: MeCN
Flow Rate:	1 mL/min
Gradient:	0-1.80 min 1-100% B, 1.80-2.10 min 100% B, 2.10-2.30 min 100-1%B

Method 2B

Column:	Acquity UPLC BEH C18 2.1 x 50 mm, 1.7 µm
Column Temp:	50 °C
Eluents:	A: H_2O, 0.1% formic acid B: MeCN
Flow Rate:	0.8 mL/min
Gradient:	0.0-1.8 min 2-98% B, 1.8-2.1 min 98% B, 2.1-2.5 min 98%A

Method 3A

Column:	Acquity LC BEH C18 2.1 x 50 mm 1.7 µm
Column Temp:	50 °C
Eluents:	A: H_2O, 0.1% formic acid, B: MeCN
Flow Rate:	0.6 mL/min
Gradient:	0.2-2.5 mins 2-98% B, 2.5-3.3 mins 98% B, 3.3-3.5 mins 98% A

Method 3B

Column:	Acquity LC BEH C18 2.1 x 50 mm 1.7 µm
Column Temp:	50 °C
Eluents:	A: H_2O, 0.1% ammonia, B: MeCN
Flow Rate:	0.6 mL/min
Gradient:	0.2-2.5 mins 2-98% B, 2.5-3.3 mins 98% B, 3.3-3.5 mins 98% A

Method 5A

Column:	YMC-Triart C18 2 x 50 mm, 5 µm.
Flow rate:	0.8 mL/min.
Eluents:	A: H_2O, B: MeCN, C: 50% H_2O / 50% MeCN + 1.0% formic acid
Gradient:	0.0-4.0 min 0-95% B, 5% C; 4.0-4.4 min 95% B, 5%C; 4.4-4.5 min 95% A, 5% B

Method 5B

Column:	Waters Alliance ZQ MS, YMC-Triart C18 50 x 2 mm, 5 µm
Column Temp:	room temperature
Eluents:	A: H_2O, B: CH_3CN, C: 50% H_2O / 50% CH_3CN + 1.0% ammonia (aq.)
Flow rate:	0.8 mL/min.
Gradient:	0.0 - 4.0 mins 0-95% B, 5% C; 4.0-4.4 mins 95% B, 5%C; 4.4-4.5 mins 95% A, 5%B

Method 7A

Column:	Phenomenex Kinetix-XB C18 2.1 x 100 mm, 1.7 µm
Column Temp:	40 °C
Eluents:	A: H_2O 0.1% formic acid, B: MeCN, 0.1% formic acid
Flow Rate:	0.6 mL/min
Gradient:	0-5.3.0 min 5-100% B, 5.3-5.8 min 100% B, 5.8-5.82 min 100-5% B, 5.82-7.00 min 5% B

Method 7B

Column:	Waters LC® BEH™ C18, 2.1 mm x 100 mm, 1.7 µm
Column Temp:	40 °C
Eluents:	A: 2 mM ammonium bicarbonate buffered to pH10, B: MeCN
Flow Rate:	0.6 mL/min
Gradient:	0-5.3.0 min 5-100% B, 5.3-5.8 min 100% B, 5.8-5.82 min 100-5% B, 5.82-7.00 min 5% B

Method 8A

Column:	Acquity UPLC BEH C18 2.1 x 100 mm, 1.7 µm
Column Temp:	50 °C
Eluents:	A: H_2O, 0.1% formic acid B: MeCN
Flow Rate:	0.6 mL/min
Gradient:	0.5-6.5 min 2-98% B 6.5-7.5 min 98% B

Method 8B

Column:	Acquity UPLC BEH C18 2.1 x 100 mm, 1.7 µm

Column Temp:	50 °C
Eluents:	A: H_2O, 0.1% ammonia B: MeCN
Flow Rate:	0.6 mL/min
Gradient:	0.5-6.5 min 2-98% B 6.5-7.5 min 98% B

Method 15A

Column:	YMC-Triart C18 2 x 50 mm, 5 µm.
Flow rate:	0.8 mL/min.
Eluents:	A: H_2O, B: MeCN, C: 50% H_2O / 50% MeCN + 1.0% formic acid
Gradient:	0.0-12.0 min 0-95% B, 5% C; 12.0-14.0 min 95% B, 5% C; 14.0-14.2 min 95% A, 5% B

Method 15B

Column:	YMC-Triart C18 50 x 2 mm, 5 µm.
Flow rate:	0.8 mL/min.
Eluents:	A: H_2O, B: MeCN, C: 50% H_2O / 50% MeCN + 1.0% ammonia (aq.)
Gradient:	0.0-12.0 min 0-95% B, 5% C; 12.0-14.0 min 95% B, 5% C; 14.0-14.2 min 95% A, 5% B

Preparative HPLC using acidic pH, early elution method

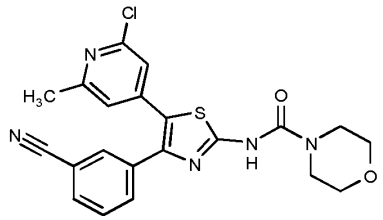
[00257] Purifications by were performed on a Gilson LC system using Waters Sunfire C18 columns (30 mm x 100 mm, 10 µM; temperature: room temperature) and a gradient of 10-95% B (A= 0.1% formic acid in water; B= 0.1% formic acid in MeCN) over 14.44 min then 95% B for 2.11 min, with an injection volume of 1500 µL and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Preparative HPLC using basic pH, early elution method

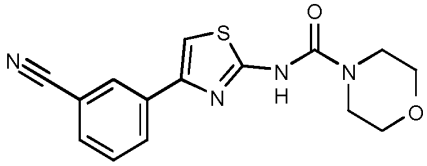
[00258] Purifications by preparative HPLC (basic pH, early elution method) were performed on a Gilson LC system using Waters Xbridge C18 columns (30 mm x 100 mm, 10 µM; temperature: room temperature) and a gradient of 10-95% (A= 0.2% ammonium hydroxide in water; B= 0.2% ammonium hydroxide in MeCN) over 14.44 min then 95% B for 2.11 min, with an injection volume of 1500 µL and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Example 1

N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]morpholine-4-carboxamide



Step 1: N-[4-(3-Cyanophenyl)thiazol-2-yl]morpholine-4-carboxamide

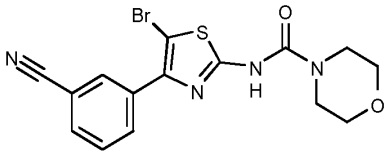


[00259] To a stirred solution of 3-(2-aminothiazol-4-yl)benzonitrile (Intermediate A)(653 mg, 3.08 mmol) in THF (10 mL) at 0 °C was added sodium hydride (60% in mineral oil) (150 mg, 3.75 mmol). After stirring at room temperature for 20 mins, morpholine-4-carbonyl chloride (520 µL, 4.55 mmol) was added and stirring continued for 18 h. The resulting mixture was diluted with THF (10 mL) then retreated with sodium hydride (60% in mineral oil) (150 mg, 3.75 mmol). After stirring for 10 mins, morpholine-4-carbonyl chloride (520 µL, 4.55 mmol) was added and stirring continued for 4 h. The reaction was quenched with water (20 mL) and extracted with EtOAc (2 x 40 mL). The aqueous layer was acidified to pH 5 using 1M HCl and extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting brown oil was purified by chromatography on silica eluting with 0-100% EtOAc in heptane to afford the title compound as a beige solid.

LC-MS (Method 2A): Rt 1.06 mins; MS m/z 315.1 = [M+H]+

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.31 (t, *J* = 1.5 Hz, 1H), 8.21 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.76 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.73 (s, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 3.67 – 3.58 (m, 4H), 3.56 – 3.48 (m, 4H).

Step 2: N-[5-Bromo-4-(3-cyanophenyl)thiazol-2-yl]morpholine-4-carboxamide



[00260] To a solution of N-[4-(3-cyanophenyl)thiazol-2-yl]morpholine-4-carboxamide (step 1) (790 mg, 2.34 mmol) in THF (20 mL) was added NBS (499 mg, 2.8mmol) and the reaction mixture was stirred at room temperature for 30 mins. The resulting mixture was diluted with EtOAc (50 mL) and washed with water (30 mL), sat. $NaHCO_3$ solution (2 x 30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a yellow solid.

LC-MS (Method 2A): Rt 1.18 mins; MS m/z 393.0/395.0 = [M+H]+

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.35 (s, 1H), 8.25 (t, *J* = 1.5 Hz, 1H), 8.21 (dt, *J* = 8.0, 1.4 Hz, 1H), 7.88 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.71 (t, *J* = 7.9 Hz, 1H), 3.63 – 3.56 (m, 4H), 3.55 – 3.48 (m, 4H).

Step 3: N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]morpholine-4-carboxamide

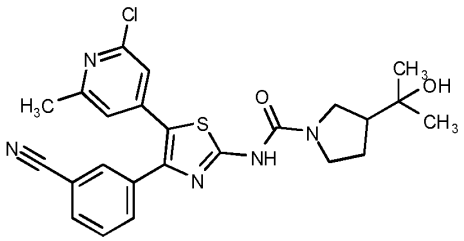
[00261] A stirred solution of N-[5-bromo-4-(3-cyanophenyl)thiazol-2-yl]morpholine-4-carboxamide (step 2) (50 mg, 0.13 mmol), (2-chloro-6-methyl-4-pyridyl)boronic acid (87 mg, 0.51 mmol) and cesium carbonate (124 mg, 0.38 mmol) in monoglyme (3 mL) and water (0.5 mL) was degassed with nitrogen for 5 mins. Bis(triphenylphosphine)palladium(II) dichloride (18 mg, 0.03 mmol) was added and the reaction mixture was heated at 85 °C for 7.5 h. After cooling to room temperature, the mixture was diluted with DCM (5 mL) and water (5 mL). The organic layer was separated, passed through a hydrophobic frit and concentrated *in vacuo*. The crude product was purified by C18 reverse phase chromatography eluting with acetonitrile/water/0.1% formic acid followed by further purification by C18 reverse phase chromatography eluting with acetonitrile/water/0.1% ammonia to afford the title compound as a bright yellow powder.

LC-MS (Method 2.5B): Rt 3.58 mins; MS m/z 440.1/442.1 = [M+H]+

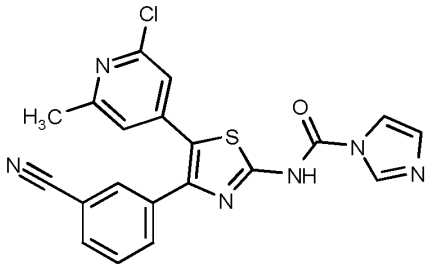
^{1}H NMR (400MHz, DMSO-d6) δ 11.40 (br s, 1H), 7.90 (t, *J* = 1.4Hz, 1H), 7.84 (dt, *J* = 7.7, 1.3Hz, 1H), 7.72 (dt, *J* = 7.9, 1.3Hz, 1H), 7.58 (t, *J* = 7.9Hz, 1H), 7.14 (s, 1H), 7.01 (s, 1H), 3.62 – 3.57 (m, 4H), 3.54 – 3.49 (m, 4H), 2.39 (s, 3H)

Example 2

N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide



Step 1: N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]imidazole-1-carboxamide



[00262] A solution of 3-[2-amino-5-(2-chloro-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate D) (73 mg, 0.17 mmol) and CDI (55 mg, 0.34 mmol) in DMA (0.5 mL) was stirred at room temperature for 24 h. A further portion of CDI (55 mg, 0.34 mmol) was added and stirring continued at room temperature for 2 h and then at 50 °C for 1 h. After cooling to room temperature, the resulting precipitate was collected by vacuum filtration to afford the title compound as a pale yellow solid.

LC-MS (Method 7B): Rt 3.76 mins; MS m/z 385.1 = [M-($C_3N_2H_5$)+(OCH_3)]+; methyl carbamate observed from reaction of title compound with MeOH.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.43 (s, 1H), 8.11 (d, *J* = 3.6 Hz, 1H), 7.90 (d, *J* = 1.5 Hz, 1H), 7.84 (d, *J* = 1.4 Hz, 1H), 7.83 – 7.79 (m, 1H), 7.76 – 7.72 (m, 1H), 7.69 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.01 (s, 1H), 6.91 (s, 1H), 2.35 (s, 3H).

Step 2: N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide

[00263] To a stirred solution of N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]imidazole-1-carboxamide (step 1) (59 mg, 0.09 mmol) in DMA (0.5 mL) was added 2-pyrrolidin-3-ylpropan-2-ol (22 mg, 0.17 mmol) and the reaction mixture was stirred at room temperature for 30 mins. A further portion of 2-pyrrolidin-3-ylpropan-2-ol (22 mg, 0.17 mmol) was added and stirring continued for 3 days. DIPEA (30 µL, 0.17 mmol) was added followed by further 2-pyrrolidin-3-ylpropan-2-ol (22 mg, 0.17 mmol) and the mixture was heated to 50 °C for 18 h. The resulting mixture was diluted with water (3 mL) and extracted with EtOAc (3 x 3 mL). The combined organic extracts were filtered through a phase

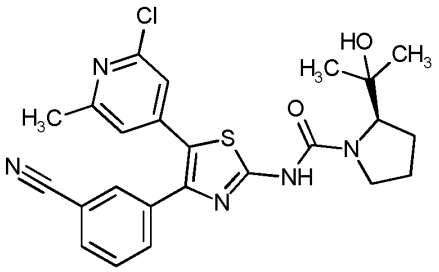
separating cartridge and concentrated *in vacuo*. Purification of the crude product by chromatography on silica eluting with 0-100% EtOAc in DCM followed by 0-10% MeOH in EtOAc afforded the title compound as an off-white solid.

LC-MS (Method 7B): Rt 3.23 mins; MS m/z 482.3/484.2 = [M+H]+

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 7.92 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.73 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 4.37 (s, 1H), 3.71 – 3.41 (m, 4H), 2.40 (s, 3H), 2.21 (s, 1H), 1.83 (s, 2H), 1.12 (s, 6H).

Example 3

(2R)-N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide



[00264] A solution of 3-[2-amino-5-(2-chloro-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate D (52 mg, 0.16 mmol) and CDI (31 mg, 0.19 mmol) in DMA (0.5 mL) was stirred at 50 °C for 22 h. Further CDI (31 mg, 0.19 mmol) was added and stirring was continued at 50 °C for a total of 46 h. The resulting mixture was allowed to cool to room temperature before being treated with 2-[(2R)-pyrrolidin-2-yl]propan-2-ol hydrochloride (40 mg, 0.24 mmol) and DIPEA (55 µL, 0.32 mmol). Stirring was continued at room temperature for 1 h and then at 50 °C for 1 h. After cooling to room temperature, the mixture was diluted with water (3 mL) and extracted with EtOAc (3 x 3 mL). The combined organic extracts were filtered through a phase separating cartridge and concentrated *in vacuo*. The resulting orange solid was purified by chromatography on silica eluting with 0-100% EtOAc in DCM followed by a second purification by chromatography on silica eluting with 0-100% EtOAc in heptane to afford the title compound as an off-white solid.

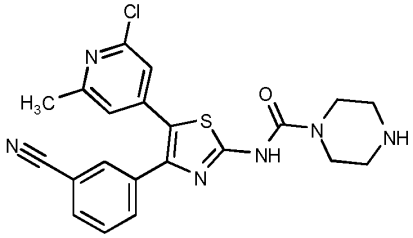
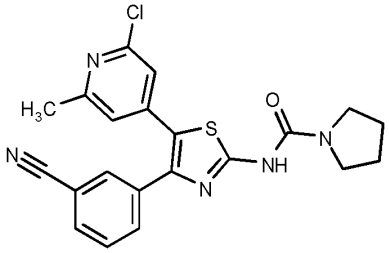
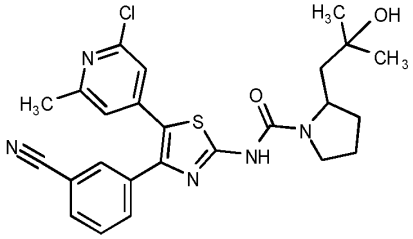
LC-MS (Method 7B): Rt 3.62 mins; MS m/z 482.3/484.3 = [M+H]+

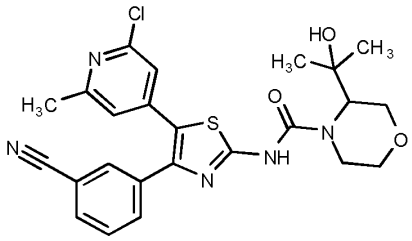
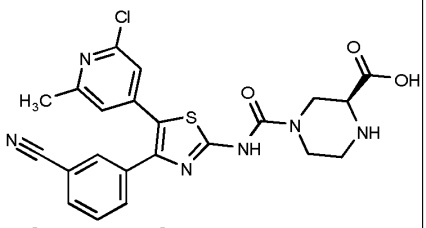
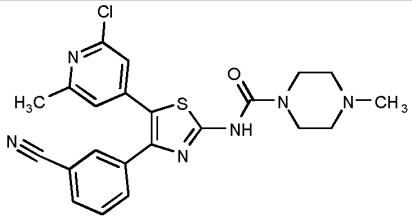
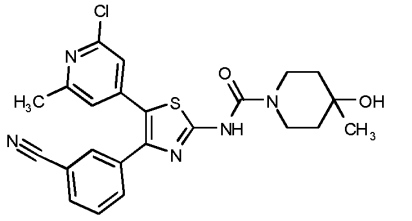
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 7.88 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.69 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.08 –

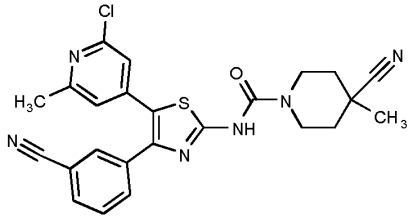
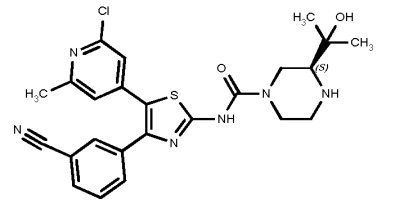
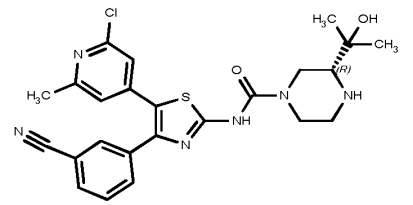
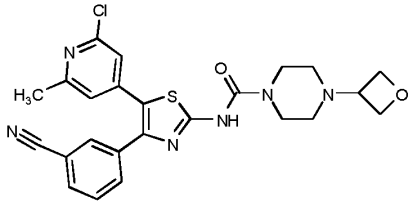
7.03 (m, 1H), 4.01 – 3.82 (m, 3H), 2.40 (s, 3H), 2.11 – 2.00 (m, 1H), 1.90 – 1.60 (m, 4H), 1.19 (s, 3H), 1.10 (s, 3H).

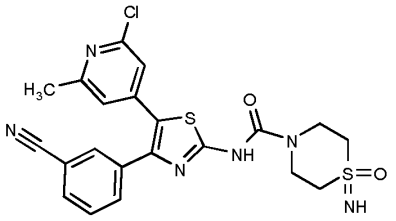
[00265] The compounds of the following tabulated Examples (Table Ex3) were prepared analogously to Example 3 from 3-[2-amino-5-(2-chloro-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate D) and the appropriate amine.

Table Ex3

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
3.1	 N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1-carboxamide	LC-MS (Method 7A): Rt 1.98 mins; MS m/z 439.1/441.2 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 (t,J= 1.5 Hz, 1H), 7.85 (dt,J= 7.7, 1.3 Hz, 1H), 7.72 (dt,J= 7.9, 1.3 Hz, 1H), 7.59 (t,J= 7.8 Hz, 1H), 7.16 (s, 1H), 7.03 (s, 1H), 3.50 – 3.43 (m, 4H), 2.75 – 2.69 (m, 4H), 2.39 (s, 3H). 2 x NH protons not observed
3.2	 N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]pyrrolidine-1-carboxamide	LC-MS (Method 7B): Rt 3.51 mins; MS m/z 424.2/426.2 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.08 (s, 1H), 7.92 (t, *J* = 1.4 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.73 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 3.47 – 3.37 (m, 4H), 2.40 (s, 3H), 1.91 – 1.81 (m, 4H).
3.3	 N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-(2-hydroxy-2-methyl-propyl)pyrrolidine-1-carboxamide	(Method 7B): Rt 3.87 mins; MS m/z 496.3/498.3 = [M+H]+ 1H NMR (400 MHz, DMSO-d6) δ 7.90 (t, *J* = 1.2 Hz, 1H), 7.84 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.15 (s, 1H), 7.02 (s, 1H), 4.13 – 4.03 (m, 1H), 3.46 – 3.34 (m, 3H), 2.39 (s, 3H), 1.92 – 1.64 (m, 6H), 1.17 (s, 3H), 1.16 (s, 3H). NH proton not observed.

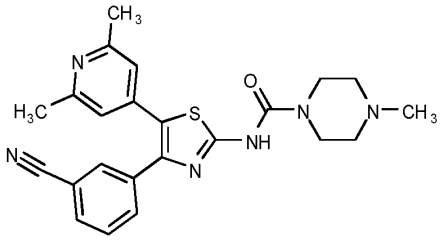
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
3.4	 N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)morpholine-4-carboxamide	LC-MS (Method 7A): Rt 3.34 mins; MS m/z 498.1/500.1 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 7.90 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 4.19 – 4.06 (m, 1H), 4.03 – 3.93 (m, 2H), 3.86 – 3.78 (m, 1H), 3.51 (dd, *J* = 12.3, 4.6 Hz, 1H), 3.48 – 3.38 (m, 2H), 2.40 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H). NH and OH protons not observed.
3.5	 (2S)-4-[[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid	LC-MS (Method 7A): Rt 2.20 mins; MS m/z 483.1/485.1 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 7.91 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.72 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.16 (s, 1H), 7.03 (s, 1H), 4.38 (d, *J* = 11.4 Hz, 2H), 4.08 – 4.00 (m, 1H), 3.08 (d, *J* = 13.0 Hz, 1H), 2.89 – 2.83 (m, 1H), 2.39 (s, 3H). NH and COOH protons not observed. 1 x CH_2 signal under H_2O signal.
3.6	 N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-methyl-piperazine-1-carboxamide	LC-MS (Method 7A): Rt 2.00 mins; MS m/z 453.2/455.1 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 3.57 – 3.50 (m, 4H), 2.40 (s, 3H), 2.35 – 2.30 (m, 4H), 2.20 (s, 3H). NH proton not observed
3.7	 N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-hydroxy-4-methyl-piperidine-1-carboxamide	LC-MS (Method 7A): Rt 3.16 mins; MS m/z 468.1/470.1 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 11.28 (br s, 1H), 7.91 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 4.39 (s, 1H), 3.82 (dt, *J* = 13.4, 3.7 Hz, 2H), 3.28 – 3.22 (m, 2H), 2.40 (s, 3H), 1.51 – 1.39 (m, 4H), 1.14 (s, 3H).

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
3.8	 N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-cyano-4-methyl-piperidine-1-carboxamide	LC-MS (Method 7A): Rt 3.63 mins; MS m/z 477.1/479.1 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 11.46 (br s, 1H), 7.91 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.20 – 7.16 (m, 1H), 7.06 (s, 1H), 4.23 (d, *J* = 14.2 Hz, 2H), 3.04 (t, *J* = 12.3 Hz, 2H), 2.40 (s, 3H), 1.92 (d, *J* = 12.7 Hz, 2H), 1.53 (td, *J* = 13.6, 3.9 Hz, 2H), 1.37 (s, 3H).
3.9	 (3S)-N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide	LC-MS (Method 7A): Rt 2.08 mins; MS m/z 497.2/499.1 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 7.92 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.59 (t, = 7.8 Hz, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 4.48 (s, 1H), 4.20 (d, *J* = 12.4 Hz, 1H), 4.10 (d, *J* = 12.9 Hz, 1H), 2.99 (dt, *J* = 11.7, 2.1 Hz, 1H), 2.78 (t, *J* = 11.7 Hz, 1H), 2.62 – 2.53 (m, 2H), 2.40 (s, 3H), 2.38 – 2.35 (m, 1H), 1.15 (s, 3H), 1.11 (s, 3H). 2 x NH protons not observed.
3.10	 3R)-N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide	LC-MS (Method 7A): Rt 2.06 mins; MS m/z 497.2/499.1 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 7.92 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.73 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 4.49 (s, 1H), 4.20 (d, *J* = 12.4 Hz, 1H), 4.10 (d, *J* = 12.6 Hz, 1H), 2.99 (d, *J* = 11.6 Hz, 1H), 2.78 (t, *J* = 11.6 Hz, 1H), 2.58 (tt, *J* = 13.3, 6.9 Hz, 2H), 2.40 (s, 3H), 2.39 – 2.36 (m, 1H), 1.15 (s, 3H), 1.11 (s, 3H). 2 x NH protons not observed.
3.11	 N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide	LC-MS (Method 7A): Rt 2.18 mins; MS m/z 495.2/497.2 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 11.35 (br s, 1H), 7.91 (s, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 4.54 (t, *J* = 6.5 Hz, 2H), 4.44 (d, *J* = 6.0 Hz, 2H), 3.60 – 3.52 (m, 4H), 3.43 (p, *J* = 6.1 Hz, 1H), 2.40 (s, 3H), 2.31 – 2.24 (m, 4H).

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
3.12	 N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide	LC-MS (Method 8B): Rt 3.12 mins; MS m/z 487.2 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.61 (br s, 1H), 7.91 (br s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 4.11 (m, 2H), 3.82 (s, 1H), 3.78 – 3.67 (m, 2H), 3.13 – 3.00 (m, 4H), 2.40 (s, 3H).

Example 4

N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperazine-1-carboxamide



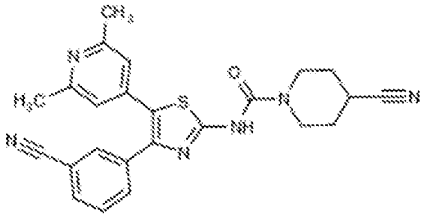
[00266] A solution of 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) (50 mg, 0.16 mmol) and CDI (40 mg, 0.24 mmol) in DMA (0.5 mL) was stirred at 50 °C for 18 h. The resulting mixture was treated with 1-methylpiperazine (36 µL, 0.33 mmol) and stirring continued at 50 °C for 1 h. After cooling to room temperature, the crude mixture was purified by preparative HPLC using acidic conditions, early elution method to afford the title compound.

LC-MS (Method 7B): Rt 2.43 mins; MS m/z 433.3 = [M+H]+

^{1}H NMR (500 MHz, DMSO-d6) δ 11.27 (br s, 1H), 7.89 (t, *J* = 1.5 Hz, 1H), 7.82 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.70 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 3.55 – 3.50 (m, 4H), 2.36 (s, 6H), 2.34 – 2.30 (m, 4H), 2.20 (s, 3H).

Example 4.1

4-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide



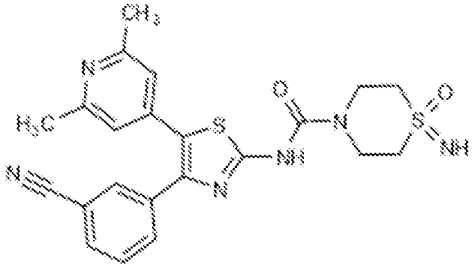
[00267] A solution of 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) (50 mg, 0.16 mmol) and CDI (53 mg, 0.33 mmol) in DMA (0.5 mL) was stirred at 50 °C for 18 h. The resulting mixture was treated with piperidine-4-carbonitrile (36 mg, 0.33 mmol) and DIPEA (90 µL, 0.49 mmol) and stirring continued at 50 °C for 30 minutes. After cooling to room temperature, purification of the crude material by C18 reverse phase chromatography eluting with 5-20% MeCN in water (+0.1% ammonium hydroxide modifier) afforded a solid that was suspended in Et_2O (2 mL), collected by filtration, washed with Et_2O (2 x 1.5 mL) and dried to afford the title compound as a yellow solid.

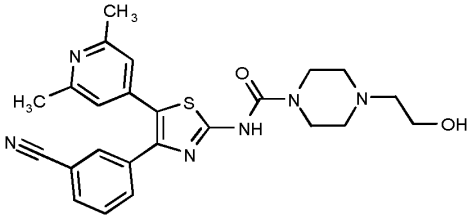
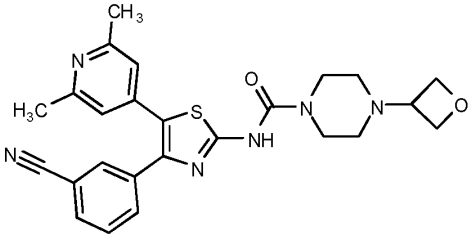
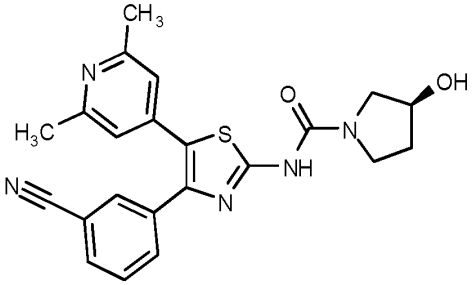
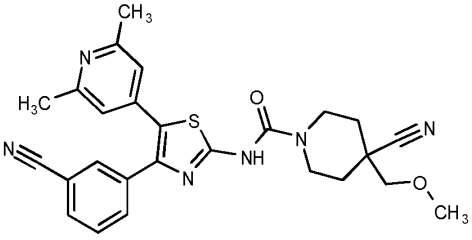
LC-MS (Method 8B): Rt 4.17 mins; MS m/z 443.3 = [M+H]+

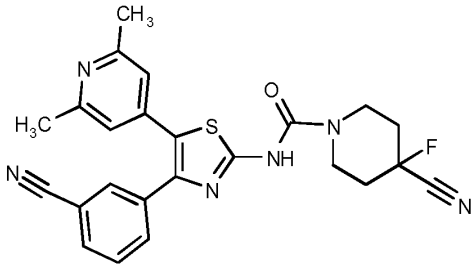
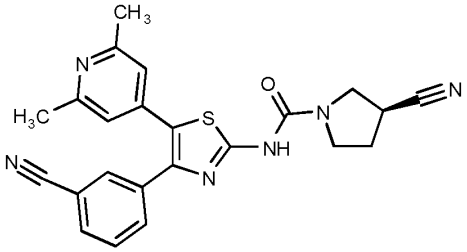
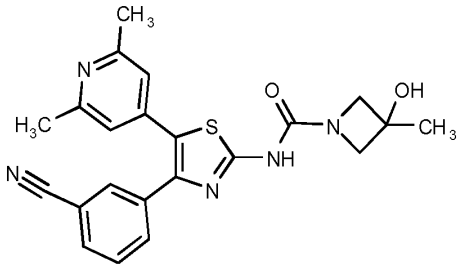
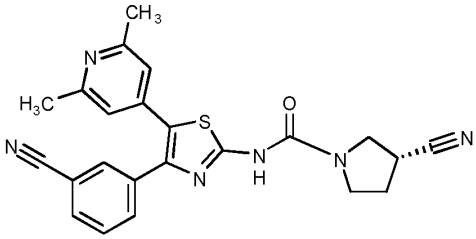
^{1}H NMR (500 MHz, DMSO-d6) δ 11.28 (s, 1H), 7.88 (s, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 6.92 (s, 2H), 3.83 – 3.76 (m, 2H), 3.45-3.38 (m, 2H), 3.14 – 3.08 (m, 1H), 2.36 (s, 6H), 1.95 – 1.86 (m, 2H), 1.75 – 1.65 (m, 2H).

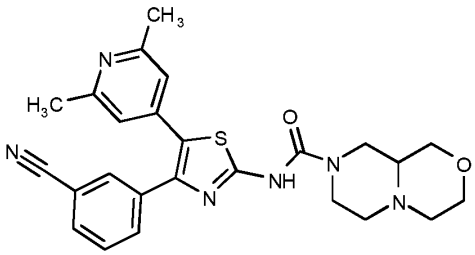
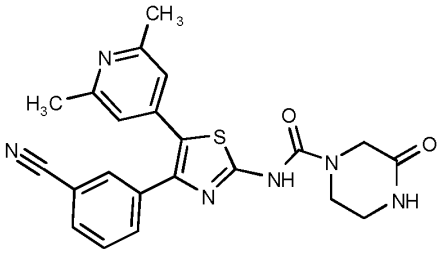
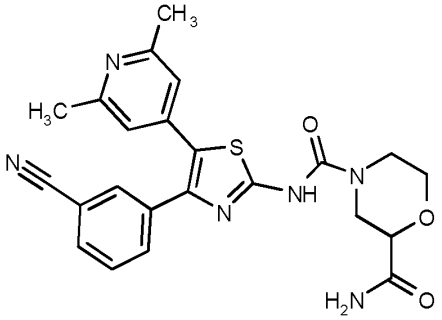
The compounds of the following tabulated Examples (Table Ex4) were prepared analogously to Example 4 or Example 4.1 from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and the appropriate amine.

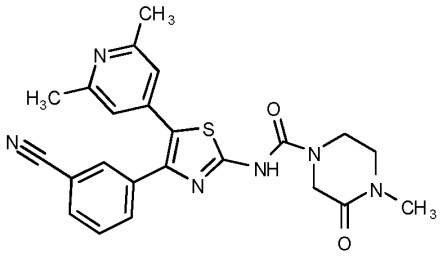
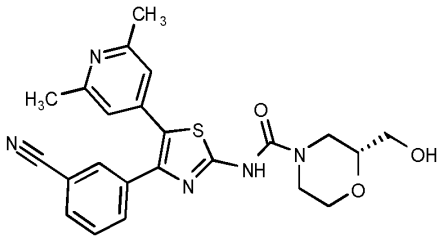
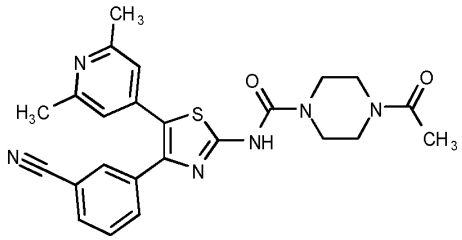
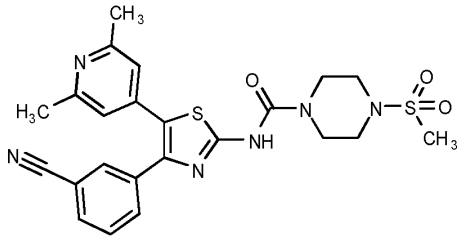
Table Ex4

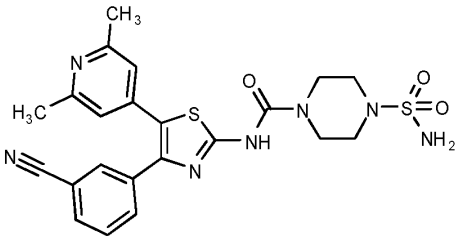
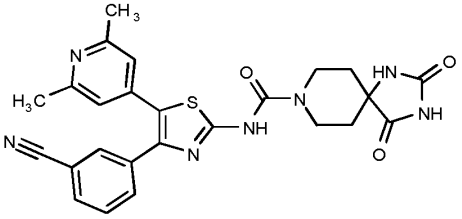
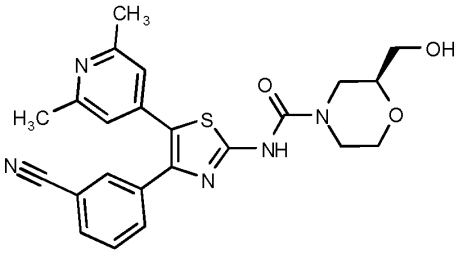
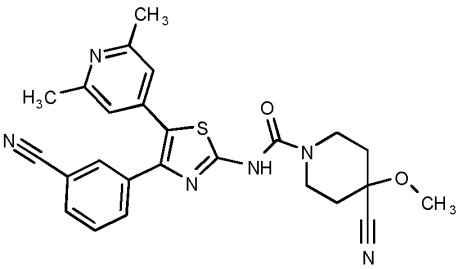
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
4.2	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide	LC-MS (Method 8B): Rt 2.65 mins; MS m/z 467.2 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.51 (br s, 1H), 7.88 (d, J = 1.7 Hz, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 4.16 – 4.04 (m, 2H), 3.81 (s, 1H), 3.78 – 3.66 (m, 2H), 3.13 - 3.02 (m, 4H), 2.36 (s, 6H).

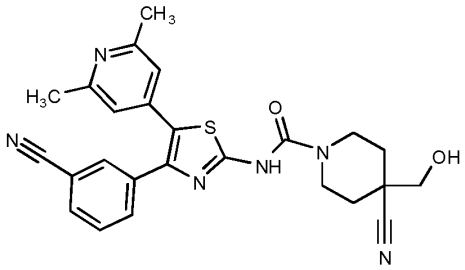
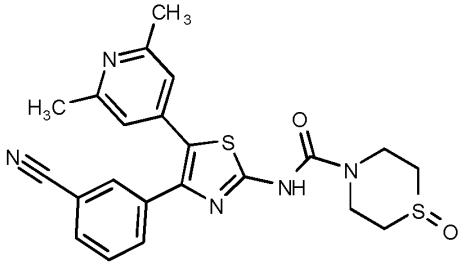
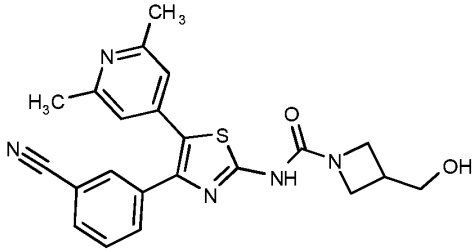
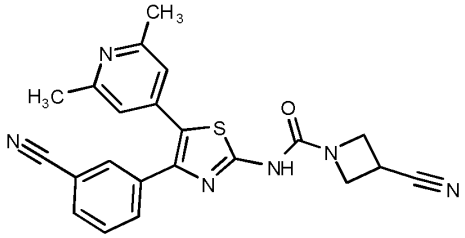
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
4.3	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxyethyl)piperazine-1-carboxamide	LC-MS (Method 8B): Rt 3.73 mins; MS m/z 463.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.24 (s, 1H), 7.89 (d, *J* = 1.7 Hz, 1H), 7.82 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.71 (dt, *J* = 8.1, 1.6 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 4.44 (t, *J* = 5.4 Hz, 1H), 3.56 – 3.49 (m, 6H), 2.46 – 2.40 (m, 6H), 2.36 (s, 6H).
4.4	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide	LC-MS (Method 8B): Rt 3.77 mins; MS m/z 475.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.25 (s, 1H), 7.88 (t, *J* = 1.6 Hz, 1H), 7.82 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.70 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.92 (s, 2H), 4.54 (apr t, *J* = 6.5 Hz, 2H), 4.45 (apr t, *J* = 6.1 Hz, 2H), 3.60 – 3.52 (m, 4H), 3.43 (apr p, *J* = 6.3 Hz, 1H), 2.36 (s, 6H), 2.30 – 2.25 (m, 4H).
4.5	 (3S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-pyrrolidine-1-carboxamide	LC-MS (Method 8B): Rt 3.66 mins; MS m/z 420.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.01 (s, 1H), 7.89 (t, *J* = 1.7 Hz, 1H), 7.81 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.71 (dt, *J* = 8.1, 1.5 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 5.01 (br s, 1H), 4.31 (br s, 1H), 3.49 (br s, 3H), 2.36 (s, 6H), 2.00 – 1.76 (m, 2H). OH proton not observed.
4.6	 4-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(methoxymethyl)piperidine-1-carboxamide	LC-MS (Method 8B): Rt 3.88 mins; MS m/z 487.2 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.32 (s, 1H), 7.88 (s, 1H), 7.82 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.70 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.92 (s, 2H), 4.26 (d, *J* = 13.7 Hz, 2H), 3.46 (s, 2H), 3.34 (s, 3H), 3.03 (t, *J* = 13.0 Hz, 2H), 2.36 (s, 6H), 1.93 (d, *J* = 13.7 Hz, 2H), 1.61 – 1.50 (m, 2H).

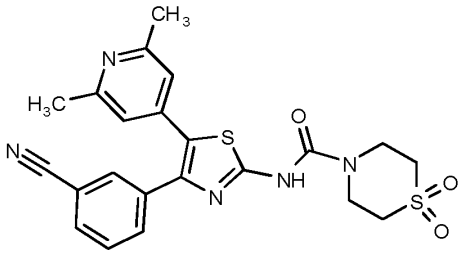
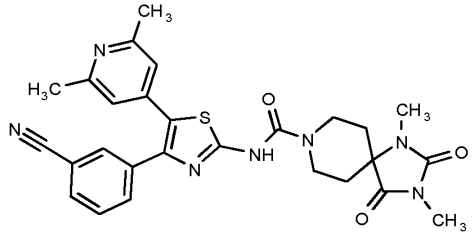
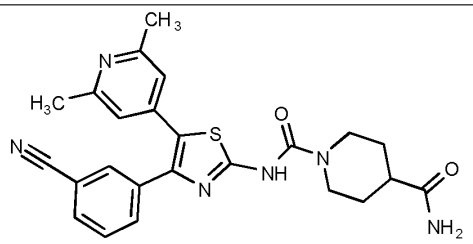
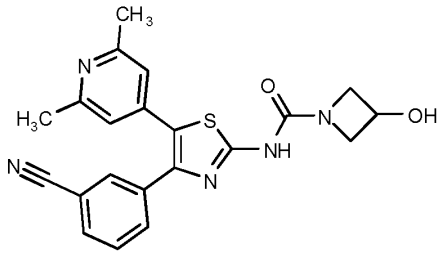
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
4.7	 4-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-fluoro-piperidine-1-carboxamide	LC-MS (Method 8B): Rt 3.68 mins; MS m/z 461.2 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.42 (s, 1H), 7.89 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 6.92 (s, 2H), 3.81 – 3.72 (m, 2H), 3.63 – 3.54 (m, 2H), 2.36 (s, 6H), 2.33 – 2.22 (m, 2H), 2.22 – 2.13 (m, 2H).
4.8	 (3S)-3-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1-carboxamide	LC-MS (Method 8B): Rt 3.88 mins; MS m/z 429.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.22 (s, 1H), 7.89 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 3.80 – 3.74 (m, 1H), 3.64 – 3.52 (m, 4H), 2.36 (s, 6H), 2.32 – 2.26 (m, 1H), 2.23 – 2.15 (m, 1H).
4.9	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-3-methyl-azetidine-1-carboxamide	LC-MS (Method 8B): Rt 3.71 mins; MS m/z 420.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.29 (s, 1H), 7.87 (s, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 6.92 (s, 2H), 5.65 (s, 1H), 3.94 – 3.82 (m, 4H), 2.36 (s, 6H), 1.38 (s, 3H).
4.10	 (3R)-3-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1-carboxamide	LC-MS (Method 8B): Rt 3.95 mins; MS m/z 429.3 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 11.23 (s, 1H), 7.89 (t, *J* = 1.7 Hz, 1H), 7.82 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.71 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 6.93 (s, 2H), 3.81 – 3.73 (m, 1H), 3.67 – 3.46 (m, 4H), 2.36 (s, 6H), 2.31 – 2.26 (m, 1H), 2.24 – 2.15 (m, 1H).

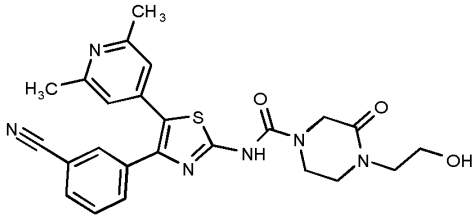
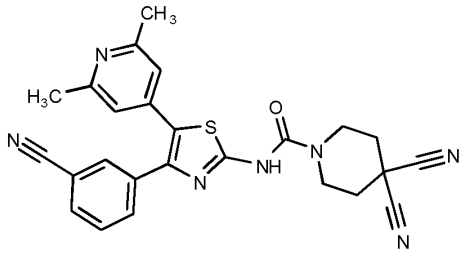
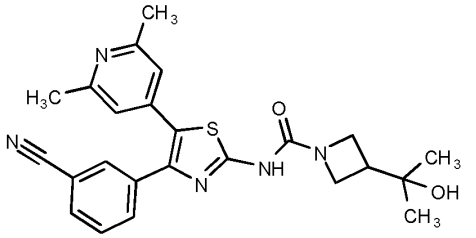
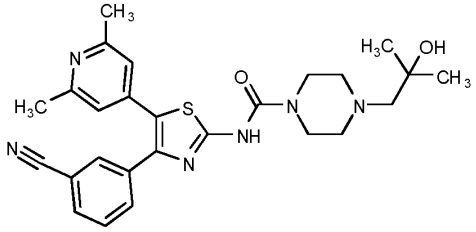
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
4.11	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carboxamide	LC-MS (Method 8B): Rt 3.75 mins; MS m/z 475.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.27 (s, 1H), 7.89 (d, J = 2.1 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 4.17 (d, J = 13.1 Hz, 1H), 4.04 (d, J = 12.8 Hz, 1H), 3.76 (dd, J = 11.6, 3.0 Hz, 1H), 3.69 (dd, J = 11.1, 3.0 Hz, 1H), 3.53 (td, J = 11.4, 2.4 Hz, 1H), 3.12 (t, J = 10.5 Hz, 1H), 3.00 (t, J = 12.6 Hz, 1H), 2.76 (d, J = 11.4 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.58 – 2.52 (m, 1H), 2.37 (s, 6H), 2.22 (td, J = 11.8, 3.3 Hz, 1H), 2.13 (dd, J = 11.9, 3.2 Hz, 1H), 2.06 (d, J = 11.1 Hz, 1H).
4.13	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-piperazine-1-carboxamide	LC-MS (Method 8B): Rt 2.95 mins; MS m/z 433.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.38 (s, 1H), 8.14 (s, 1H), 7.90 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 2H), 4.08 (s, 2H), 3.71 (t, *J* = 5.4 Hz, 2H), 3.26 (q, *J* = 6.1, 4.3 Hz, 2H), 2.37 (s, 6H).
4.14	 N4-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]morpholine-2,4-dicarboxamide	LC-MS (Method 8B): Rt 3.01 mins; MS m/z 461.2 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.44 (s, 1H), 7.90 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.40 (s, 1H), 7.33 (s, 1H), 6.94 (s, 2H), 4.31 (d, *J* = 13.4 Hz, 1H), 4.02 (d, *J* = 13.4 Hz, 1H), 3.94 (d, *J* = 11.6 Hz, 1H), 3.90 (dd, *J* = 10.1, 3.0 Hz, 1H), 3.61 – 3.52 (m, 1H), 3.09 (t, *J* = 12.1 Hz, 1H), 2.95 (s, 1H), 2.37 (s, 6H).

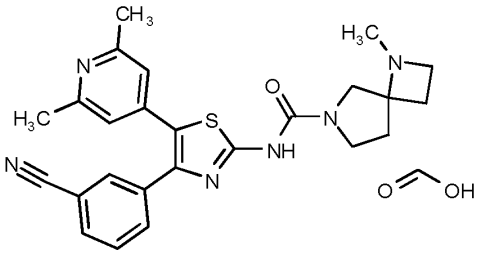
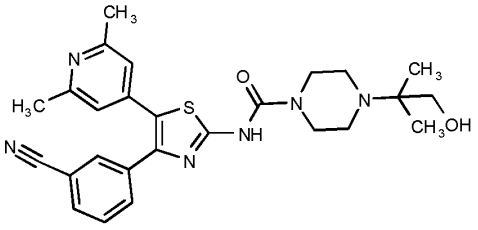
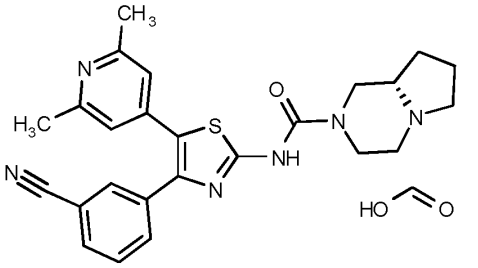
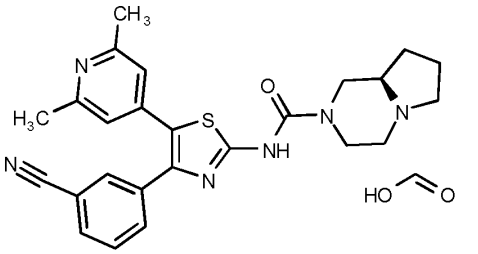
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
4.15	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-3-oxo-piperazine-1-carboxamide	LC-MS (Method 8B): Rt 3.50 mins; MS m/z 447.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.44 (s, 1H), 7.90 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 2H), 4.13 (s, 2H), 3.80 (t, *J* = 5.4 Hz, 2H), 3.39 (dd, *J* = 6.4, 4.3 Hz, 2H), 2.88 (s, 3H), 2.37 (s, 6H).
4.16	 (2R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)morpholine-4-carboxamide	LC-MS (Method 8B): Rt 3.16 mins; MS m/z 450.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.31 (s, 1H), 7.90 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 2H), 4.83 (t, *J* = 5.4 Hz, 1H), 4.17 (d, *J* = 13.3 Hz, 1H), 4.05 (d, *J* = 13.3 Hz, 1H), 3.88 (dd, *J* = 11.5, 3.2 Hz, 1H), 3.50 – 3.42 (m, 2H), 3.40 (d, *J* = 4.6 Hz, 2H), 2.99 (t, *J* = 11.8 Hz, 1H), 2.74 (t, *J* = 11.6 Hz, 1H), 2.37 (s, 6H).
4.17	 4-Acetyl-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide	LC-MS (Method 8B): Rt 3.45 mins; MS m/z 461.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.34 (s, 1H), 7.89 (t, *J* = 1.9 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 3.60 – 3.55 (m, 2H), 3.53 – 3.45 (m, 6H), 2.36 (s, 6H), 2.03 (s, 3H).
4.18	 N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methylsulfonyl-piperazine-1-carboxamide	LC-MS (Method 8B): Rt 3.22 mins; MS m/z 497.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.42 (s, 1H), 7.89 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 6.93 (s, 2H), 3.73 – 3.61 (m, 4H), 3.19 – 3.12 (m, 4H), 2.91 (s, 3H), 2.36 (s, 6H).

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
4.19	 N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-sulfamoyl-piperazine-1-carboxamide	LC-MS (Method 8B): Rt 3.29 mins; MS m/z 498.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.39 (s, 1H), 7.89 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 6.88 (s, 2H), 3.64 (apr br t ,*J* = 5.1 Hz, 4H), 2.98 (apr br t ,*J* = 5.1 Hz, 4H), 2.36 (s, 6H).
4.20	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 3.33 mins; MS m/z 502.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.34 (s, 1H), 10.75 (s, 1H), 8.58 (s, 1H), 7.89 (s, 1H), 7.82 (d,*J* = 7.8 Hz, 1H), 7.70 (d,*J* = 7.8 Hz, 1H), 7.56 (t,*J* = 7.8 Hz, 1H), 6.93 (s, 2H), 4.10 – 4.03 (m, 2H), 3.31 - 3.25 (m, 2H), 2.36 (s, 6H), 1.82 – 1.74 (m, 2H), 1.64 – 1.56 (m, 2H).
4.21	 (2S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)morpholine-4-carboxamide	LC-MS (Method 8B): Rt 3.18 mins; MS m/z 450.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.29 (s, 1H), 7.89 (t, *J* = 1.8 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 4.82 (t, *J* = 5.5 Hz, 1H), 4.17 (d, *J* = 13.2 Hz, 1H), 4.04 (d, *J* = 13.2 Hz, 1H), 3.90 – 3.84 (m, 1H), 3.50 – 3.42 (m, 2H), 3.42 - 3.38 (m, 2H), 3.02 – 2.94 (m, 1H), 2.77 – 2.69 (m, 1H), 2.36 (s, 6H).
4.22	 4-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methoxy-piperidine-1-carboxamide	LC-MS (Method 8B): Rt 3.93 mins; MS m/z 473.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.37 (s, 1H), 7.89 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 3.75 – 3.65 (m, 2H), 3.55 – 3.47 (m, 2H), 3.40 (s, 3H), 2.36 (s, 6H), 2.17 – 2.09 (m, 2H), 1.93–1.86 (m, 2H).

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
4.23	 4-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(hydroxymethyl)piperidine-1-carboxamide (Prepared using Intermediate E)	LC-MS (Method 8B): Rt 3.66 mins; MS m/z 473.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.32 (s, 1H), 7.88 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.92 (s, 2H), 5.50 (t, *J* = 5.7 Hz, 1H), 4.28 (d, *J* = 13.9 Hz, 2H), 3.50 (d, *J* = 5.7 Hz, 2H), 3.00 (t, *J* = 13.0 Hz, 2H), 2.35 (s, 6H), 1.88 (d, *J* = 13.6 Hz, 2H), 1.53 – 1.45 (m, 2H).
4.24	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide	LC-MS (Method 8B): Rt 3.25 mins; MS m/z 452.2 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.46 (s, 1H), 7.90 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 4.12 (d, J = 14.6 Hz, 2H), 3.79 (t, J = 13.0 Hz, 2H), 2.94 (t, J = 12.5 Hz, 2H), 2.76 (d, J = 13.6 Hz, 2H), 2.37 (s, 6H).
4.25	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)azetidine-1-carboxamide	LC-MS (Method 8B): Rt 3.66 mins; MS m/z 420.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.26 (s, 1H), 7.88 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 4.84 (t, *J* = 5.3 Hz, 1H), 4.03 (s, 2H), 3.77 (s, 2H), 3.53 (t, *J* = 5.7 Hz, 2H), 2.72 – 2.66 (m, 1H), 2.36 (s, 6H).
4.26	 3-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]azetidine-1-carboxamide	LC-MS (Method 8B): Rt 3.58 mins; MS m/z 415.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.51 (s, 1H), 7.87 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 4.32 (t, *J* = 9.0 Hz, 2H), 4.19 (t, *J* = 7.3 Hz, 2H), 3.85 – 3.75 (m, 1H), 2.36 (s, 6H).

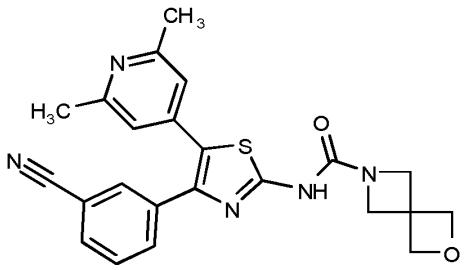
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
4.27	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,1-dioxo-1,4-thiazinane-4-carboxamide	LC-MS (Method 8B): Rt 3.20 mins; MS m/z 468.2 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.58 (s, 1H), 7.89 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.92 (s, 2H), 4.01 – 3.92 (m, 4H), 3.25 – 3.18 (m, 4H), 2.36 (s, 6H).
4.28	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3-dimethyl-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 4.09 mins; MS m/z 530.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.33 (s, 1H), 7.90 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 2H), 4.25 (d, *J* = 13.1 Hz, 2H), 3.48 (t, *J* = 13.0 Hz, 2H), 2.87 (s, 3H), 2.77 (s, 3H), 2.37 (s, 6H), 1.93 (td, *J* = 13.2, 4.7 Hz, 2H), 1.73 (d, *J* = 13.3 Hz, 2H).
4.29	 N1-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1,4-dicarboxamide	LC-MS (Method 8B): Rt 3.60 mins; MS m/z 461.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.23 (s, 1H), 7.90 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.30 (s, 1H), 6.93 (s, 2H), 6.83 (s, 1H), 4.19 (d, *J* = 13.3 Hz, 2H), 2.90 (t, *J* = 12.7 Hz, 2H), 2.36 (s, 6H), 2.36 – 2.29 (m, 1H), 1.74 (d, *J* = 12.6 Hz, 2H), 1.47 (qd, *J* = 12.4, 3.9 Hz, 2H).
4.30	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-azetidine-1-carboxamide	LC-MS (Method 8B): Rt 3.33 mins; MS m/z 406.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (s, 1H), 7.88 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 2H), 5.74 (d, *J* = 6.5 Hz, 1H), 4.50 – 4.43 (m, 1H), 4.28 – 4.19 (m, 2H), 3.81 – 3.74 (m, 2H), 2.36 (s, 6H).

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
4.31	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxyethyl)-3-oxo-piperazine-1-carboxamide	LC-MS (Method 8B): Rt 3.29 mins; MS m/z 477.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.42 (s, 1H), 7.90 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 2H), 4.77 (t, *J* = 5.5 Hz, 1H), 4.13 (s, 2H), 3.78 (t, *J* = 5.4 Hz, 2H), 3.53 (q, *J* = 5.8 Hz, 2H), 3.48 (t, *J* = 5.4 Hz, 2H), 3.39 (t, *J* = 5.9 Hz, 2H), 2.37 (s, 6H).
4.32	 4,4-Dicyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide (Prepared using Intermediate F)	LC-MS (Method 8B): Rt 3.86 mins; MS m/z 468.3 = [M+H]+ ^{1}H NMR (500 MHz, Methanol-d4) δ 7.92 (s, 1H), 7.72 (t, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.02 (s, 2H), 3.83 (t, *J* = 5.5 Hz, 4H), 2.45 (s, 6H), 2.38 (t, *J* = 5.5 Hz, 4H). NH proton not observed.
4.33	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)azetidine-1-carboxamide	LC-MS (Method 8B): Rt 3.93 mins; MS m/z 448.3 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.25 (s, 1H), 7.88 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 4.58 (s, 1H), 3.93 (s, 4H), 2.59 (p ,*J* = 7.6 Hz, 1H), 2.36 (s, 6H), 1.04 (s, 6H).
4.34	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxy-2-methyl-propyl)piperazine-1-carboxamide	LC-MS (Method 7B): Rt 2.94 mins; MS m/z = 491.4 [M+H]+ 1H NMR (400 MHz, DMSO-d6) δ 11.18 (s, 1H), 7.88 (t, J = 1.5 Hz, 1H), 7.82 (dt, J = 7.7, 1.3 Hz, 1H), 7.70 (dt, J = 8.0, 1.3 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.92 (s, 2H), 4.13 (s, 1H), 3.55 – 3.48 (m, 4H), 2.55 – 2.52 (m, 4H), 2.36 (s, 6H), 2.22 (s, 2H), 1.10 (s, 6H).

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
4.36	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-methyl-1,7-diazaspiro[3.4]octane-7-carboxamide formate salt	LC-MS (Method 7B): Rt 2.75 mins; MS m/z 459.4 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.25 (s, 1H), 7.89 (t, J = 1.6 Hz, 1H), 7.82 (dt, J = 7.7, 1.4 Hz, 1H), 7.71 (dt, J = 7.7, 1.3 Hz, 1H), 7.56 (dd, J = 7.8 Hz, 1H), 6.93 (s, 2H), 3.59 – 3.45 (m, 3H), 3.12 – 3.08 (m, 1H), 3.03 – 2.98 (m, 1H), 2.36 (s, 6H), 2.13 (s, 3H), 2.10 – 2.02 (m, 2H), 2.01 – 1.88 (m, 3H).
4.37	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxy-1,1-dimethyl-ethyl)piperazine-1-carboxamide	LC-MS (Method 7B): Rt 2.99 mins; MS m/z 491.4 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.90 (t, J = 1.7 Hz, 1H), 7.71 (dt, J = 7.9, 1.5 Hz, 1H), 7.68 (dt, J = 7.8, 1.4 Hz, 1H), 7.49 (dd, J = 7.8, 7.8 Hz, 1H), 7.00 (s, 2H), 3.61 – 3.56 (m, 4H), 3.46 (s, 2H), 2.74 – 2.68 (m, 4H), 2.43 (s, 6H), 1.07 (s, 6H). Exchangeable protons not observed.
4.38	 (8aS)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxamide formate salt	LC-MS (Method 7B): Rt 2.93 mins; MS m/z 459.4 = [M+H]+ 1H NMR (400 MHz, Methanol-d4) δ 7.92 (t, J = 1.8 Hz, 1H), 7.76 – 7.68 (m, 2H), 7.51 (dd, J = 7.9, 7.9 Hz, 1H), 7.03 (s, 2H), 4.36 (d, J = 13.3 Hz, 1H), 4.22 (d, J = 13.2 Hz, 1H), 3.23 – 3.14 (m, 3H), 2.87 (dd, J = 13.0, 10.4 Hz, 1H), 2.46 (s, 6H), 2.43 – 2.36 (m, 2H), 2.33 – 2.23 (m, 1H), 2.06 – 1.97 (m, 1H), 1.97 – 1.84 (m, 2H), 1.62 – 1.47 (m, 1H). Exchangeable protons not observed
4.39	 (8aR)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxamide formate salt	LC-MS (Method 7B): Rt 2.93 mins; MS m/z 459.4 = [M+H]+ 1H NMR (400 MHz, Methanol-d4) δ 7.91 (t, J = 1.7 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.70 – 7.66 (m, 1H), 7.49 (dd, J = 7.8, 7.8 Hz, 1H), 7.01 (s, 2H), 4.34 (d, J = 12.9 Hz, 1H), 4.20 (d, J = 13.2 Hz, 1H), 3.18 – 3.09 (m, 3H), 2.79 (dd, J = 12.7, 10.7 Hz, 1H), 2.44 (s, 6H), 2.33 – 2.23 (m, 2H), 2.18 – 2.08 (m, 1H), 1.99 – 1.92 (m, 1H), 1.90 – 1.79 (m, 2H), 1.50 (td, J = 11.2, 6.8 Hz, 1H). Exchangeable protons not observed

Example 4.12

N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

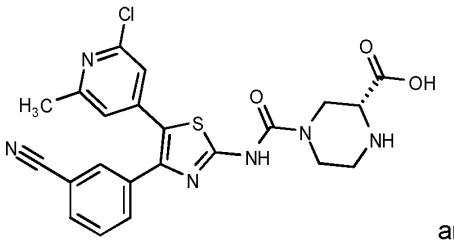


[00268] CDI (1.27 g, 7.83 mmol) and DIPEA (2.05 mL, 11.75 mmol) were added to a stirred solution of 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C)(1.2 g, 3.92 mmol) in DMA (12 mL) and the solution was heated at 50 °C overnight. 2-Oxa-6-azaspiro[3.3]heptane (0.73 mL, 7.83 mmol) and additional DIPEA (2.05 mL, 11.75 mmol) were added and the solution was stirred at 50 °C for 40 mins. The resulting mixture was allowed to cool to room temperature before being diluted with EtOAc (150 mL), washed with 90% brine (100 mL), 50% brine (3 X 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica eluting with a gradient of 0 to 4% MeOH in DCM afforded the title compound as an off-white solid.

LC-MS (Method 8B): Rt 2.82 mins; MS m/z 432.0 = [M+H]+

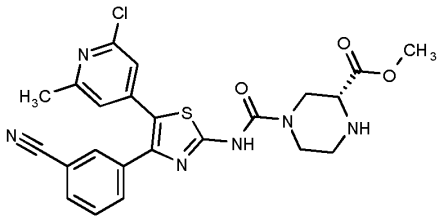
1H NMR (500 MHz, DMSO-d6) δ 11.35 (s, 1H), 7.88 (t, J = 1.7 Hz, 1H), 7.82 (dt, J = 7.7, 1.4 Hz, 1H), 7.70 (dt, J = 8.0, 1.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 4.68 (s, 4H), 4.21 (s, 4H), 2.36 (s, 6H).

Example 5: (2R)-4-[[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid

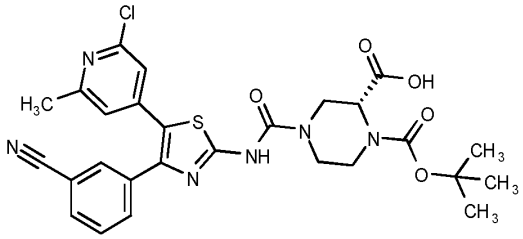


and

Example 5.1: Methyl (2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylate



Step 1: (2R)-1-*tert*-Butoxycarbonyl-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid



[00269] A solution of 3-[2-amino-5-(2-chloro-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate D) (50 mg, 0.15 mmol) and CDI (50 mg, 0.31 mmol) in DMA (0.5 mL) was stirred at 50 °C for 20 h. The reaction mixture was treated with (2R)-1-*tert*-butoxycarbonylpiperazine-2-carboxylic acid (106 mg, 0.46 mmol) and DIPEA (53 µL, 0.31 mmol) and stirring continued heating at 50 °C for 1 h. After cooling to room temperature, the resulting mixture was diluted with water (2 mL) and extracted with EtOAc (3 x 2 mL). The combined organic extracts were filtered through a phase separating cartridge and concentrated *in vacuo*. The crude product was dissolved in DCM (4 mL) and heptane (10 mL) added resulting in the formation of a precipitate. The solid was collected under vacuum filtration to afford the title compound as a brown solid.

LC-MS (Method 2A): Rt 1.25 mins; MS m/z 583.2/585.2 = [M+H]+

^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 (t, J = 1.5 Hz, 1H), 7.86 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 4.68 – 4.57 (m, 1H), 4.51 (d, *J* = 30.0 Hz, 2H), 4.17 – 4.08 (m, 2H), 3.77 – 3.69 (m, 2H), 2.40 (s, 3H), 1.39 (d, *J* = 7.0 Hz, 9H). NH and OH protons not observed

Step 2: (2R)-4-[[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid and methyl (2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylate

[00270] To a solution of (2R)-1-*tert*-butoxycarbonyl-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid (step 1)(94 mg, 0.13 mmol) in DCM (2 mL) and MeOH (0.2 mL) was added 4M HCl in 1,4-dioxane (322 µL, 1.29 mmol) and the reaction mixture was stirred at room temperature for 16 h. The resulting mixture

was concentrated *in vacuo* and purification of the crude mixture by HPLC using acidic conditions, early elution method afforded the following compounds:

Example 5: (2R)-4-[[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid as an off-white solid.

LC-MS (Method 7A): Rt 2.08 mins; MS m/z 483.2/485.1 = [M+H]+ (99% @ 215nm)

^{1}H NMR (500 MHz, DMSO-d6) δ 7.91 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 4.37 (dd, *J* = 10.9, 3.2 Hz, 2H), 4.02 (d, *J* = 13.0 Hz, 1H), 3.11 (dd, *J* = 9.5, 6.1 Hz, 1H), 2.92 – 2.85 (m, 1H), 2.40 (s, 3H). 2 x NH and COOH protons not observed. 2 x CH signals under H_2O signal.

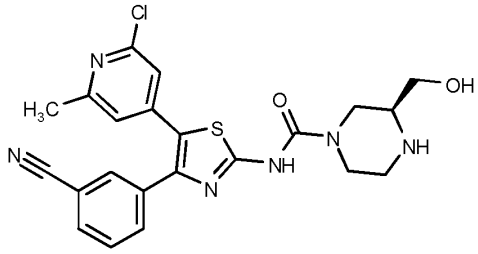
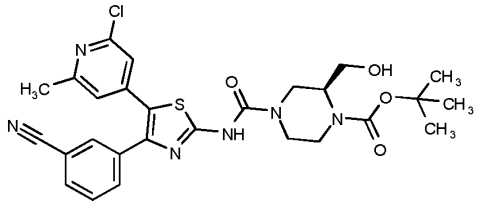
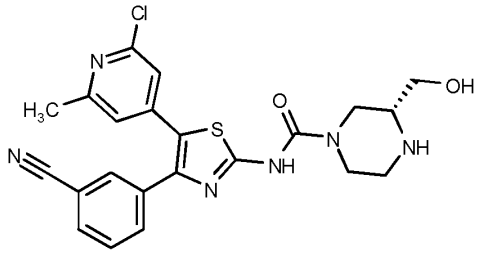
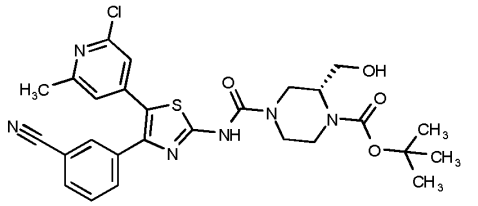
Example 5.1: Methyl (2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylate as an off-white solid.

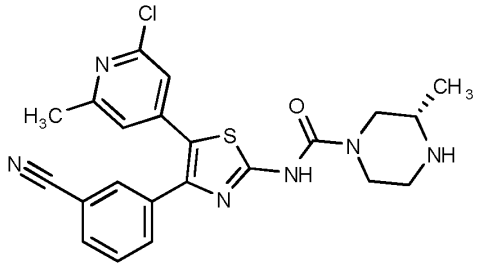
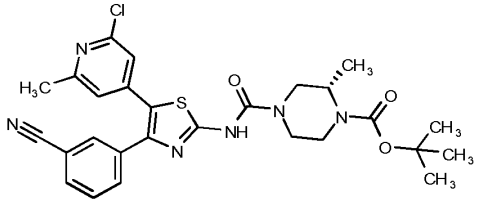
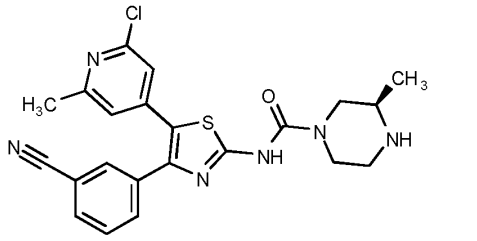
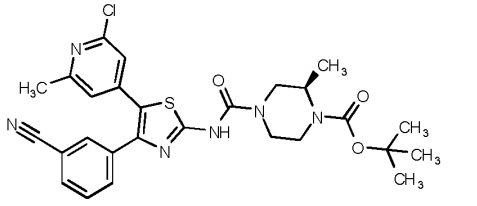
LC-MS (Method 7A): Rt 2.10 mins; MS m/z 497.2/499.1 = [M+H]+ (99% @ 215nm)

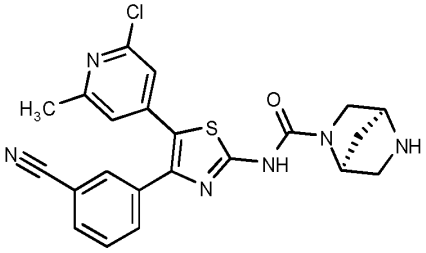
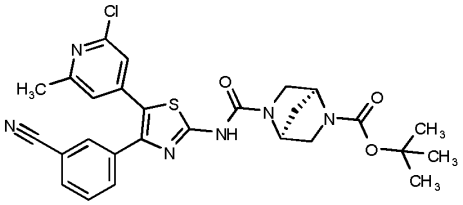
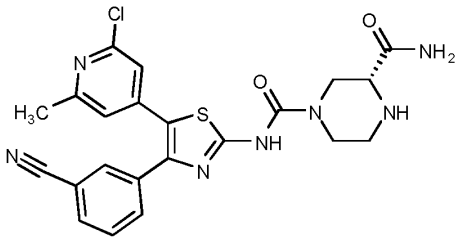
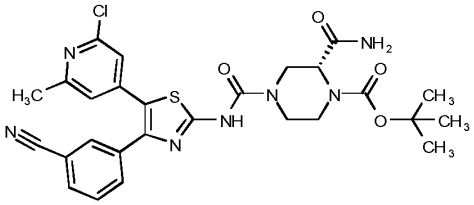
^{1}H NMR (500 MHz, DMSO-d6) δ 7.92 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.72 (dt, *J* = 8.0, 1.4 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 4.07 – 4.00 (m, 1H), 3.74 (d, *J* = 12.9 Hz, 1H), 3.66 (s, 3H), 3.46 (dd, *J* = 8.3, 3.5 Hz, 1H), 3.22 – 3.17 (m, 1H), 2.91 (dt, *J* = 11.9, 3.3 Hz, 1H), 2.62 – 2.58 (m, 1H), 2.40 (s, 3H). 2 x NH protons not observed. 1 x CH signal under H_2O signal.

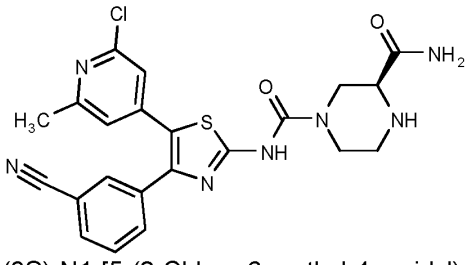
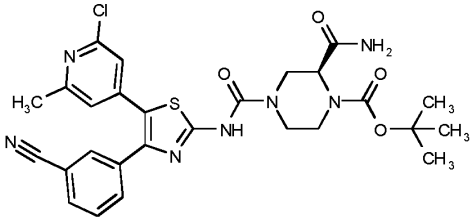
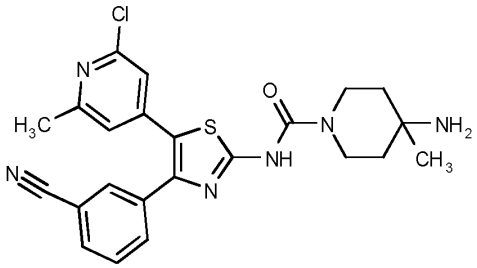
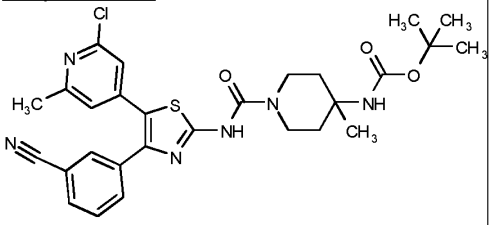
[00271] The compounds of the following tabulated Examples (Table Ex5) were prepared analogously to Example 5 from 3-[2-amino-5-(2-chloro-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate D) and the appropriate amine (step 1) followed by deprotection using 4M HCl in 1,4-dioxane (step 2).

Table Ex5

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
5.2	 (3S)-N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(hydroxymethyl)piperazine-1-carboxamide Prepared via:  *tert*-Butyl (2S)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]-2-(hydroxymethyl)piperazine-1-carboxylate	LC-MS (Method 7A): Rt 1.96 mins; MS m/z 469.2/471.1 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.72 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 4.15 (d, *J* = 10.9 Hz, 1H), 4.07 (d, *J* = 12.7 Hz, 1H), 2.91 (dd, *J* = 26.9, 12.8 Hz, 2H), 2.66 – 2.55 (m, 3H), 2.40 (s, 3H). 2 x NH and OH protons not observed. 1 x CH_2 signal under H_2O signal. Intermediate Data: LC-MS (Method 7A): Rt 3.60 mins; MS m/z 569.2 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 11.32 (s, 1H), 7.91 (t, *J* = 1.3 Hz, 1H), 7.86 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.19 (s, 1H), 7.07 (s, 1H), 4.87 (s, 1H), 4.21 (d, *J* = 12.8 Hz, 1H), 4.08 – 3.94 (m, 2H), 3.76 (d, *J* = 11.6 Hz, 1H), 3.45 – 3.36 (m, 2H), 3.12 (dd, *J* = 13.3, 3.5 Hz, 1H), 3.05 – 2.97 (m, 2H), 2.40 (s, 3H), 1.42 (s, 9H).
5.3	 (3R)-N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(hydroxymethyl)piperazine-1-carboxamide Prepared via:  *tert*-Butyl (2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]-2-(hydroxymethyl)piperazine-1-carboxylate	LC-MS (Method 7A): Rt 1.92 mins; MS m/z 469.2/471.1 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (t, *J* = 1.5 Hz, 1H), 7.86 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.73 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 4.15 (d, *J* = 10.5 Hz, 1H), 4.07 (d, *J* = 12.2 Hz, 1H), 2.91 (dd, *J* = 26.5, 12.2 Hz, 2H), 2.66 – 2.57 (m, 3H), 2.41 (s, 3H). 2 x NH and OH protons not observed. 1 x CH_2 signal under H_2O signal. Intermediate Data: LC-MS (Method 7A): Rt 3.60 mins; MS m/z 569.2 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 (t, *J* = 1.4 Hz, 1H), 7.86 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.72 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 4.22 (d, *J* = 13.0 Hz, 1H), 4.08 – 3.95 (m, 2H), 3.79 – 3.72 (m, 1H), 3.46 – 3.37 (m, 2H), 3.11 (dd, *J* = 13.7, 3.7 Hz, 1H), 3.00 (t, *J* = 8.4 Hz, 2H), 2.40 (s, 3H), 1.41 (s, 9H). NH and OH protons not observed.

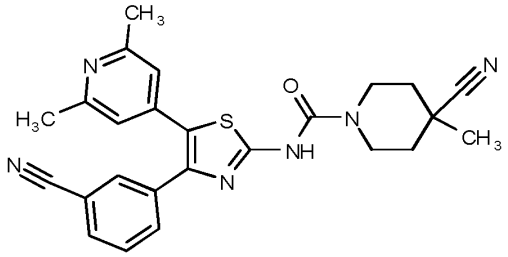
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
5.4	 (3S)-N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide Prepared via:  *tert*-Butyl (2S)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]-2-methyl-piperazine-1-carboxylate	LC-MS (Method 7A): Rt 2.02 mins; MS m/z 453.2/455.2 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 7.91 (t, *J* = 1.4 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 4.09 (t, *J* = 10.9 Hz, 2H), 2.92 (d, *J* = 11.9 Hz, 1H), 2.87 – 2.80 (m, 1H), 2.71 – 2.64 (m, 2H), 2.53 – 2.52 (m, 1H), 2.40 (s, 3H), 1.00 (d, *J* = 6.3 Hz, 3H). 2 x NH protons not observed Intermediate Data: LC-MS (Method 2A): Rt 1.39 mins; MS m/z 553.1/555.0 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 7.92 (t, *J* = 1.5 Hz, 1H), 7.86 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.73 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.19 (s, 1H), 7.06 (s, 1H), 4.19 – 4.10 (m, 2H), 4.03 (dd, *J* = 10.2, 2.9 Hz, 1H), 3.74 (dt, *J* = 12.9, 2.5 Hz, 1H), 3.17 – 3.11 (m, 1H), 3.08 – 3.01 (m, 1H), 2.98 – 2.91 (m, 1H), 2.40 (s, 3H), 1.41 (s, 9H), 1.07 (d, *J* = 6.7 Hz, 3H). NH proton not observed.
5.5	 (3R)-N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide Prepared via:  *tert*-Butyl (2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]-2-methyl-piperazine-1-carboxylate	LC-MS (Method 7A): Rt 2.03 mins; MS m/z 453.2/455.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 7.92 (t, *J* = 1.5 Hz, 1H), 7.86 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.19 – 7.17 (m, 1H), 7.06 (s, 1H), 4.15 (t, *J* = 11.0 Hz, 2H), 3.08 (d, *J* = 12.4 Hz, 1H), 3.02 – 2.97 (m, 1H), 2.93 – 2.89 (m, 1H), 2.82 – 2.77 (m, 1H), 2.74 – 2.68 (m, 1H), 2.40 (s, 3H), 1.09 (d, *J* = 6.4 Hz, 3H). 2 x NH protons not observed Intermediate Data: LC-MS (Method 2A): Rt 1.40 mins; MS m/z 553.1/555.0 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 11.41 (br s, 1H), 7.92 (t, *J* = 1.4 Hz, 1H), 7.86 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.73 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.19 (s, 1H), 7.07 (s, 1H), 4.18 – 4.10 (m, 2H), 4.02 (d, *J* = 13.4 Hz, 1H), 3.74 (dq, *J* = 12.9, 2.5, 0.2 Hz, 1H), 3.17 – 3.12 (m, 1H), 3.05 (t, *J* = 11.5 Hz, 1H), 2.95 (t, *J* = 12.1 Hz, 1H), 2.40 (s, 3H), 1.41 (s, 9H), 1.07 (d, *J* = 6.7 Hz, 3H).

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
5.6	 (1S,4S)-N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide Prepared via:  *tert*-Butyl (1S,4S)-5-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	LC-MS (Method 7A): Rt 1.99 mins; MS m/z 451.2/453.2 = [M+H]+ ^{1}H NMR (500 MHz, Methanol-d4) δ 7.93 (t, *J* = 1.4 Hz, 1H), 7.76 – 7.68 (m, 2H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 4.82 (s, 1H), 4.24 (s, 1H), 3.67 (d, *J* = 10.2 Hz, 1H), 3.59 (d, *J* = 10.5 Hz, 1H), 3.28 (s, 1H), 3.23 (d, *J* = 10.8 Hz, 1H), 2.45 (s, 3H), 2.11 (d, *J* = 10.6 Hz, 1H), 1.95 (d, *J* = 10.7 Hz, 1H). 2 x NH protons not observed. Intermediate Data: LC-MS (Method 7A): Rt 3.85 mins; MS m/z 551.2 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 11.00 (br s, 1H), 7.91 (t, *J* = 1.3 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 4.98 – 4.58 (m, 1H), 4.42 (d, *J* = 19.1 Hz, 1H), 3.55 – 3.36 (m, 4H), 3.24 (d, *J* = 10.0 Hz, 2H), 2.40 (s, 3H), 1.39 (s, 9H).
5.7	 (3R)-N1-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1,3-dicarboxamide Prepared via:  *tert*-Butyl (2R)-2-carbamoyl-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-1-carboxylate	LC-MS (Method 7B): Rt 2.11 mins; MS m/z 482.2/484.2 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 11.28 (s, 1H), 7.92 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.34 (s, 1H), 7.19 (s, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 4.08 (dd, *J* = 12.9, 2.2 Hz, 1H), 3.85 (d, *J* = 13.3 Hz, 1H), 3.20 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.08 – 2.99 (m, 2H), 2.90 (dt, *J* = 12.9, 3.2 Hz, 1H), 2.66 – 2.59 (m, 1H), 2.40 (s, 3H). NH proton not observed. Intermediate Data: LC-MS (Method 2A): Rt 1.19 mins; MS m/z 582.2/584.2 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 11.31 (s, 1H), 7.91 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.46 (s, 1H), 7.19 (s, 1H), 7.13 (s, 1H), 7.07 (s, 1H), 4.50 – 4.35 (m, 3H), 4.07 – 3.99 (m, 1H), 3.74 – 3.68 (m, 1H), 3.43 – 3.35 (m, 2H), 2.40 (s, 3H), 1.39 (s, 9H).

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
5.8	 (3S)-N1-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1,3-dicarboxamide Prepared via:  *tert*-Butyl (2S)-2-carbamoyl-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-1-carboxylate	LC-MS (Method 7B): Rt 2.12 mins; MS m/z 482.2/484.2 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 11.29 (s, 1H), 7.92 (t, *J* = 1.5 Hz, 1H), 7.85 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.34 (s, 1H), 7.21 – 7.17 (m, 2H), 7.06 (s, 1H), 4.08 (dd, *J* = 13.2, 2.4 Hz, 1H), 3.85 (d, *J* = 12.5 Hz, 1H), 3.21 (dd, *J* = 9.3, 3.2 Hz, 1H), 3.10 – 2.98 (m, 2H), 2.90 (dt, *J* = 12.4, 2.9 Hz, 1H), 2.66 – 2.59 (m, 1H), 2.40 (s, 3H). NH proton not observed. Intermediate Data: LC-MS (Method 7A): Rt 3.37 mins; MS m/z 582.2/584.2 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 11.31 (s, 1H), 7.94 – 7.89 (m, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.46 (s, 1H), 7.19 (s, 1H), 7.13 (s, 1H), 7.07 (s, 1H), 4.56 – 4.34 (m, 3H), 4.08 – 3.99 (m, 1H), 3.76 – 3.66 (m, 1H), 3.42 – 3.34 (m, 2H), 2.40 (s, 3H), 1.38 (s, 9H).
5.9	 4-Amino-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide Prepared via:  *tert*-Butyl N-[1-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]-4-methyl-4-piperidyl]carbamate	LC-MS (Method 7A): Rt 2.08 mins; MS m/z 467.2/469.1 = [M+H]+ ^{1}H NMR (500 MHz, DMSO-d6) δ 7.90 (t, *J* = 1.5 Hz, 1H), 7.84 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.12 (s, 1H), 6.99 (s, 1H), 3.81 – 3.72 (m, 2H), 3.42 – 3.37 (m, 2H), 2.38 (s, 3H), 1.53 (t, *J* = 5.4 Hz, 4H), 1.22 (s, 3H). 3 x NH protons not observed. 1 x CH_2 signal under H_2O signal. Intermediate Data: LC-MS (Method 2A): Rt 1.38 mins; MS m/z 567.2/569.2 = [M+H]+ ^{1}H NMR (400 MHz, DMSO-d6) δ 11.25 (s, 1H), 7.92 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 6.59 (s, 1H), 3.77 (d, *J* = 13.6 Hz, 2H), 3.20 (t, *J* = 11.5 Hz, 2H), 2.40 (s, 3H), 2.05 (d, *J* = 13.3 Hz, 2H), 1.39 (s, 9H), 1.38 – 1.33 (m, 2H), 1.23 (s, 3H).

Example 6

4-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide



[00272] A solution of 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) (50 mg, 0.16 mmol) and CDI (40 mg, 0.24 mmol) in DMA (0.5 mL) was stirred at 50°C for 18 h. The resulting mixture was treated with 4-methylpiperidine-4-carbonitrile hydrochloride (52 mg, 0.33 mmol) and DIPEA (85 µL, 0.49 mmol) and stirring continued at 50°C for 1 h. After cooling to room temperature, the crude mixture was purified by preparative HPLC using acidic conditions, early elution method to afford to afford the title compound as a colorless solid.

Example 6 was also prepared using the following procedure:

[00273] CDI (1.27 g, 7.83mmol) and DIPEA (2.05 mL, 11.75 mmol) were added to a stirred solution of 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) (1.20 g, 3.92 mmol) in DMA (12 mL) and the solution was heated at 50 °C overnight. 4-Methylpiperidine-4-carbonitrile hydrochloride (1.26 g, 7.83 mmol) and additional DIPEA (2.05 mL, 11.75 mmol) were added and the solution was stirred at 50 °C for 30 mins. The resulting mixture was cooled to room temperature before being diluted with EtOAc (150 mL), washed with 90% aqueous brine (100 mL), 50% aqueous brine (3 x 100 mL) dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica eluting with a gradient of 1 to 3% MeOH in DCM afforded a yellow solid. Addition of MeOH (15 mL) afforded a white solid which was collected by filtration, washed with MeOH (2 mL), Et_2O (20 mL) and dried to afford the title compound as a colorless solid.

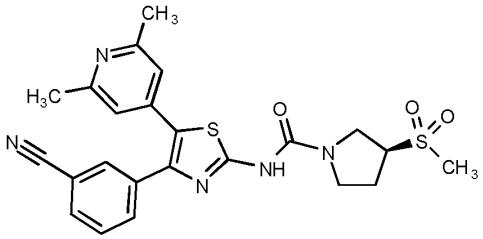
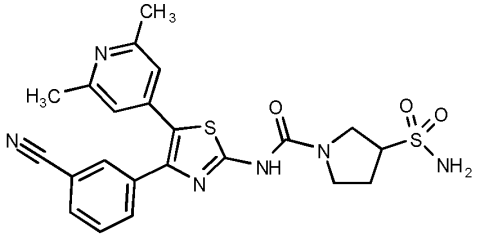
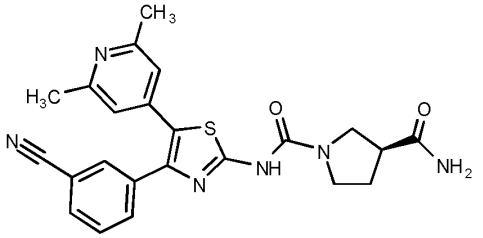
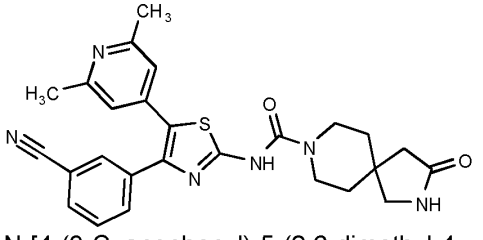
LC-MS (Method 8B): Rt 3.24 mins; MS m/z 457.2 = [M+H]+

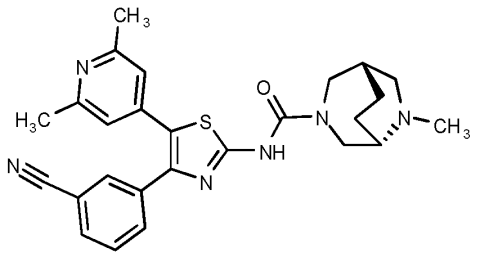
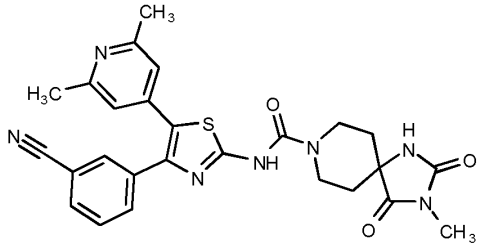
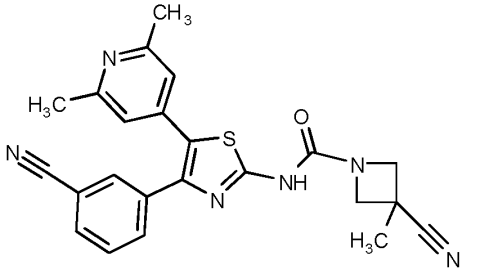
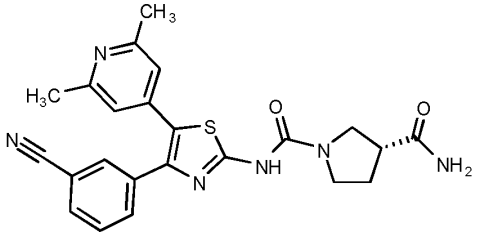
1H NMR (500 MHz, DMSO-d6) δ 11.31 (s, 1H), 7.89 (t, J = 1.8 Hz, 1H), 7.82 (dt, J = 7.7, 1.4 Hz, 1H), 7.70 (dt, J = 8.0, 1.5 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 6.93 (s, 2H), 4.22 (d, J = 14.0 Hz, 2H), 3.03 (t, J = 12.6 Hz, 2H), 2.36 (s, 6H), 1.92 (d, J = 13.4 Hz, 2H), 1.53 (td, J = 13.2, 4.0 Hz, 2H), 1.37 (s, 3H).

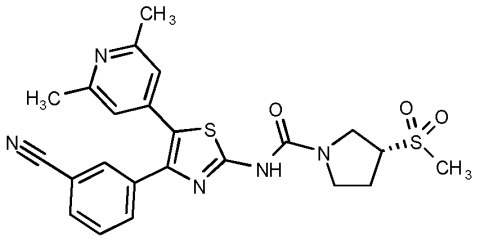
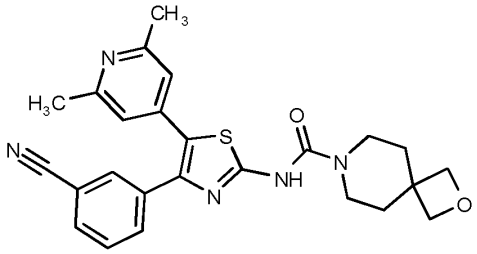
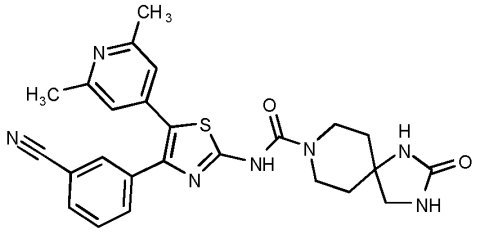
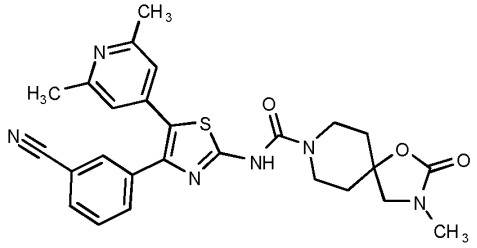
[00274] The compounds of the following tabulated Examples (Table Ex6) were prepared analogously to Example 6 from either 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-

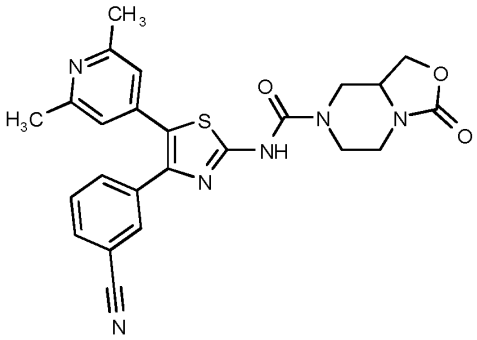
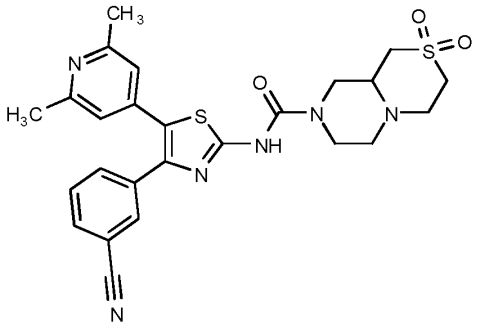
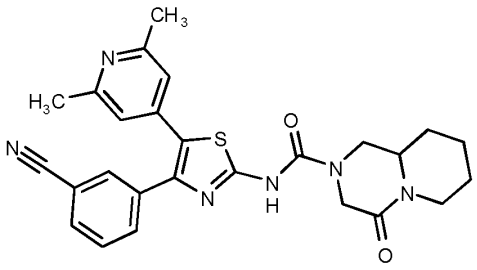
4-yl]benzonitrile (Intermediate C) or the appropriate starting Intermediate and the appropriate amine.

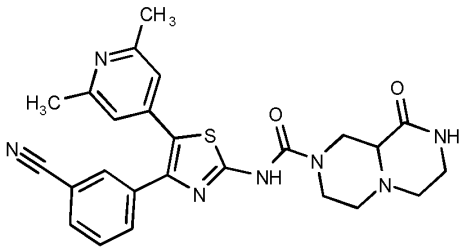
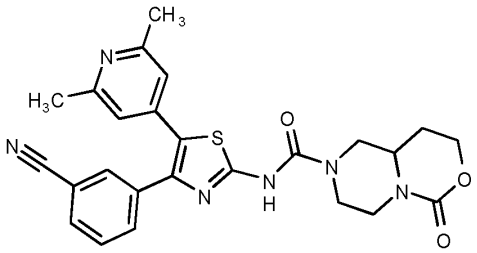
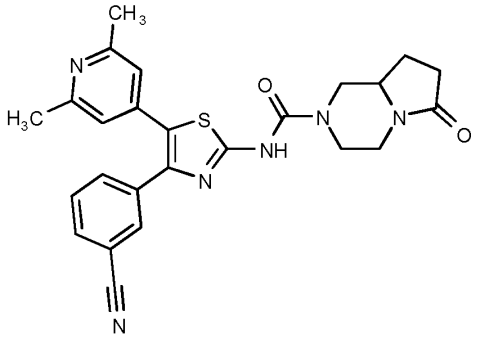
Table Ex6

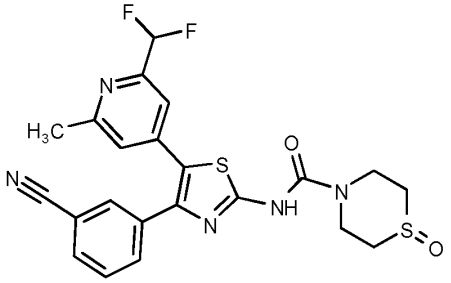
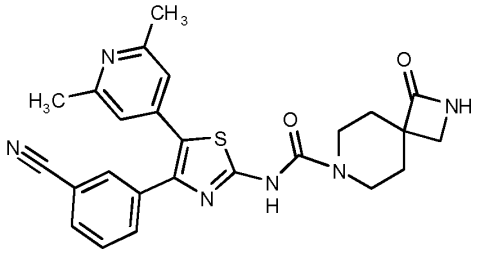
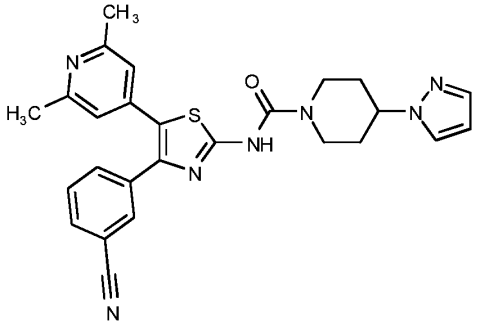
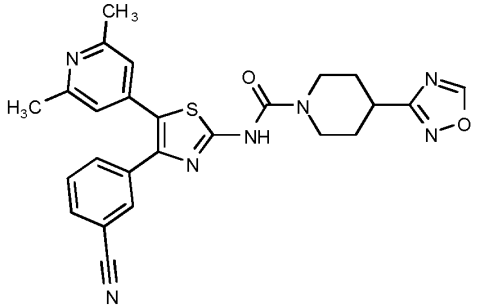
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.1	 (3S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methylsulfonyl-pyrrolidine-1-carboxamide	LC-MS (Method 8B): Rt 3.69 mins; MS m/z 482.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.20 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.07 – 3.97 (m, 1H), 3.93 – 3.84 (m, 1H), 3.84 – 3.76 (m, 1H), 3.66 – 3.60 (m, 1H), 3.60 – 3.50 (m, 1H), 3.07 (s, 3H), 2.40 – 2.28 (m, 8H).
6.2	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-sulfamoyl-pyrrolidine-1-carboxamide	LC-MS (Method 8B): Rt 3.57 mins; MS m/z 483.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.17 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 7.09 (s, 2H), 6.93 (s, 2H), 3.85 – 3.74 (m, 3H), 3.67 – 3.60 (m, 1H), 3.57 – 3.50 (m, 1H), 2.36 (s, 6H), 2.33 – 2.25 (m, 2H).
6.3	 (3S)-N1-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1,3-dicarboxamide	LC-MS (Method 8B): Rt 3.51 mins; MS m/z 447.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.05 (s, 1H), 7.89 (s, 1H), 7.81 (d,J= 7.8 Hz, 1H), 7.71 (d,J= 7.8 Hz, 1H), 7.56 (t,J= 7.8 Hz, 1H), 7.49 (s, 1H), 6.99 (s, 1H), 6.92 (s, 2H), 3.64 – 3.49 (m, 3H), 3.00 – 2.91 (m, 1H), 2.36 (s, 6H), 2.13 – 1.92 (m, 3H).
6.4	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-2,8-diazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 3.84 mins; MS m/z 487.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.24 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.6 Hz, 1H), 7.70 (d, J= 8.0 Hz, 1H), 7.60 – 7.51 (m, 2H), 6.92 (s, 2H), 3.66 – 3.59 (m, 2H), 3.45 – 3.40 (m, 2H), 3.07 (s, 2H), 2.36 (s, 6H), 2.11 (s, 2H), 1.54 (t, J= 5.7 Hz, 4H).

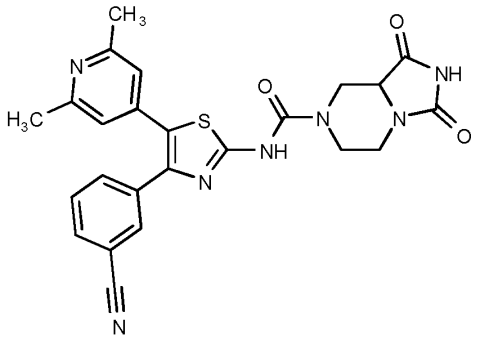
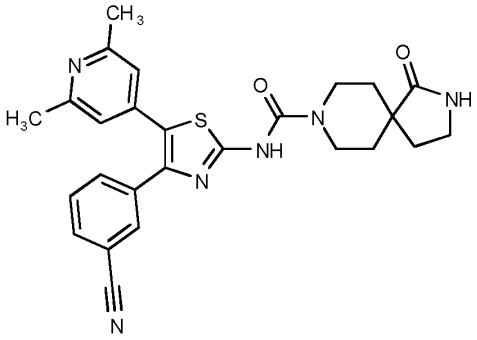
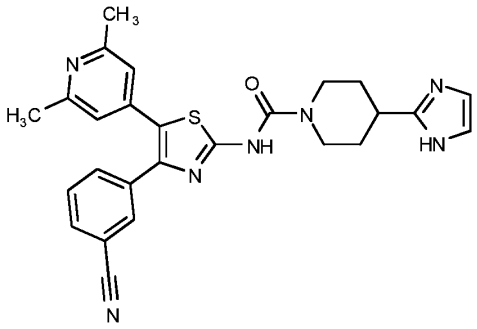
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.5	 (1S,5S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-methyl-3,6-diazabicyclo[3.2.2]nonane-3-carboxamide	LC-MS (Method 7A): Rt 1.00 mins; MS m/z 473.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 7.89 (t, J = 1.7 Hz, 1H), 7.81 (dt, J = 7.7, 1.4 Hz, 1H), 7.70 (dt, J = 7.9, 1.4 Hz, 1H), 7.56 (dd, J = 7.8, 7.8 Hz, 1H), 6.92 (s, 2H), 4.13 (dd, J = 13.9, 6.1 Hz, 1H), 3.99 – 3.92 (m, 1H), 3.43 – 3.37 (m, 2H), 2.84 (t, J = 5.3 Hz, 1H), 2.75 – 2.68 (m, 2H), 2.36 (s, 6H), 2.31 (s, 3H), 2.14 – 2.10 (m, 1H), 1.91 – 1.85 (m, 1H), 1.58 – 1.48 (m, 3H). NH proton not observed
6.6	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 3.37 mins; MS m/z 516.3 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.93 (s, 1H), 7.76 – 7.68 (m, 2H), 7.51 (t, J= 7.9 Hz, 1H), 7.02 (s, 2H), 4.13 (dt, J= 14.0, 4.9 Hz, 2H), 3.51 (ddd, J= 13.7, 9.9, 3.3 Hz, 2H), 2.99 (s, 3H), 2.45 (s, 6H), 2.04 (ddd, J= 13.9, 9.9, 4.2 Hz, 2H), 1.76 (dt, J= 13.9, 4.3 Hz, 2H). 2 x NH protons not observed.
6.7	 3-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-azetidine-1-carboxamide	LC-MS (Method 8B): Rt 3.54 mins; MS m/z 429.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.54 (s, 1H), 7.87 (s, 1H), 7.82 (d,J= 7.8 Hz, 1H), 7.70 (d,J= 7.8 Hz, 1H), 7.56 (t,J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.34 (d,J= 8.8 Hz, 2H), 4.01 (d,J= 8.8 Hz, 2H), 2.36 (s, 6H), 1.63 (s, 3H).
6.8	 (3R)-N1-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1,3-dicarboxamide	LC-MS (Method 8B): Rt 3.51 mins; MS m/z 447.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.05 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 7.49 (s, 1H), 6.99 (s, 1H), 6.93 (s, 2H), 3.64 – 3.52 (m, 3H), 2.99 – 2.92 (m, 1H), 2.36 (s, 6H), 2.14 – 1.92 (m, 3H).

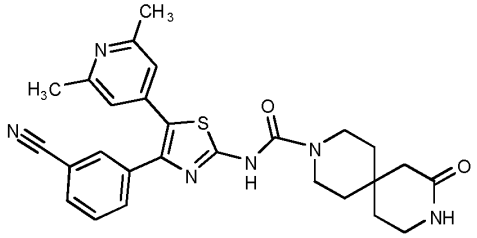
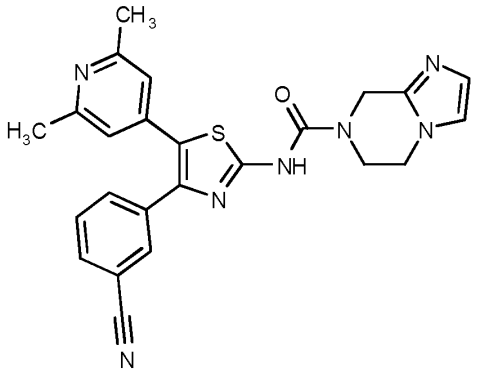
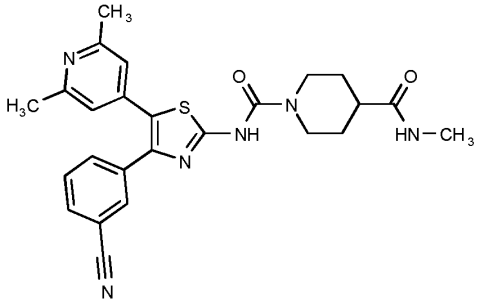
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.9	 (3R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methylsulfonyl-pyrrolidine-1-carboxamide	LC-MS (Method 8B): Rt 3.70 mins; MS m/z 482.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.20 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.06 – 3.98 (m, 1H), 3.93 – 3.85 (m, 1H), 3.85 – 3.76 (m, 1H), 3.67 – 3.60 (m, 1H), 3.60 – 3.51 (m, 1H), 3.07 (s, 3H), 2.41 – 2.26 (m, 8H).
6.10	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-7-azaspiro[3.5]nonane-7-carboxamide	LC-MS (Method 8B): Rt 4.15 mins; MS m/z 460.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.26 (s, 1H), 7.89 (s, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 7.9 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.34 (s, 4H), 3.46 (t, J= 5.6 Hz, 4H), 2.36 (s, 6H), 1.79 (t, J= 5.6 Hz, 4H).
6.11	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 3.63 mins; MS m/z 488.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.28 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 8.0 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 6.78 (s, 1H), 6.22 (s, 1H), 3.65 – 3.51 (m, 4H), 3.14 (s, 2H), 2.36 (s, 6H), 1.66 – 1.53 (m, 4H).
6.12	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 3.93 mins; MS m/z 503.3 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.93 (s, 1H), 7.76 – 7.68 (m, 2H), 7.51 (t, J = 7.8 Hz, 1H), 7.03 (s, 2H), 4.04 – 3.96 (m, 2H), 3.55 – 3.45 (m, 2H), 3.45 (s, 2H), 2.90 (s, 3H), 2.46 (s, 6H), 2.03 – 1.96 (m, 2H), 1.94 – 1.84 (m, 2H). NH proton not observed.

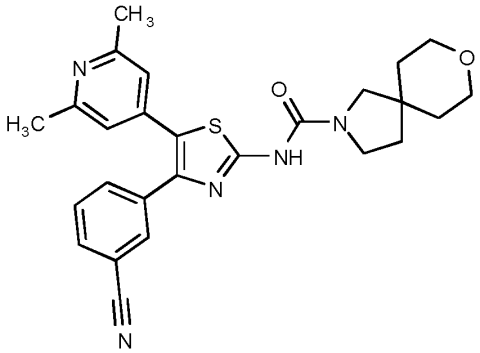
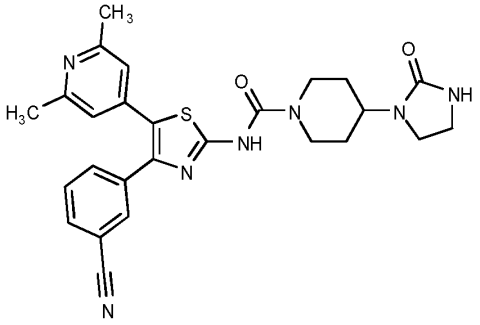
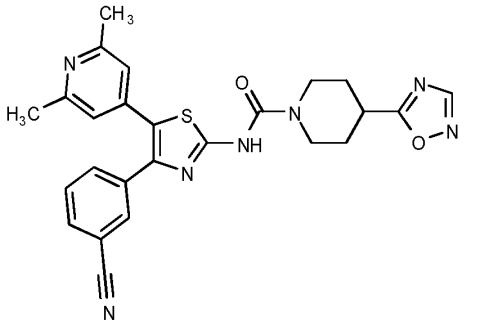
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.13	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-5,6,8,8a-tetrahydro-1H-oxazolo[3,4-a]pyrazine-7-carboxamide	LC-MS (Method 8B): Rt 3.69 mins; MS m/z 475.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.40 (s, 1H), 7.89 (d, J= 1.8 Hz, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 8.0 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.41 (t, J= 8.5 Hz, 1H), 4.36 (d, J= 13.3 Hz, 1H), 4.24 (d, J= 13.3 Hz, 1H), 4.00 (dd, J= 8.9, 5.6 Hz, 1H), 3.89 – 3.83 (m, 1H), 3.62 (dd, J= 13.5, 3.4 Hz, 1H), 3.08 – 2.99 (m, 1H), 2.89 (dt, J= 25.1, 12.7 Hz, 2H), 2.37 (s, 6H).
6.14	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,2-dioxo-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]thiazine-8-carboxamide	LC-MS (Method 8B): Rt 3.58 mins; MS m/z 523.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.31 (s, 1H), 7.89 (s, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 8.2 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.11 (dd, J= 21.0, 13.4 Hz, 2H), 3.24 (td, J= 13.3, 4.0 Hz, 1H), 3.19 – 3.11 (m, 3H), 3.02 (dt, J= 24.7, 12.7 Hz, 2H), 2.90 (d, J= 11.7 Hz, 1H), 2.83 – 2.74 (m, 1H), 2.69 – 2.61 (m, 2H), 2.37 (s, 6H), 2.22 (td, J= 11.6, 2.9 Hz, 1H).
6.15	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-oxo-3,6,7,8,9,9a-hexahydro-1H-pyrido[1,2-a]pyrazine-2-carboxamide	LC-MS (Method 8B): Rt 3.95 mins; MS m/z 487.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.47 (s, 1H), 7.89 (s, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 6.93 (s, 2H), 4.46 (d, J = 12.9 Hz, 1H), 4.27 (d, J = 17.4 Hz, 1H), 4.09 (d, J = 12.1 Hz, 1H), 4.03 (d, J = 17.4 Hz, 1H), 3.48 – 3.38 (m, 3H), 2.36 (s, 6H), 1.78 (d, J = 13.0 Hz, 1H), 1.72 (d, J = 13.0 Hz, 1H), 1.65 (d, J = 13.0 Hz, 1H), 1.45 (dd, J = 15.1, 11.2 Hz, 1H), 1.30 – 1.14 (m, 2H).

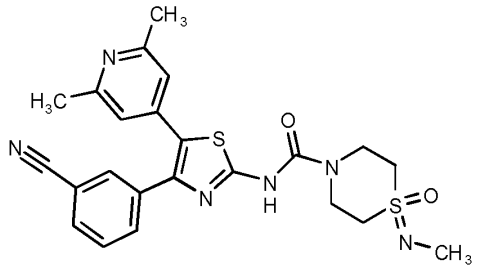
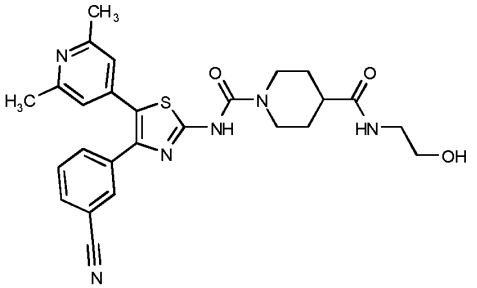
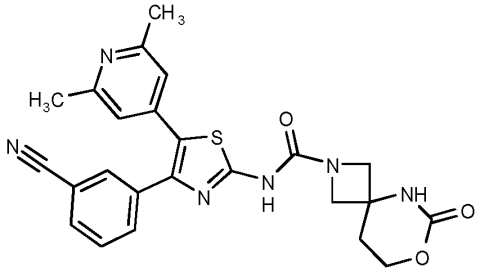
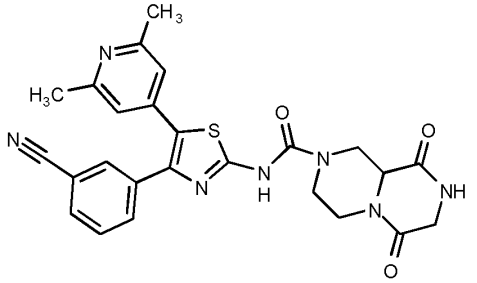
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.16	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-9-oxo-3,4,6,7,8,9a-hexahydro-1H-pyrazino[1,2-a]pyrazine-2-carboxamide	LC-MS (Method 8B): Rt 3.39 mins; MS m/z 488.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.41 (s, 1H), 7.90 (d, J= 1.8 Hz, 1H), 7.85 – 7.80 (m, 2H), 7.71 (d, J= 8.0 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.56 (d, J= 13.1 Hz, 1H), 4.16 (d, J= 13.0 Hz, 1H), 3.31 – 3.24 (m, 1H), 3.08 (d, J= 11.7 Hz, 1H), 2.99 (t, J= 12.2 Hz, 1H), 2.90 (d, J= 11.2 Hz, 2H), 2.73 (t, J= 12.1 Hz, 1H), 2.58 (d, J= 10.6 Hz, 1H), 2.45 – 2.39 (m, 1H), 2.37 (s, 6H), 2.22 – 2.14 (m, 1H).
6.17	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-1,3,4,8,9,9a-hexahydropyrazino[1,2-c][1,3]oxazine-2-carboxamide	LC-MS (Method 8B): Rt 3.64 mins; MS m/z 489.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.36 (s, 1H), 7.88 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.70 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.92 (s, 2H), 4.29 – 4.08 (m, 5H), 3.52 – 3.45 (m, 1H), 2.96 – 2.82 (m, 2H), 2.75 (t, J= 11.9 Hz, 1H), 2.36 (s, 6H), 2.14 – 2.07 (m, 1H), 1.76 – 1.68 (m, 1H).
6.18	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-1,3,4,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-2-carboxamide	LC-MS (Method 8B): Rt 3.65 mins; MS m/z 473.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.39 (s, 1H), 7.90 (s, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 7.9 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.38 (d, J= 12.2 Hz, 1H), 4.27 (d, J= 9.3 Hz, 1H), 3.89 – 3.81 (m, 1H), 3.55 (dtd, J= 11.1, 7.1, 3.6 Hz, 1H), 2.78 (d, J= 9.2 Hz, 2H), 2.67 (d, J= 12.1 Hz, 1H), 2.37 (s, 6H), 2.34 – 2.20 (m, 2H), 2.13 (qd, J= 12.2, 10.1, 4.2 Hz, 1H), 1.63 – 1.52 (m, 1H).

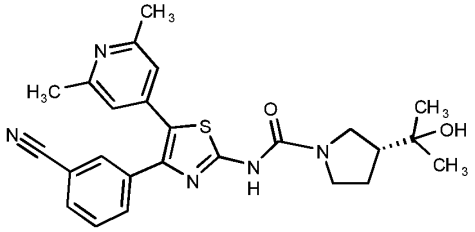
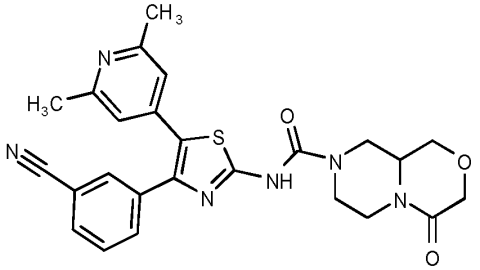
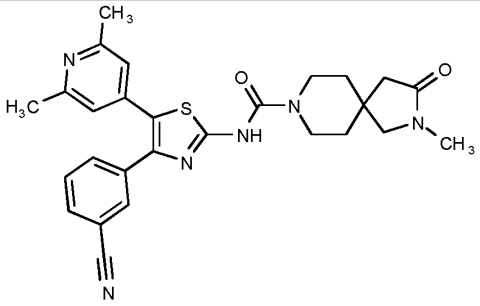
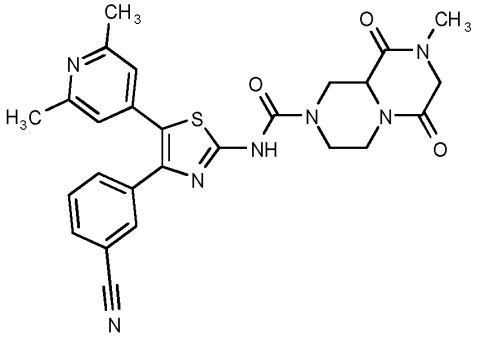
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.19	 N-[4-(3-Cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide (Prepared from Intermediate G)	LC-MS (Method 8B): Rt 2.93 mins; MS m/z 488.1 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.89 (s, 1H), 7.72 (d, J = 7.8 Hz, 2H), 7.52 (t, J = 7.9 Hz, 1H), 7.31 (s, 1H), 7.27 (s, 1H), 6.59 (t, J = 55.3 Hz, 1H), 4.23 (d, J = 14.7 Hz, 2H), 4.02 – 3.95 (m, 2H), 3.02 (t, J = 12.9 Hz, 2H), 2.88 (d, J = 14.0 Hz, 2H), 2.51 (s, 3H).
6.20	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-2,7-diazaspiro[3.5]nonane-7-carboxamide	LC-MS (Method 8B): Rt 3.70 mins; MS m/z 473.2 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.91 (s, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.01 (s, 2H), 3.97 – 3.89 (m, 2H), 3.56 – 3.47 (m, 2H), 3.24 (s, 2H), 2.44 (s, 6H), 2.01 – 1.93 (m, 2H), 1.92 – 1.84 (m, 2H). 2 x NH protons not observed.
6.21	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-pyrazol-1-yl-piperidine-1-carboxamide	LC-MS (Method 8B): Rt 4.07 mins; MS m/z 484.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.34 (s, 1H), 7.90 (t, J = 1.7 Hz, 1H), 7.85 – 7.79 (m, 2H), 7.72 (dt, J = 8.1, 1.4 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.45 (d, J = 1.8 Hz, 1H), 6.94 (s, 2H), 6.25 (t, J = 2.0 Hz, 1H), 4.46 (td, J = 11.3, 5.5 Hz, 1H), 4.32 (d, J = 13.6 Hz, 2H), 3.07 (t, J = 13.0 Hz, 2H), 2.37 (s, 6H), 2.04 (d, J = 11.8 Hz, 2H), 1.86 (qd, J = 12.2, 3.9 Hz, 2H).
6.22	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(1,2,4-oxadiazol-3-yl)piperidine-1-carboxamide	LC-MS (Method 8B): Rt 4.22 mins; MS m/z 486.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.30 (s, 1H), 9.54 (s, 1H), 7.90 (s, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 4.21 (d, J = 13.5 Hz, 2H), 3.19 (s, 1H), 3.13 (t, J = 12.4 Hz, 2H), 2.37 (s, 6H), 2.01 (d, J = 13.1 Hz, 2H), 1.71 – 1.60 (m, 2H).

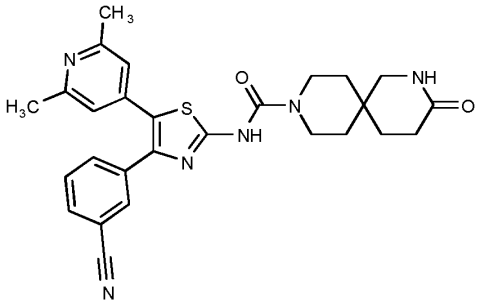
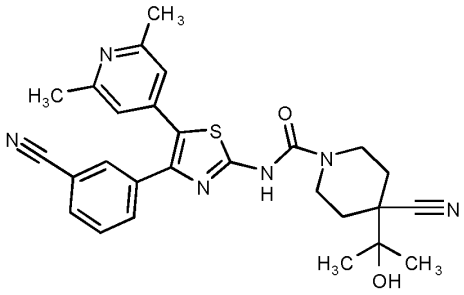
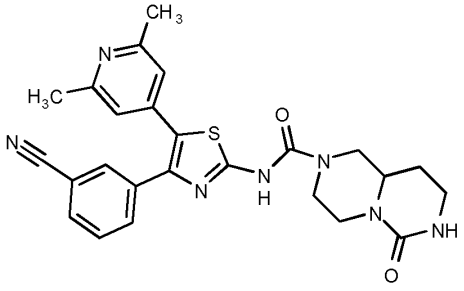
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.23	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3-dioxo-5,6,8,8a-tetrahydroimidazo[1,5-a]pyrazine-7-carboxamide	LC-MS (Method 8B): Rt 2.96 mins; MS m/z 488.1 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.58 (s, 1H), 11.03 (s, 1H), 7.90 (s, 1H), 7.84 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 7.9 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.50 (d, J= 13.0 Hz, 1H), 4.23 (d, J= 10.8 Hz, 1H), 4.17 (dd, J= 11.3, 4.6 Hz, 1H), 3.87 (d, J= 10.0 Hz, 1H), 3.06 (t, J= 12.2 Hz, 1H), 2.96 (q, J= 11.9, 10.4 Hz, 2H), 2.37 (s, 6H).
6.24	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-2,8-diazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 3.69 mins; MS m/z 487.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.25 (s, 1H), 7.90 (s, 1H), 7.83 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 8.0 Hz, 1H), 7.63 (s, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.09 (d, J= 13.5 Hz, 2H), 3.20 (t, J= 6.8 Hz, 2H), 3.10 (t, J= 12.5 Hz, 2H), 2.37 (s, 6H), 2.01 (t, J= 6.8 Hz, 2H), 1.60 (td, J= 12.7, 12.1, 4.1 Hz, 2H), 1.41 (d,J = 13.6 Hz, 2H).
6.25	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(1H-imidazol-2-yl)piperidine-1-carboxamide	LC-MS (Method 8B): Rt 3.66 mins; MS m/z 484.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.71 (s, 1H), 11.28 (s, 1H), 7.90 (d, J= 2.0 Hz, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.72 (d, J= 7.9 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.99 (s, 1H), 6.94 (s, 2H), 6.77 (s, 1H), 4.22 (d, J= 13.4 Hz, 2H), 3.05 (t, J= 12.5 Hz, 2H), 2.95 (s, 1H), 2.37 (s, 6H), 1.92 (d, J= 12.6 Hz, 2H), 1.70 – 1.58 (m, 2H).

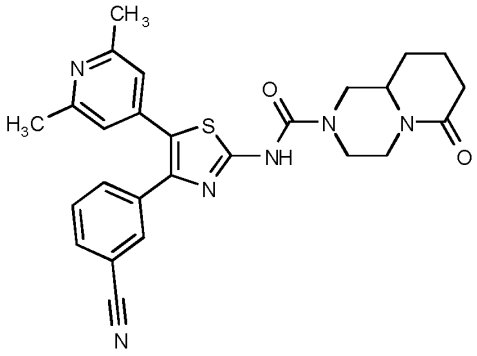
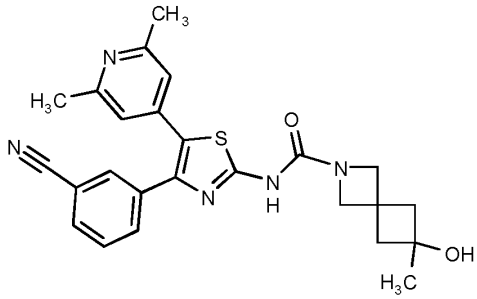
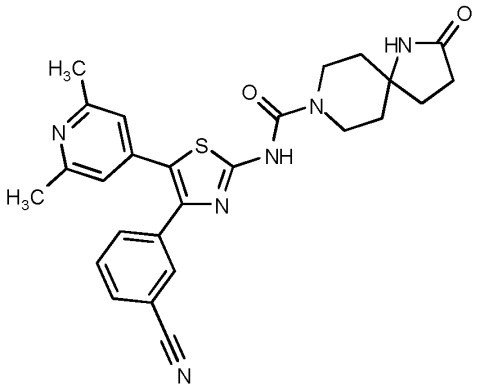
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.26	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-10-oxo-3,9-diazaspiro[5.5]undecane-3-carboxamide	LC-MS (Method 8B): Rt 3.84 mins; MS m/z 501.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.21 (s, 1H), 7.89 (s, 1H), 7.82 (d,J= 7.8 Hz, 1H), 7.70 (d,J= 7.8 Hz, 1H), 7.56 (t,J= 7.8 Hz, 1H), 7.43 (s, 1H), 6.92 (s, 2H), 3.61 – 3.47 (m, 4H), 3.20 – 3.12 (m, 2H), 2.36 (s, 6H), 2.09 (s, 2H), 1.67 – 1.59 (m, 2H), 1.47 – 1.34 (m, 4H).
6.27	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxamide	LC-MS (Method 8B): Rt 3.04 mins; MS m/z 456.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.62 (s, 1H), 7.90 (s, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.72 (d, J= 8.0 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 7.13 (d, J= 1.3 Hz, 1H), 6.94 (s, 2H), 6.90 (d, J= 1.3 Hz, 1H), 4.77 (s, 2H), 4.07 (t ,J= 5.3 Hz, 2H), 3.99 (t, J= 5.3 Hz, 2H), 2.36 (s, 6H).
6.28	 N1-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-N4-methyl-piperidine-1,4-dicarboxamide	LC-MS (Method 8B): Rt 3.45 mins; MS m/z 475.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.22 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.7 Hz, 1H), 7.78 (d, J= 5.0 Hz, 1H), 7.71 (d, J= 7.9 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.19 (d, J= 13.3 Hz, 2H), 2.89 (t, J= 12.9 Hz, 2H), 2.57 (d, J= 4.5 Hz, 3H), 2.36 (s, 6H), 2.31 (s, 1H), 1.70 (d, J= 12.5 Hz, 2H), 1.54 – 1.42 (m, 2H).

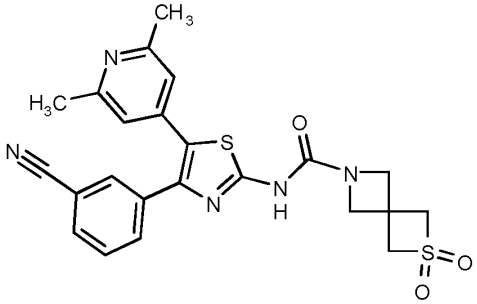
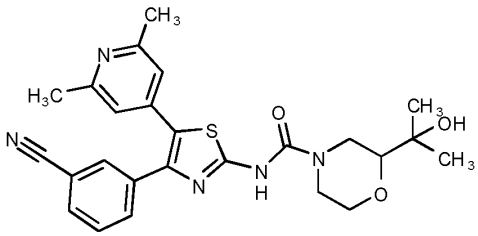
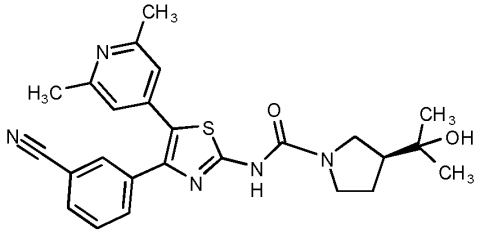
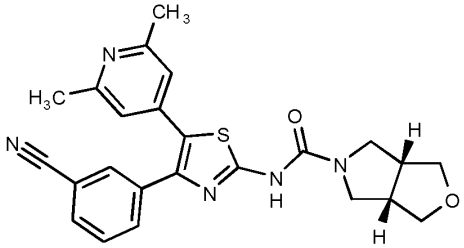
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.29	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide	LC-MS (Method 8B): Rt 4.28 mins; MS m/z 474.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 10.99 (s, 1H), 7.89 (t, J= 1.7 Hz, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 3.68 – 3.58 (m, 2H), 3.57 – 3.45 (m, 4H), 3.44 - 3.31 (m, 2H), 2.36 (s, 6H), 1.81 (s, 2H), 1.55 – 1.44 (m, 4H).
6.30	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-oxoimidazolidin-1-yl)piperidine-1-carboxamide	LC-MS (Method 8B): Rt 3.82 mins; MS m/z 502.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.24 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.70 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 6.29 (s, 1H), 4.30 (d, J= 13.3 Hz, 2H), 3.77 – 3.69 (m, 1H), 3.29 – 3.24 (m, 2H), 3.22 – 3.16 (m, 2H), 2.90 (t, J= 12.8 Hz, 2H), 2.36 (s, 6H), 1.63 – 1.48 (m, 4H).
6.31	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide	LC-MS (Method 5B): Rt 1.57 mins; MS m/z 486.2 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 8.61 (s, 1H), 7.91 (s, 1H), 7.76 – 7.66 (m, 2H), 7.49 (t, J = 7.8 Hz, 1H), 7.01 (s, 2H), 4.24 (d, J = 13.8 Hz, 2H), 3.44 – 3.39 (m, 1H), 3.28 – 3.21 (m, 2H), 2.44 (s, 6H), 2.24 – 2.15 (m, 2H), 1.93 – 1.83 (m, 2H). NH proton not observed

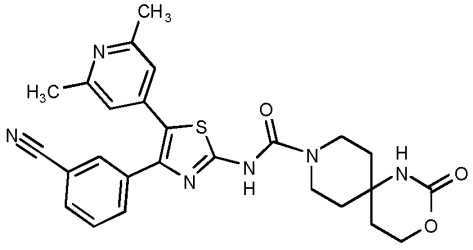
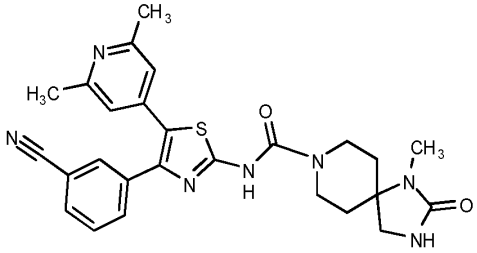
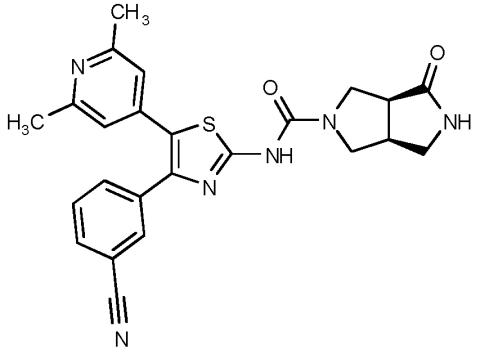
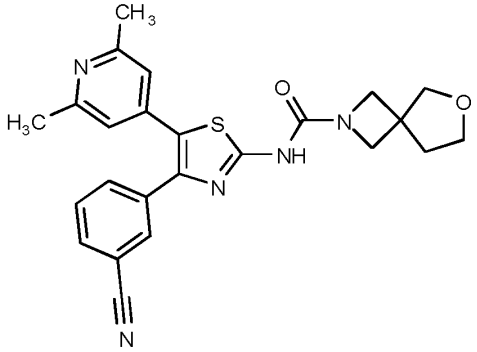
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.32	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-methylimino-1-oxo-1,4-thiazinane-4-carboxamide (Prepared from Intermediate S)	LC-MS (Method 8B): Rt 3.09 mins; MS m/z 481.1 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.55 (s, 1H), 7.89 (s, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 6.93 (s, 2H), 4.14 (d, J = 14.8 Hz, 2H), 3.67 – 3.59 (m, 2H), 3.27 – 3.21 (m, 2H), 3.16 – 3.08 (m, 2H), 2.66 (s, 3H), 2.36 (s, 6H).
6.33	 N1-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-N4-(2-hydroxyethyl)piperidine-1,4-dicarboxamide	LC-MS (Method 8B): Rt 3.55 mins; MS m/z 505.2 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.93 (t, J= 1.7 Hz, 1H), 7.72 (ddt, J= 13.4, 7.8, 1.5 Hz, 2H), 7.51 (t, J= 7.8 Hz, 1H), 7.02 (s, 2H), 4.29 (d, J= 13.4 Hz, 2H), 3.62 (t, J= 5.8 Hz, 2H), 3.02 (t, J= 12.7 Hz, 2H), 2.56 – 2.48 (m, 1H), 2.45 (s, 6H), 1.89 (d ,J= 12.1 Hz, 2H), 1.71 (qd, J= 12.3, 4.1 Hz, 2H). 2 x NH, 1 x OH and 1 x CH_2 signal not observed.
6.34	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-7-oxa-2,5-diazaspiro[3.5]nonane-2-carboxamide	LC-MS (Method 8B): Rt 3.44 mins; MS m/z 475.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.46 (s, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 7.82 (d,J= 7.8 Hz, 1H), 7.70 (d,J= 7.8 Hz, 1H), 7.56 (t,J= 7.8 Hz, 1H), 6.92 (s, 2H), 4.16 (t,J= 5.3 Hz, 2H), 4.08 – 3.94 (m, 4H), 2.36 (s, 6H), 2.13 (t,J= 5.3 Hz, 2H).
6.35	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6,9-dioxo-1,3,4,7,8,9a-hexahydropyrazino[1,2-a]pyrazine-2-carboxamide	LC-MS (Method 8B): Rt 2.72 mins; MS m/z 502.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.59 (s, 1H), 8.30 (s, 1H), 7.90 (s, 1H), 7.83 (d, J= 7.8 Hz, 1H), 7.72 (d, J= 7.8 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.60 (d, J= 13.3 Hz, 1H), 4.31 (d, J= 13.3 Hz, 1H), 4.25 (d, J= 13.3 Hz, 1H), 4.08 (d, J= 10.3 Hz, 1H), 3.94 – 3.81 (m, 2H), 3.04 – 2.90 (m, 2H), 2.74 (t, J= 12.6 Hz, 1H), 2.37 (s, 6H).

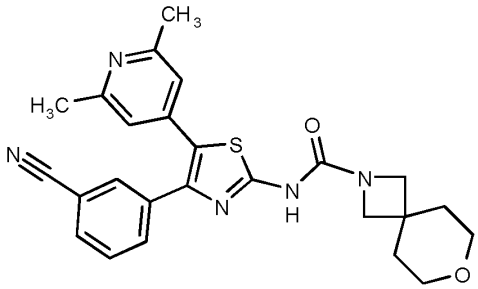
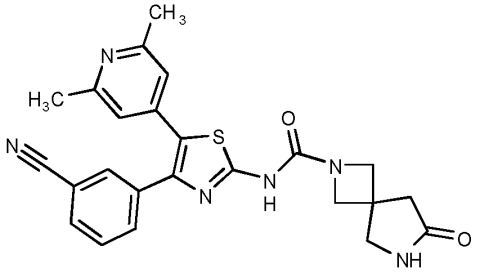
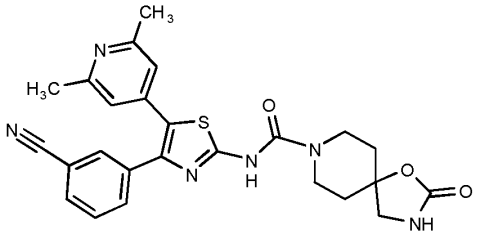
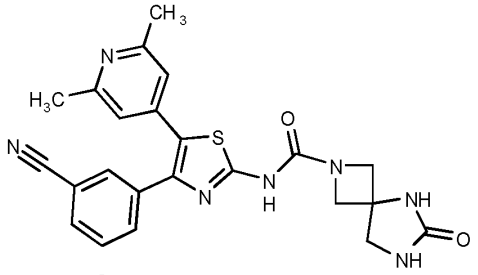
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.36	 (3R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide	LC-MS (Method 8B): Rt 4.10 mins; MS m/z 462.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 10.88 (s, 1H), 7.89 (s, 1H), 7.81 (d,J= 7.8 Hz, 1H), 7.71 (d,J= 7.8 Hz, 1H), 7.55 (t,J= 7.8 Hz, 1H), 6.92 (s, 2H), 4.38 (s, 1H), 3.68 – 3.49 (m, 3H), 2.36 (s, 6H), 2.26 – 2.15 (m, 1H), 1.90 – 1.73 (m, 2H), 1.11 (s, 6H). 1 x CH proton not observed.
6.37	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-oxo-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carboxamide	LC-MS (Method 8B): Rt 3.02 mins; MS m/z 489.1 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.37 (s, 1H), 7.89 (s, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 6.93 (s, 2H), 4.38 (d, J = 13.1 Hz, 1H), 4.29 – 4.18 (m, 2H), 4.07 (s, 2H), 4.04 – 3.97 (m, 1H), 3.63 – 3.54 (m, 2H), 2.90 (t, J = 12.3 Hz, 1H), 2.84 – 2.77 (m, 1H), 2.74 (td, J = 12.6, 2.6 Hz, 1H), 2.36 (s, 6H).
6.38	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-3-oxo-2,8-diazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 3.80 mins; MS m/z 501.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.24 (s, 1H), 7.90 (s, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 8.0 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 3.65 – 3.57 (m, 2H), 3.51 – 3.43 (m, 2H), 3.20 (s, 2H), 2.72 (s, 3H), 2.36 (s, 6H), 2.21 (s, 2H), 1.60 – 1.50 (m, 4H).
6.39	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-8-methyl-6,9-dioxo-3,4,7,9a-tetrahydro-1H-pyrazino[1,2-a]pyrazine-2-carboxamide	LC-MS (Method 8B): Rt 2.32 mins; MS m/z 516.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.58 (s, 1H), 7.90 (s, 1H), 7.84 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 4.63 (d, J = 13.4 Hz, 1H), 4.33 (d, J = 13.0 Hz, 1H), 4.26 (d, J = 13.5 Hz, 1H), 4.10 (d, J = 11.1 Hz, 1H), 4.07 – 3.96 (m, 2H), 3.02 – 2.87 (m, 2H), 2.86 (s, 3H), 2.74 (dd, J = 14.3, 11.1 Hz, 1H), 2.37 (s, 6H).

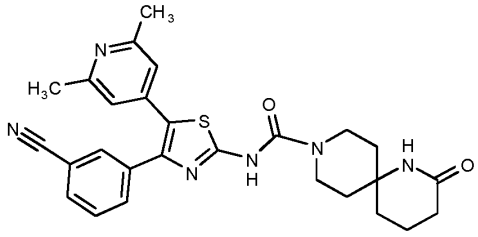
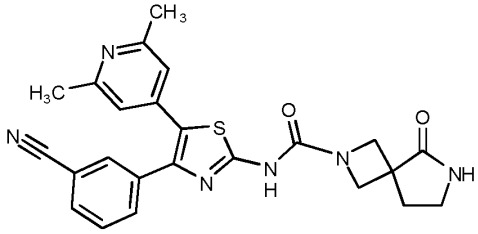
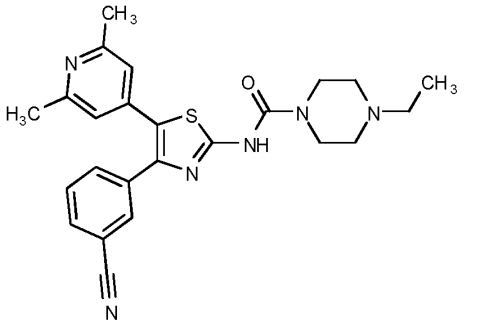
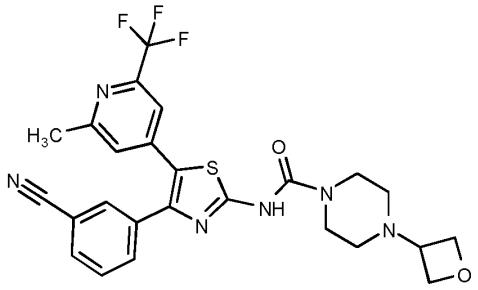
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.40	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-2,9-diazaspiro[5.5]undecane-9-carboxamide	LC-MS (Method 8B): Rt 3.94 mins; MS m/z 501.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.22 (s, 1H), 7.90 (s, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 7.9 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 7.42 (s, 1H), 6.94 (s, 2H), 3.60 – 3.48 (m, 4H), 3.00 (d, J= 2.6 Hz, 2H), 2.37 (s, 6H), 2.16 (t,J= 7.0 Hz, 2H), 1.67 (t, J= 7.0 Hz, 2H), 1.45 (t, J= 5.9 Hz, 4H).
6.41	 4-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(1-hydroxy-1-methyl-ethyl)piperidine-1-carboxamide	LC-MS (Method 8B): Rt 4.10 mins; MS m/z 501.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.34 (s, 1H), 7.89 (s, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.92 (s, 2H), 5.12 (s, 1H), 4.38 (d, J = 13.4 Hz, 2H), 2.94 (t, J = 13.4 Hz, 2H), 2.36 (s, 6H), 1.88 (d, J = 13.4 Hz, 2H), 1.63 (td, J = 13.4, 4.1 Hz, 2H), 1.23 (s, 6H).
6.42	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-3,4,7,8,9,9a-hexahydro-1H-pyrazino[1,2-c]pyrimidine-2-carboxamide	LC-MS (Method 8B): Rt 3.21 mins; MS m/z 488.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.31 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 6.46 (s, 1H), 4.27 – 4.12 (m, 3H), 3.28 – 3.23 (m, 1H), 3.17 – 3.07 (m, 2H), 2.83 (t, J= 12.6 Hz, 1H), 2.69-2.56 (m, 2H), 2.36 (s, 6H), 1.97 – 1.92 (m, 1H), 1.64 – 1.55 (m, 1H).

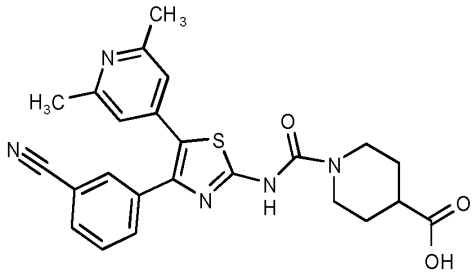
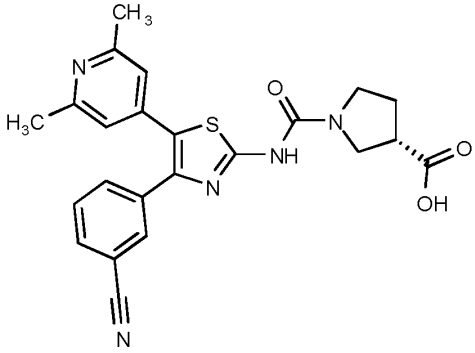
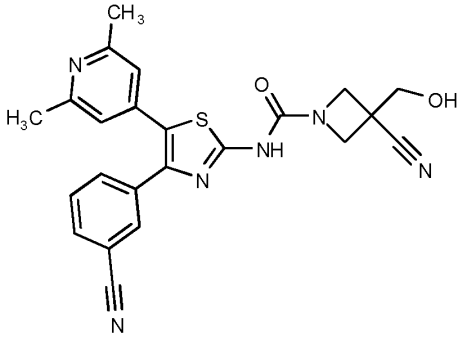
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.43	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-3,4,7,8,9,9a-hexahydro-1H-pyrido[1,2-a]pyrazine-2-carboxamide	LC-MS (Method 8B): Rt 3.96 mins; MS m/z 487.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.35 (s, 1H), 7.90 (s, 1H), 7.83 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 7.8 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.45 (d, J= 13.1 Hz, 1H), 4.23 (d, J= 13.1 Hz, 2H), 2.87 – 2.81 (m, 1H), 2.74 – 2.68 (m, 1H), 2.64 – 2.57 (m, 2H), 2.37 (s, 6H), 2.29 – 2.22 (m, 2H), 2.00 – 1.93 (m, 1H), 1.82 – 1.74 (m, 1H), 1.69 – 1.59 (m, 1H), 1.49 – 1.39 (m, 1H).
6.44	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-hydroxy-6-methyl-2-azaspiro[3.3]heptane-2-carboxamide	LC-MS (Method 8B): Rt 3.98 mins; MS m/z 460.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.25 (s, 1H), 7.87 (s, 1H), 7.81 (d, J= 7.8 Hz, 1H), 7.69 (d, J= 7.8 Hz, 1H), 7.55 (t, J= 7.8 Hz, 1H), 6.92 (s, 2H), 4.91 (s, 1H), 4.10 – 3.91 (m, 4H), 2.35 (s, 6H), 2.18 (s, 4H), 1.16 (s, 3H).
6.45	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-1,8-diazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 3.85 mins; MS m/z 487.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.27 (s, 1H), 8.05 (s, 1H), 7.89 (d, J = 1.9 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 3.67 (dt, J = 12.3, 5.8 Hz, 2H), 3.53 – 3.45 (m, 2H), 2.36 (s, 6H), 2.22 (t, J = 7.9 Hz, 2H), 1.88 (t, J = 8.0 Hz, 2H), 1.63 – 1.53 (m, 4H).

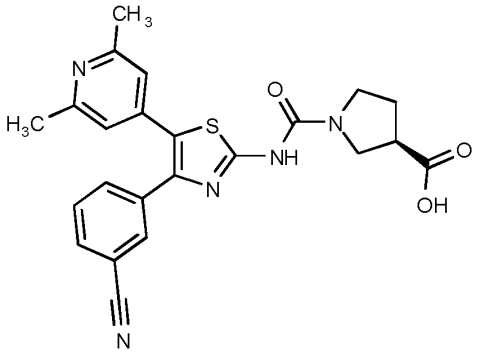
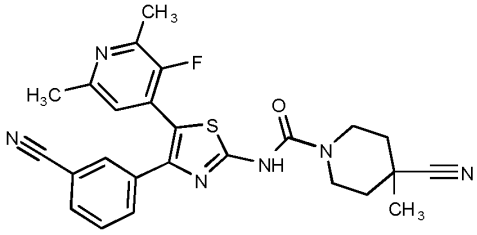
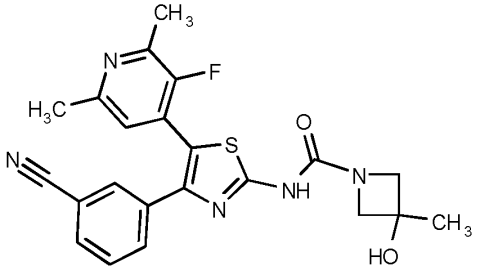
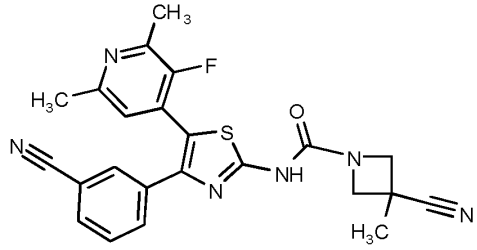
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.46	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,2-dioxo-2λ^{6}-thia-6-azaspiro[3.3]heptane-6-carboxamide	LC-MS (Method 8B): Rt 3.69 mins; MS m/z 480.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.48 (s, 1H), 7.87 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.70 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.92 (s, 2H), 4.47 (s, 4H), 4.27 (s, 4H), 2.36 (s, 6H).
6.47	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)morpholine-4-carboxamide	LC-MS (Method 8B): Rt 3.63 mins; MS m/z 478.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.34 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.51 (s, 1H), 4.25 (d, J= 13.1 Hz, 1H), 4.05 (d, J= 13.1 Hz, 1H), 3.92 (d, J= 11.5 Hz, 1H), 3.44 (t, J= 11.5 Hz, 1H), 3.10 (d, J= 10.7 Hz, 1H), 2.93 (t, J= 12.2 Hz, 1H), 2.77 (t, J= 12.2 Hz, 1H), 2.36 (s, 6H), 1.13 (s, 3H), 1.09 (s, 3H).
6.48	 (3S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide	LC-MS (Method 15B): Rt 6.86 mins; MS m/z 462.4 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 10.96 (s, 1H), 7.89 (s, 1H), 7.81 (d, J= 7.8 Hz, 1H), 7.70 (d, J= 7.8 Hz, 1H), 7.55 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.39 (s, 1H), 3.74– 3.47 (m, 3H), 3.33 – 3.21 (m, 1H),2.36 (s, 6H), 2.26 – 2.15 (m, 1H), 1.92 – 1.72 (m, 2H), 1.11 (s, 6H).
6.49	 (3aR,6aS)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrole-5-carboxamide	LC-MS (Method 8B): Rt 4.04 mins; MS m/z 446.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.06 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.92 (s, 2H), 3.82 – 3.76 (m, 2H), 3.67 – 3.61 (m, 2H), 3.55 – 3.51 (m, 2H), 3.43 – 3.39 (m, 2H), 2.98 – 2.92 (m, 2H), 2.36 (s, 6H).

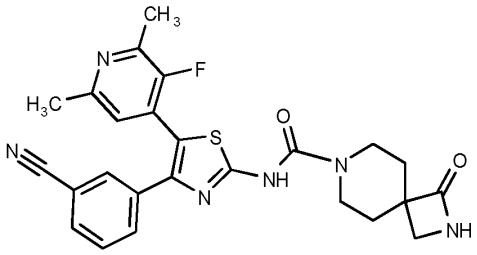
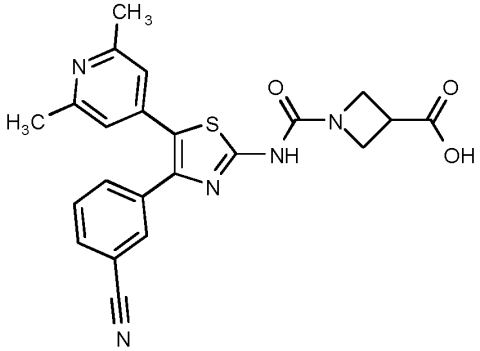
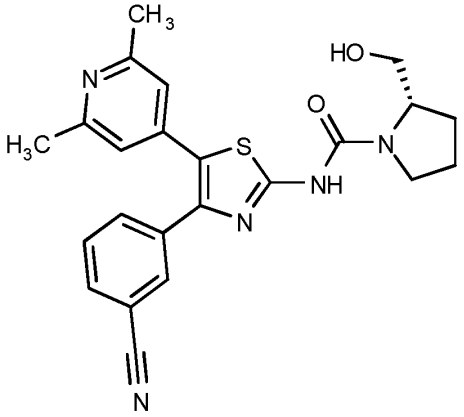
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.50	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-3-oxa-1,9-diazaspiro[5.5]undecane-9-carboxamide	LC-MS (Method 8B): Rt 2.58 mins; MS m/z 503.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.26 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.70 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 7.35 (s, 1H), 6.92 (s, 2H), 4.18 (t, J= 5.0 Hz, 2H), 3.85 (d, J= 13.6 Hz, 2H), 2.36 (s, 6H), 1.89 (t, J= 5.0 Hz, 2H), 1.70 – 1.54 (m, 4H). 1 x CH_2 signal not observed.
6.51	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-methyl-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 2.67 mins; MS m/z 500.5 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.31 (s, 1H), 7.90 (s, 1H), 7.83 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 7.8 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 6.39 (s, 1H), 4.25 (d, J= 13.4 Hz, 2H), 3.23 (s, 2H), 2.93 (t, J= 13.4 Hz, 2H), 2.52 (s, 3H), 2.37 (s, 6H), 1.78 (td, J= 13.4, 4.0 Hz, 2H), 1.49 (d, J= 12.7 Hz, 2H).
6.52	 (3aS,6aS)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxamide	LC-MS (Method 8B): Rt 3.58 mins; MS m/z 459.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.14 (s, 1H), 7.90 (s, 1H), 7.85 – 7.79 (m, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 3.86 (t, J = 10.0 Hz, 1H), 3.80 (d, J = 10.9 Hz, 1H), 3.55 (t, J = 9.2 Hz, 1H), 3.44 (dd, J = 10.3, 6.0 Hz, 1H), 3.20 (d, J = 10.7 Hz, 1H), 3.07 (d, J = 10.3 Hz, 2H), 3.04 – 2.99 (m, 1H), 2.36 (s, 6H).
6.53	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxa-2-azaspiro[3.4]octane-2-carboxamide	LC-MS (Method 8B): Rt 3.95 mins; MS m/z 446.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.39 – 11.35 (m, 1H), 7.88 (s, 1H), 7.82 (d, J= 7.7 Hz, 1H), 7.70 (d, J= 7.9 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.01 (s, 4H), 3.77 (s, 2H), 3.71 (t, J= 7.0 Hz, 2H), 2.36 (s, 6H), 2.12 (t, J= 7.0 Hz, 2H)

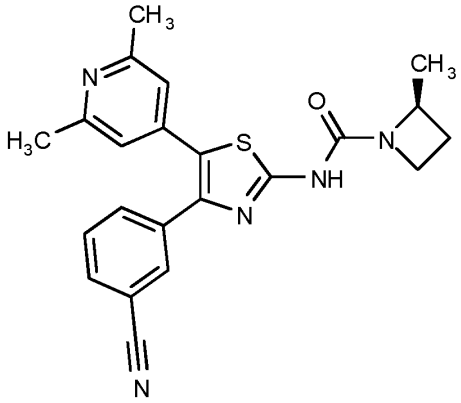
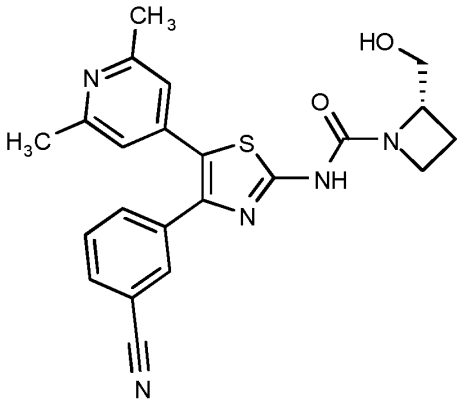
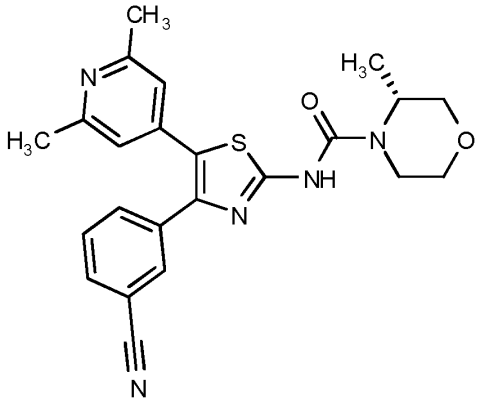
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.54	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-7-oxa-2-azaspiro[3.5]nonane-2-carboxamide	LC-MS (Method 8B): Rt 3.28 mins; MS m/z 458.4 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.31 (s, 1H), 7.87 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.70 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.92 (s, 2H), 3.86 – 3.68 (m, 4H), 3.57 – 3.45 (m, 4H), 2.36 (s, 6H), 1.75 – 1.64 (m, 4H).
6.55	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-2,7-diazaspiro[3.4]octane-2-carboxamide	LC-MS (Method 8B): Rt 2.59 mins; MS m/z 457.4 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.37 (s, 1H), 7.87 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.70 (d, J= 7.8 Hz, 1H), 7.65 (s, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.92 (s, 2H), 4.08 – 3.86 (m, 4H), 3.44 (s, 2H), 3.31 (s, 2H), 2.36 (s, 6H).
6.56	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 2.90 mins; MS m/z 487.4 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.32 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 7.9 Hz, 1H), 7.61 – 7.50 (m, 2H), 6.92 (s, 2H), 3.85 – 3.76 (m, 2H), 3.43 – 3.38 (m, 2H), 3.28 (s, 2H), 2.36 (s, 6H), 1.86 – 1.70 (m, 4H).
6.57	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-2,5,7-triazaspiro[3.4]octane-2-carboxamide	LC-MS (Method 8B): Rt 2.57 mins; MS m/z 458.3 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.41 (s, 1H), 7.87 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.70 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 7.09 (s, 1H), 6.93 (s, 2H), 6.40 (s, 1H), 4.17 – 4.02 (m, 4H), 3.54 (s, 2H), 2.36 (s, 6H).

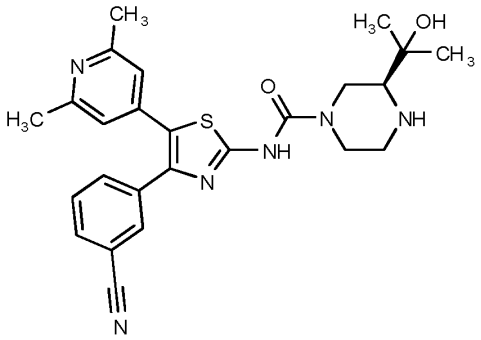
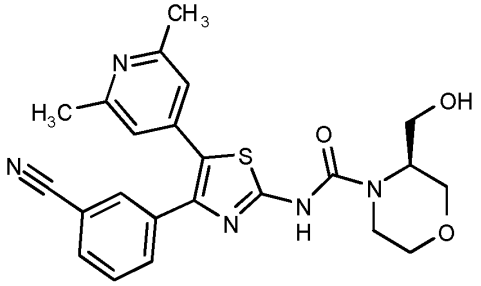
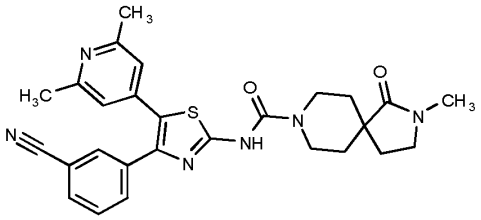
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.58	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-1,9-diazaspiro[5.5]undecane-9-carboxamide	LC-MS (Method 8B): Rt 3.05 mins; MS m/z 499.4 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.24 (s, 1H), 7.90 (s, 1H), 7.83 (d, J= 7.6 Hz, 1H), 7.71 (d, J= 8.0 Hz, 1H), 7.57 (t, J= 7.8 Hz, 2H), 6.93 (s, 2H), 3.87 – 3.80 (m, 2H), 2.37 (s, 6H), 2.12 (s, 2H), 1.72 – 1.65 (m, 4H), 1.63 – 1.57 (m, 4H). 1 x CH_2 not observed.
6.59	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5-oxo-2,6-diazaspiro[3.4]octane-2-carboxamide	LC-MS (Method 8B): Rt 3.53 mins; MS m/z 459.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.43 (s, 1H), 7.90 – 7.86 (m, 2H), 7.83 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 7.9 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.02 (d, J= 74.8 Hz, 4H), 3.17 (t, J= 6.7 Hz, 2H), 2.37 (s, 6H), 2.37 – 2.32 (m, 2H).
6.60	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-ethyl-piperazine-1-carboxamide	LC-MS (Method 8B): Rt 4.25 mins; MS m/z 447.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.27 (s, 1H), 7.89 (s, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 8.0 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 3.53 (t, J= 5.1 Hz, 4H), 2.40 – 2.31 (m, 12H), 1.02 (t, J= 7.1 Hz, 3H).
6.61	 N-[4-(3-Cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide (Prepared from Intermediate H)	LC-MS (Method 8B): Rt 4.34 mins; MS m/z 529.2 = [M-H]+ H NMR (500 MHz, Methanol-d4) δ 7.92 (s, 1H), 7.75 – 7.69 (m, 2H), 7.52 (t, J= 7.8 Hz, 1H), 7.45 (s, 1H), 7.36 (s, 1H), 4.71 (t, J= 6.6 Hz, 2H), 4.63 (t, J= 6.2 Hz, 2H), 3.66 (t, J= 4.9 Hz, 4H), 3.55 (p, J= 6.3 Hz, 1H), 2.55 (s, 3H), 2.42 (t, J= 5.0 Hz, 4H). NH proton not observed.

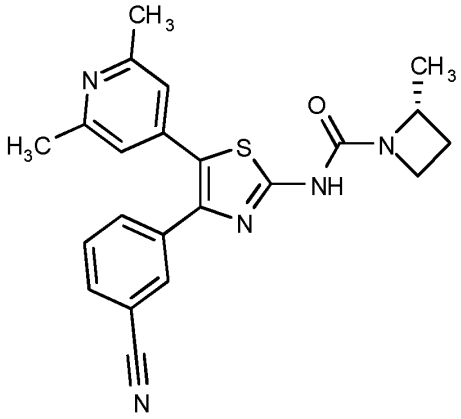
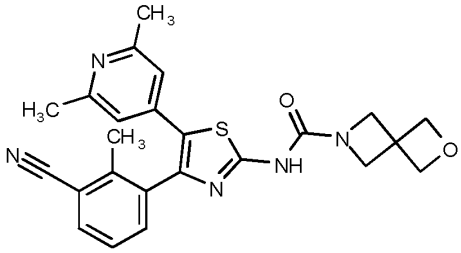
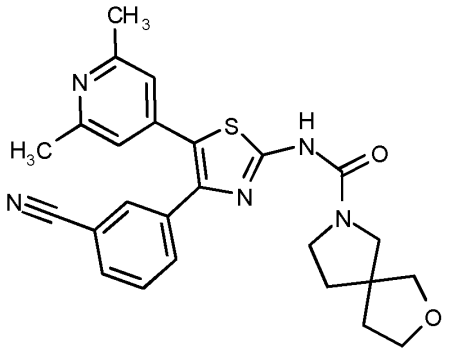
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.62	 1-[[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]piperidine-4-carboxylic acid	LC-MS (Method 8B): Rt 2.39 mins; MS m/z 462.2 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.91 (s, 1H), 7.72 (d, J= 8.0 Hz, 1H), 7.69 (d, J= 7.7 Hz, 1H), 7.49 (t, J= 7.9 Hz, 1H), 7.01 (s, 2H), 4.15 (d, J= 13.5 Hz, 2H), 3.10 (t, J= 12.4 Hz, 2H), 2.59 – 2.53 (m, 1H), 2.44 (s, 6H), 1.99 (d, J= 13.5 Hz, 2H), 1.73 – 1.62 (m, 2H). NH and OH protons not observed.
6.63	 (3S)-1-[[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]pyrrolidine-3-carboxylic acid	LC-MS (Method 8B): Rt 2.91 mins; MS m/z 448.2 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.93 (s, 1H), 7.72 (dd, J = 16.0, 7.8 Hz, 2H), 7.51 (t, J = 7.8 Hz, 1H), 7.06 (s, 2H), 3.82 – 3.72 (m, 2H), 3.65 (dt, J = 10.0, 6.8 Hz, 1H), 3.58 (dt, J = 10.1, 7.1 Hz, 1H), 3.23 (s, 1H), 2.46 (s, 6H), 2.29 (s, 2H). NH and OH protons not observed.
6.64	 3-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)azetidine-1-carboxamide	LC-MS (Method 8B): Rt 2.98 mins; MS m/z 445.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.57 (s, 1H), 7.87 (s, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.70 (d, J= 8.3 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 5.77 (t, J= 5.7 Hz, 1H), 4.28 – 4.24 (m, 2H), 4.13 – 4.07 (m, 2H), 3.78 (d, J= 5.7 Hz, 2H), 2.37 (s, 6H).

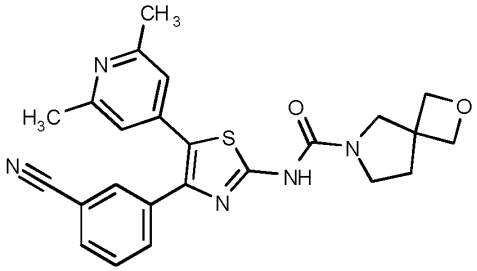
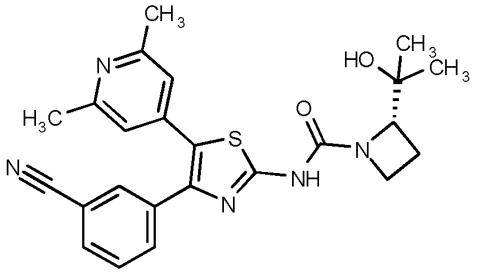
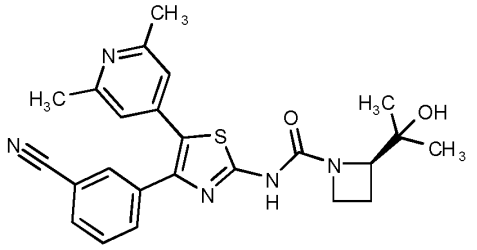
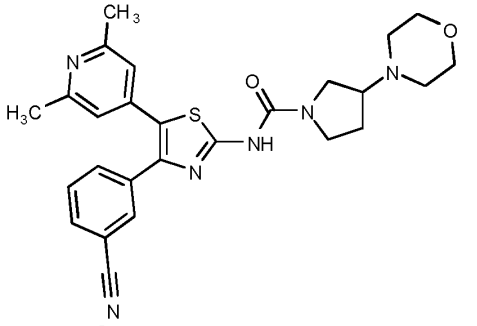
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.65	 (3R)-1-[[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]pyrrolidine-3-carboxylic acid	LC-MS (Method 8B): Rt 2.42 mins; MS m/z 448.2 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.93 (s, 1H), 7.77 – 7.69 (m, 2H), 7.51 (t, J= 7.8 Hz, 1H), 7.08 (s, 2H), 3.82 – 3.72 (m, 2H), 3.65 (dt, J= 10.3, 6.9 Hz, 1H), 3.58 (dt, J= 10.3, 7.2 Hz, 1H), 3.24 (s, 1H), 2.47 (s, 6H), 2.32 – 2.27 (m, 2H). NH and OH protons not observed.
6.66	 4-Cyano-N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide (Prepared from Intermediate M)	LC-MS (Method 8B): Rt 3.66 mins; MS m/z 473.3 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.38 (s, 1H), 7.88 (s, 1H), 7.80 (d, J= 7.8 Hz, 1H), 7.67 (d, J= 7.8 Hz, 1H), 7.54 (t, J= 7.8 Hz, 1H), 7.10 (d, J= 4.5 Hz, 1H), 4.23 (d, J= 13.6 Hz, 2H), 3.07 – 2.98 (m, 2H), 2.40 – 2.32 (m, 6H), 1.92 (d, J= 13.6 Hz, 2H), 1.57 – 1.49 (m, 2H), 1.37 (s, 3H).
6.67	 N-[4-(3-Cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-3-methyl-azetidine-1-carboxamide (Prepared from Intermediate M)	LC-MS (Method 8B): Rt 3.06 mins; MS m/z 436.3 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.36 (s, 1H), 7.87 (s, 1H), 7.80 (d, J= 7.7 Hz, 1H), 7.66 (d, J= 7.9 Hz, 1H), 7.54 (t, J= 7.9 Hz, 1H), 7.10 (d, J= 4.9 Hz, 1H), 5.67 (s, 1H), 3.96 – 3.81 (m, 4H), 2.40 – 2.33 (m, 6H), 1.38 (s, 3H).
6.68	 3-Cyano-N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-azetidine-1-carboxamide (Prepared from Intermediate M)	LC-MS (Method 8B): Rt 3.05 mins; MS m/z 445.3 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.61 (s, 1H), 7.86 (s, 1H), 7.81 (d, J= 7.8 Hz, 1H), 7.66 (d, J= 7.8 Hz, 1H), 7.54 (t, J= 7.8 Hz, 1H), 7.10 (d, J= 5.0 Hz, 1H), 4.41 – 4.28 (m, 2H), 4.07 – 3.95 (m, 2H), 2.41 – 2.32 (m, 6H), 1.63 (s, 3H).

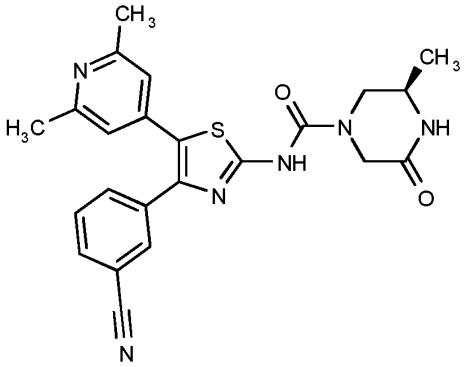
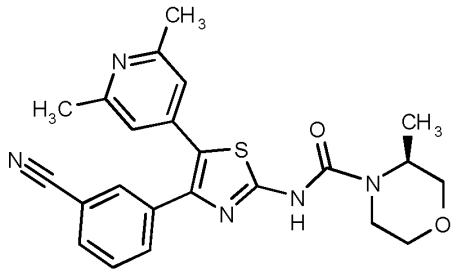
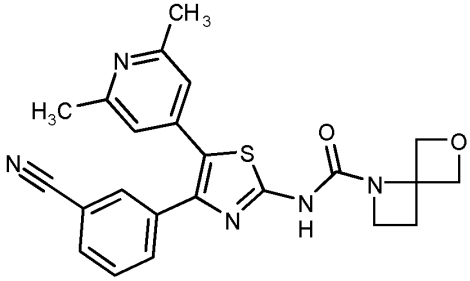
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.69	 N-[4-(3-Cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-2,7-diazaspiro[3.5]nonane-7-carboxamide (Prepared from Intermediate M)	LC-MS (Method 8B): Rt 3.08 mins; MS m/z 489.3 = [M-H]- 1H NMR (500 MHz, Methanol-d4) δ 7.93 (s, 1H), 7.74 – 7.65 (m, 2H), 7.49 (t, J = 7.9 Hz, 1H), 7.13 (d, J = 5.0 Hz, 1H), 3.99 – 3.92 (m, 2H), 3.58 – 3.52 (m, 2H), 3.26 (s, 2H), 2.53 – 2.36 (m, 6H), 2.03 – 1.95 (m, 2H), 1.94 – 1.86 (m, 2H). 2 x NH protons not observed.
6.70	 1-[[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]azetidine-3-carboxylic acid	LC-MS (Method 8A): Rt 2.04 mins; MS m/z 434.8 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 12.72 (s, 1H), 11.40 (s, 1H), 7.88 (s, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.70 (d, J= 7.9 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.29 – 4.17 (m, 2H), 4.12 – 4.01 (m, 2H), 3.44 (td, J= 9.2, 4.7 Hz, 1H), 2.37 (s, 6H).
6.71	 (2S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)pyrrolidine-1-carboxamide	LC-MS (Method 8B): Rt 3.14 mins; MS m/z 432.4 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.7 Hz, 1H), 7.70 (d, J= 7.9 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.77 (v. br s, 1H), 4.01 (s, 1H), 3.51 – 3.47 (m, 4H), 2.37 (s, 6H), 1.93 – 1.81 (m, 4H).

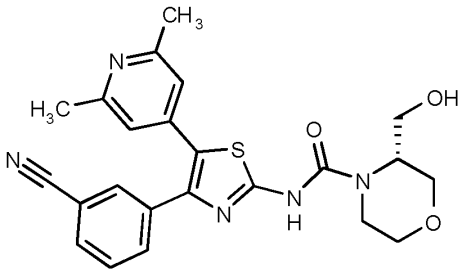
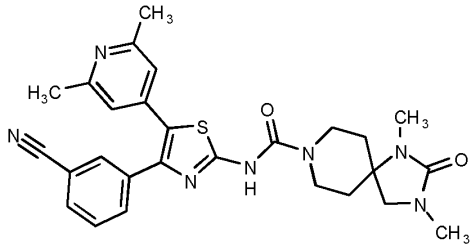
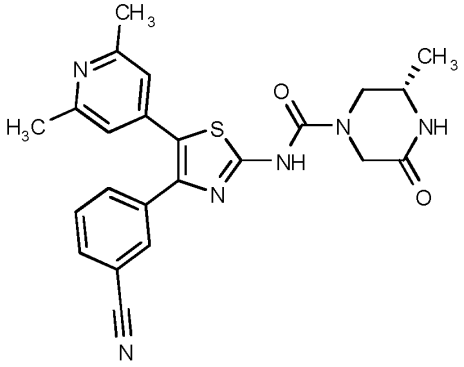
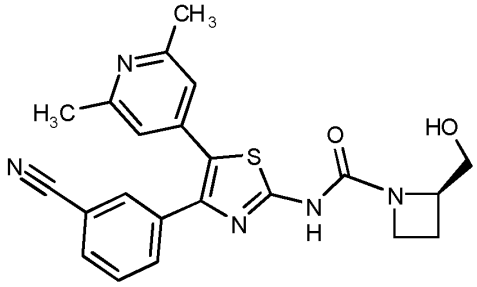
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.72	 (2S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-azetidine-1-carboxamide	LC-MS (Method 8B): Rt 3.54 mins; MS m/z 402.3 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.15 (s, 1H), 7.88 (d, J= 1.9 Hz, 1H), 7.82 (d, J= 7.7 Hz, 1H), 7.70 (d, J= 7.9 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.47 – 4.41 (m, 1H), 4.06 (q, J= 8.2 Hz, 1H), 3.95 (t, J= 8.3 Hz, 1H), 2.36 (s, 7H), 1.81 (tt, J= 11.0, 6.5 Hz, 1H), 1.38 (d, J= 6.2 Hz, 3H).
6.73	 (2S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)azetidine-1-carboxamide	LC-MS (Method 8B): Rt 2.90 mins; MS m/z 418.3 = [MH]- 1H NMR (500 MHz, DMSO-d6) δ 11.06 (s, 1H), 7.86 (s, 1H), 7.82 (d, J= 7.7 Hz, 1H), 7.68 (d, J= 8.0 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.48 (s, 1H), 3.94 (q, J= 8.1 Hz, 1H), 3.86 – 3.82 (m, 1H), 3.78 – 3.71 (m, 1H), 3.66 – 3.59 (m, 1H), 2.36 (s, 6H), 2.27 – 2.18 (m, 1H), 2.03 (s, 1H). 1 proton not observed.
6.74	 (3R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-morpholine-4-carboxamide	LC-MS (Method 8B): Rt 4.07 mins; MS m/z 434.3 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.91 (s, 1H), 7.75 – 7.66 (m, 2H), 7.49 (t, J= 7.9 Hz, 1H), 7.01 (s, 2H), 4.28 – 4.21 (m, 1H), 3.94 (dd, J= 11.6, 3.6 Hz, 1H), 3.84 (d, J= 13.1 Hz, 1H), 3.78 – 3.72 (m, 1H), 3.67 (dd, J= 11.6, 3.2 Hz, 1H), 3.52 (dd, J= 13.1, 9.9 Hz, 1H), 3.36 (dd, J= 13.1, 3.6 Hz, 1H), 2.44 (s, 6H), 1.35 (d, J= 6.9 Hz, 3H). NH proton not observed.

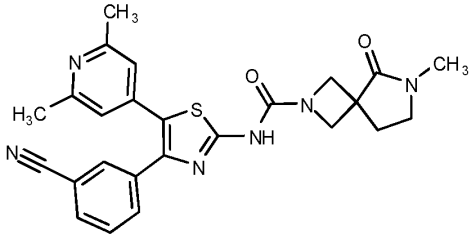
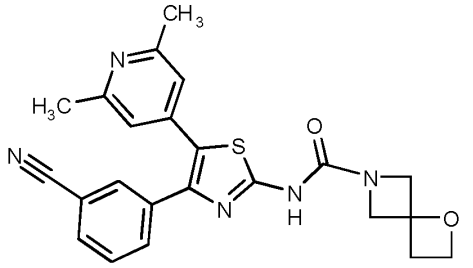
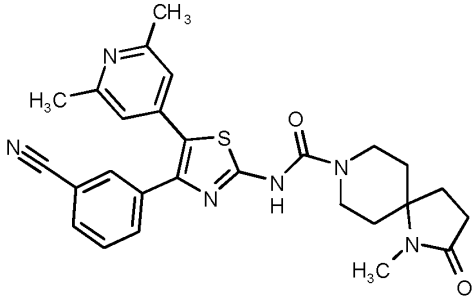
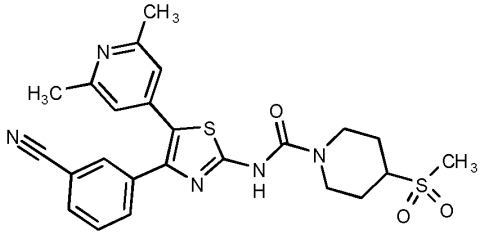
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.75	 (3S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide (Prepared from Intermediate T)	LC-MS (Method 8B): Rt 1.38 mins; MS m/z 477.3 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.91 (t, J= 1.6 Hz, 1H), 7.73 – 7.67 (m, 2H), 7.49 (t, J= 7.8 Hz, 1H), 7.00 (s, 2H), 4.29 (apr d, J= 12.9 Hz, 1H), 4.13 (apr d, J= 12.9 Hz, 1H), 3.10 (apr d, J= 12.1 Hz, 1H), 2.97 (apr t, J= 12.5 Hz, 1H), 2.78 (apr dd, J= 12.2, 3.2 Hz, 1H), 2.74 (apr d, J= 12.1 Hz, 1H), 2.55 (apr dd, J= 11.0, 2.7 Hz, 1H), 2.44 (s, 6H), 1.28 (s, 3H), 1.25 (s, 3H). 2 x NH and 1 x OH protons not observed.
6.76	 (3S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)morpholine-4-carboxamide	LC-MS (Method 8B): Rt 2.46 mins; MS m/z 448.3 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.88 (s, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.70 (dt, J = 7.8, 1.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 4.92 (v br s, 1H), 4.12 (t, J = 7.2 Hz, 1H), 3.92 – 3.81 (m, 3H), 3.65 (dd, J = 10.6, 7.9 Hz, 1H), 3.60 – 3.53 (m, 1H), 3.47 (dd, J = 11.6, 3.3 Hz, 1H), 3.40 (dd, J = 12.1, 3.1 Hz, 1H), 3.15 – 3.07 (m, 1H), 2.36 (s, 6H).
6.77	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-1-oxo-2,8-diazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 4.01 mins; MS m/z 501.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.24 (s, 1H), 7.90 (s, 1H), 7.82 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 8.0 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.09 (d, J= 14.1 Hz, 2H), 3.31 – 3.28 (m, 2H), 3.10 (t, J= 12.5 Hz, 2H), 2.73 (s, 3H), 2.36 (s, 6H), 1.97 (t, J= 6.8 Hz, 2H), 1.61 (td, J= 12.8, 4.1 Hz, 2H), 1.39 (d, J= 13.3 Hz, 2H).

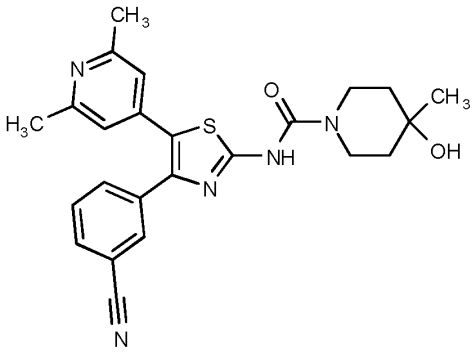
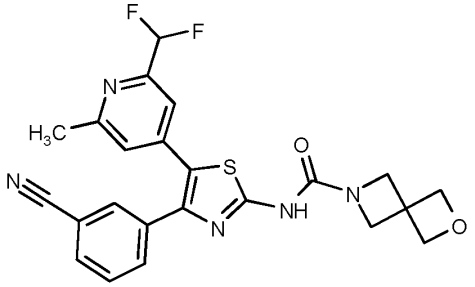
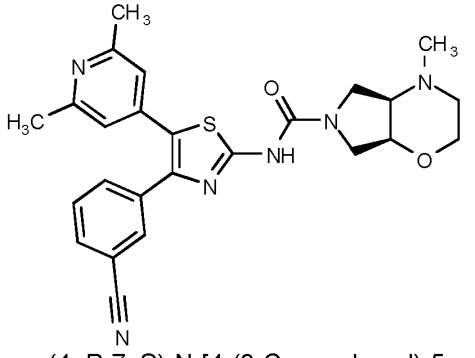
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.78	 (2R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-azetidine-1-carboxamide	LC-MS (Method 8B): Rt 4.31 mins; MS m/z 404.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.15 (s, 1H), 7.88 (s, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 6.93 (s, 2H), 4.48 – 4.42 (m, 1H), 4.06 (q, J = 8.0 Hz, 1H), 3.94 (q, J = 8.2 Hz, 1H), 2.38 – 2.34 (m, 7H), 1.86 – 1.76 (m, 1H), 1.38 (d, J = 6.2 Hz, 3H).
6.79	 N-[4-(3-Cyano-2-methyl-phenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide (Prepared from Intermediate O)	LC-MS (Method 8B): Rt 2.92 mins; MS m/z 444.3 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.35 (s, 1H), 7.88 (dd, J = 7.8, 1.5 Hz, 1H), 7.52 (dd, J = 7.8, 1.5 Hz, 1H), 7.43 (t, J = 7.7 Hz, 1H), 6.66 (s, 2H), 4.67 (s, 4H), 4.20 (s, 4H), 2.27 (s, 6H), 2.26 (s, 3H).
6.80	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide	LC-MS (Method 8B): Rt 4.14 mins; MS m/z 460.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.02 (s, 1H), 7.89 (t, J = 1.5 Hz, 1H), 7.81 (dt, J = 7.9, 1.5 Hz, 1H), 7.71 (dt, J = 7.9, 1.5 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 6.92 (s, 2H), 3.82 – 3.75 (m, 2H), 3.58 – 3.48 (m, 4H), 3.44 – 3.39 (m, 2H), 2.36 (s, 6H), 1.95 – 1.81 (m, 4H).

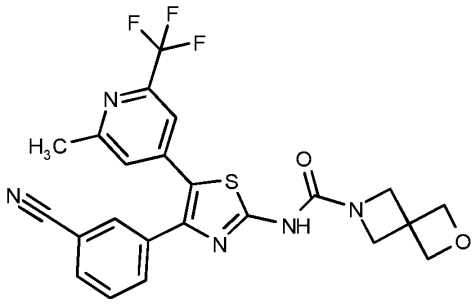
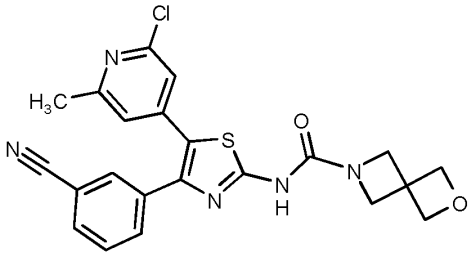
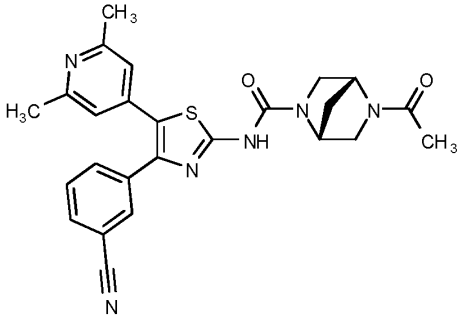
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.81	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-7-azaspiro[3.4]octane-7-carboxamide	LC-MS (Method 8B): Rt 3.88 mins; MS m/z 446.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.07 (s, 1H), 7.89 (d, J= 2.0 Hz, 1H), 7.82 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 7.9 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.56 (d, J= 6.2 Hz, 2H), 4.49 (d, J= 6.2 Hz, 2H), 3.68 (s, 2H), 3.45 (s, 2H), 2.36 (s, 6H), 2.19 (s, 2H).
6.82	 (2S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)azetidine-1-carboxamide	LC-MS (Method 8B): Rt 4.22 mins; MS m/z 448.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.37 (s, 1H), 7.85 (s, 1H), 7.81 (d, J= 7.7 Hz, 1H), 7.67 (d, J= 8.0 Hz, 1H), 7.55 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 6.31 (s, 1H), 4.33 (t, J= 7.8 Hz, 1H), 3.92 (q, J= 8.3 Hz, 1H), 3.68 (s, 1H), 2.36 (s, 6H), 2.27 – 2.17 (m, 1H), 1.99 (p, J= 8.4 Hz, 1H), 1.27 (s, 3H), 1.10 (s, 3H).
6.83	 (2R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)azetidine-1-carboxamide	LC-MS (Method 8B): Rt 4.26 mins; MS m/z 448.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.34 (s, 1H), 7.85 (t, J = 1.4 Hz, 1H), 7.81 (dt, J = 7.8, 1.4 Hz, 1H), 7.66 (dt, J = 7.8, 1.5 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 6.92 (s, 2H), 6.31 (s, 1H), 4.32 (t, J = 7.8 Hz, 1H), 3.91 (q, J = 8.4 Hz, 1H), 3.71 – 3.64 (m, 1H), 2.36 (s, 6H), 2.25 – 2.17 (m, 1H), 2.02 – 1.94 (m, 1H), 1.26 (s, 3H), 1.09 (s, 3H).
6.84	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-morpholino-pyrrolidine-1-carboxamide hemi formate salt	LC-MS (Method 8B): Rt 4.00 mins; MS m/z 489.2 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 8.18 (s, 0.5H), 7.91 (t, J = 1.6 Hz, 1H), 7.72 (dt, J = 7.8, 1.6 Hz, 1H), 7.69 (dt, J = 7.8, 1.6 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.04 (s, 2H), 3.84 (dd, J = 10.1, 7.1 Hz, 1H), 3.77 – 3.70 (m, 5H), 3.52 – 3.45 (m, 1H), 3.29 - 3.33 (m, 1H), 3.04 – 2.94 (m, 1H), 2.67 – 2.59 (m, 2H), 2.59 - 2.50 (m, 2H), 2.45 (s, 6H), 2.34 – 2.21 (m, 1H), 1.96 – 1.82 (m, 1H). NH proton not observed.

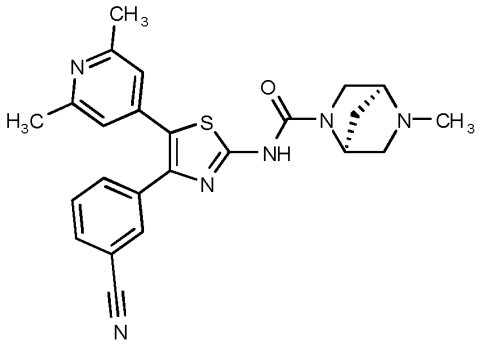
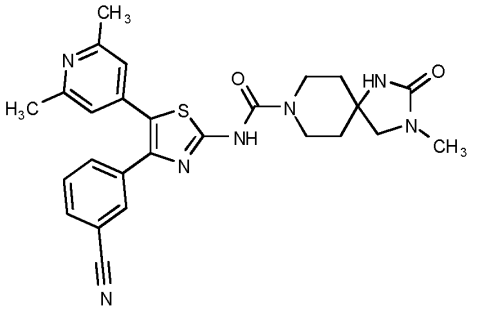
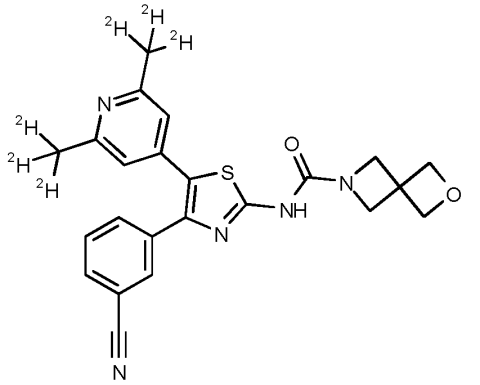
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.85	 (3R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-5-oxo-piperazine-1-carboxamide	LC-MS (Method 8B): Rt 3.36 mins; MS m/z 447.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.38 (s, 1H), 8.14 (s, 1H), 7.89 (t, J= 1.6 Hz, 1H), 7.82 (dt, J= 7.8, 1.6 Hz, 1H), 7.71 (dt, J= 7.8, 1.6 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.18 (apr d, J= 17.6 Hz, 1H), 4.02 – 3.95 (m, 1H), 3.92 (apr d, J= 17.6 Hz, 1H), 3.58 – 3.49 (m, 1H), 3.22 – 3.14 (m, 1H), 2.36 (s, 6H), 1.10 (d, J= 6.4 Hz, 3H).
6.86	 (3S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-morpholine-4-carboxamide	LC-MS (Method 8B): Rt 4.15 mins; MS m/z 434.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.23 (s, 1H), 7.89 (d, J = 1.5 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.71 (dt, J = 7.8, 1.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.92 (s, 2H), 4.30 – 4.23 (m, 1H), 3.91 – 3.82 (m, 2H), 3.65 (d, J = 11.5 Hz, 1H), 3.53 (dd, J = 11.5, 2.9 Hz, 1H), 3.41 – 3.36 (m, 1H), 3.17 (td, J = 13.1, 2.9 Hz, 1H), 2.36 (s, 6H), 1.21 (d, J = 6.7 Hz, 3H).
6.87	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxa-1-azaspiro[3.3]heptane-1-carboxamide	LC-MS (Method 8B): Rt 3.04 mins; MS m/z 432.2 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.89 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.01 (s, 2H), 5.38 (d, J = 7.1 Hz, 2H), 4.72 (d, J = 7.1 Hz, 2H), 4.03 (t, J = 7.3 Hz, 2H), 2.61 (t, J = 7.4 Hz, 2H), 2.44 (s, 6H). NH proton not observed.

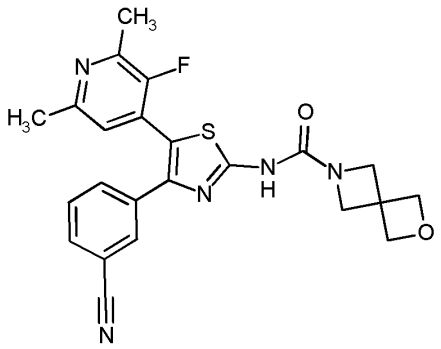
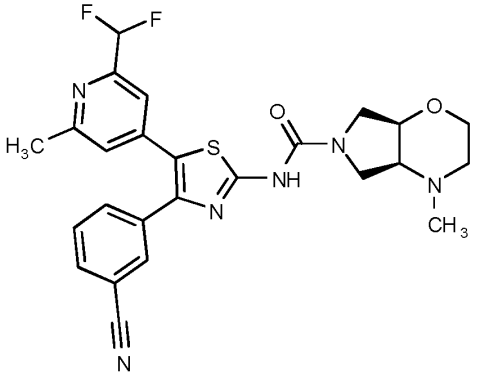
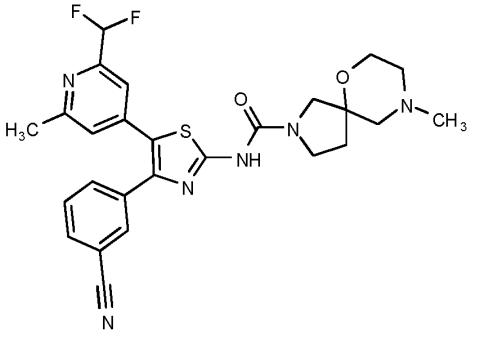
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.88	 (3R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)morpholine-4-carboxamide	LC-MS (Method 8B): Rt 3.43 mins; MS m/z 450.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.07 (s, 1H), 7.89 (t, J= 1.8 Hz, 1H), 7.82 (dt, J= 7.7, 1.5 Hz, 1H), 7.71 (dt, J= 8.0, 1.5 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.92 (s, 1H), 4.12 (d, J= 8.3 Hz, 1H), 3.93 – 3.82 (m, 3H), 3.69 – 3.62 (m, 1H), 3.57 (t, J= 9.1 Hz, 1H), 3.48 (dd, J= 11.7, 3.3 Hz, 1H), 3.40 (td, J= 11.8, 3.1 Hz, 1H), 3.12 (td, J= 13.9, 13.2, 3.7 Hz, 1H), 2.37 (s, 6H).
6.89	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3-dimethyl-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 3.85 mins; MS m/z 516.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.30 (s, 1H), 7.89 (s, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 8.0 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.27 (d, J= 13.3 Hz, 2H), 3.25 (s, 2H), 2.99 – 2.90 (m, 2H), 2.67 (s, 3H), 2.56 (s, 3H), 2.37 (s, 6H), 1.81 (td, J= 13.1, 4.6 Hz, 2H), 1.47 (d, J= 12.8 Hz, 2H).
6.90	 (3S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-5-oxo-piperazine-1-carboxamide	LC-MS (Method 8B): Rt 3.43 mins; MS m/z 447.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.38 (s, 1H), 8.16 (s, 1H), 7.90 (d, J= 1.8 Hz, 1H), 7.83 (dt, J= 7.8, 1.5 Hz, 1H), 7.71 (dt, J= 8.0, 1.5 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 4.18 (d, J= 17.6 Hz, 1H), 3.99 (d, J= 13.2 Hz, 1H), 3.93 (d, J= 17.6 Hz, 1H), 3.58 – 3.51 (m, 1H), 3.20 (dd, J= 13.5, 8.0 Hz, 1H), 2.37 (s, 6H), 1.10 (d, J= 6.4 Hz, 3H).
6.91	 (2R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)azetidine-1-carboxamide	LC-MS (Method 8B): Rt 3.12 mins; MS m/z 418.3 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.01 (s, 1H), 7.86 (d, J = 1.5 Hz, 1H), 7.82 (dt, J = 7.9, 1.5 Hz, 1H), 7.69 (dt, J = 7.9, 1.5 Hz, 1H), 7.55 (t, J = 7.9 Hz, 1H), 6.93 (s, 2H), 4.48 (s, 1H), 3.94 (q, J = 8.3 Hz, 1H), 3.84 (s, 1H), 3.75 (dd, J = 11.2, 3.5 Hz, 1H), 3.67 – 3.59 (m, 1H), 2.36 (s, 6H), 2.28 – 2.19 (m, 1H), 2.03 (s, 1H). One proton not observed

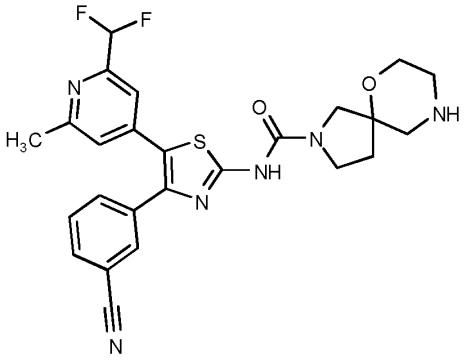
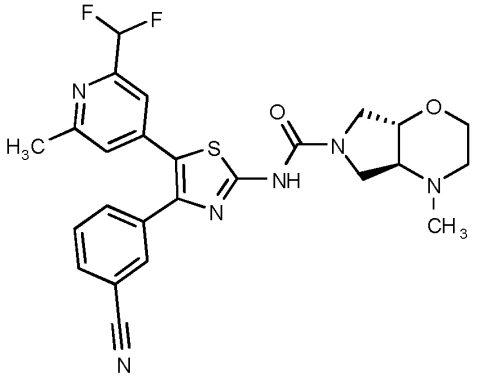
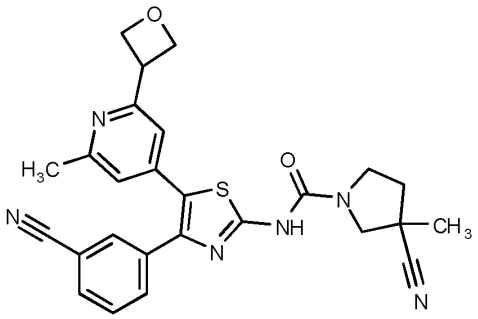
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.92	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-methyl-5-oxo-2,6-diazaspiro[3.4]octane-2-carboxamide	LC-MS (Method 8B): Rt 3.64 mins; MS m/z 473.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.41 (s, 1H), 7.87 (t, J = 1.5 Hz, 1H), 7.81 (dt, J = 7.7, 1.5 Hz, 1H), 7.70 (dt, J = 8.0, 1.5 Hz, 1H), 7.56 (apr t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 4.09 (s, 2H), 3.94 (s, 2H), 3.27 (t, J = 6.8 Hz, 2H), 2.76 (s, 3H), 2.36 (s, 6H), 2.32 (t, J = 6.8 Hz, 2H)
6.93	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxa-6-azaspiro[3.3]heptane-6-carboxamide	LC-MS (Method 8B): Rt 2.68 mins; MS m/z 432.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.35 (s, 1H), 7.87 (t, J= 1.5 Hz, 1H), 7.81 (dt, J= 7.8, 1.5 Hz, 1H), 7.69 (dt, J= 7.8, 1.5 Hz, 1H), 7.55 (t, J= 7.8 Hz, 1H), 6.92 (s, 2H), 4.41 (t, J= 7.5 Hz, 2H), 4.28 (d, J= 10.3 Hz, 2H), 4.12 (d, J= 10.3 Hz, 2H), 2.83 (t, J= 7.5 Hz, 2H), 2.36 (s, 6H).
6.94	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-methyl-2-oxo-1,8-diazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 3.92 mins; MS m/z 501.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.29 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.92 (s, 2H), 4.29 (d, J= 13.5 Hz, 2H), 2.96 (d, J= 14.5 Hz, 2H), 2.60 (s, 3H), 2.36 (s, 6H), 2.27 (t, J= 8.0 Hz, 2H), 1.97 (t, J= 8.0 Hz, 2H), 1.79 (t, J= 14.5, 10.1 Hz, 2H), 1.42 (d, J= 12.7 Hz, 2H).
6.95	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methylsulfonyl-piperidine-1-carboxamide	LC-MS (Method 8B): Rt 3.62 mins; MS m/z 496.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.32 (s, 1H), 7.89 (t, J= 1.7 Hz, 1H), 7.83 (dt, J= 7.8, 1.4 Hz, 1H), 7.71 (dt, J= 8.1, 1.4 Hz, 1H), 7.57 (t, J= 7.9 Hz, 1H), 6.93 (s, 2H), 4.36 (d, J= 13.5 Hz, 2H), 3.43 – 3.33 (m, 1H), 2.96 (s, 3H), 2.96 – 2.87 (m, 2H), 2.37 (s, 6H), 2.11 – 2.04 (m, 2H), 1.55 (qd, J= 12.4, 4.1 Hz, 2H).

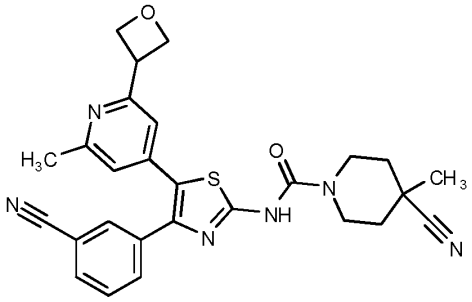
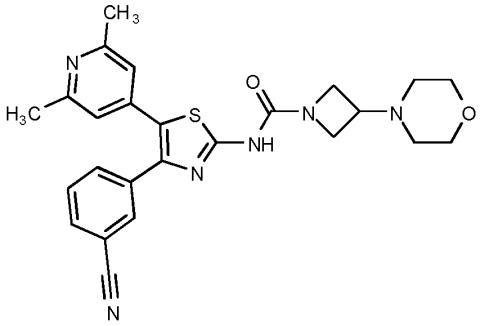
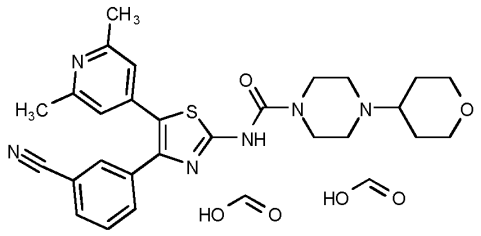
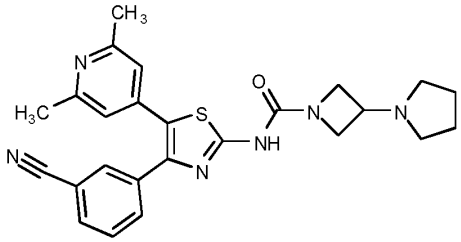
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.96	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-hydroxy-4-methyl-piperidine-1-carboxamide	LC-MS (Method 8B): Rt 3.95 mins; MS m/z 448.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.16 (s, 1H), 7.89 (d, J= 1.8 Hz, 1H), 7.82 (dt, J= 7.8, 1.5 Hz, 1H), 7.71 (dt, J= 7.9, 1.5 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.40 (s, 1H), 3.83 (dt, J= 13.5, 4.2 Hz, 2H), 3.29 – 3.23 (m, 2H), 2.36 (s, 6H), 1.53 – 1.39 (m, 4H), 1.15 (s, 3H).
6.97	 N-[4-(3-Cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide (Prepared from Intermediate G)	LC-MS (Method 8B): Rt 3.77 mins; MS m/z 468.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.33 (br s, 1H), 7.88 (d, J= 1.8 Hz, 1H), 7.85 (dt, J= 7.8, 1.5 Hz, 1H), 7.72 (dt, J= 8.1, 1.5 Hz, 1H), 7.58 (t, J= 7.8 Hz, 1H), 7.36 (s, 1H), 7.20 (s, 1H), 6.83 (t, J= 54.9 Hz, 1H), 4.67 (s, 4H), 4.21 (s, 4H), 2.48 (s, 3H).
6.98	 rac-(4aR,7aS)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxamide	LC-MS (Method 8B): Rt 4.00 mins; MS m/z 475.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.05 (s, 1H), 7.89 (t, J= 1.6 Hz, 1H), 7.81 (dt, J= 7.8, 1.6 Hz, 1H), 7.71 (dt, J= 7.8, 1.6 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.11 – 3.96 (m, 1H), 3.76 (dt, J= 11.2, 2.9 Hz, 1H), 3.65 – 3.35 (m, 6H), 2.62 - 2.53 (m, 1H), 2.36 (s, 7H), 2.29 (s, 3H).

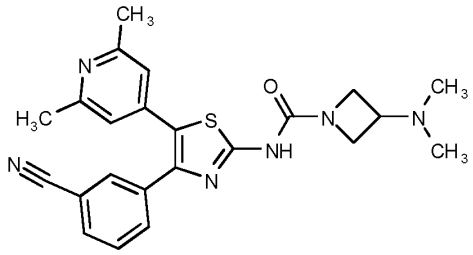
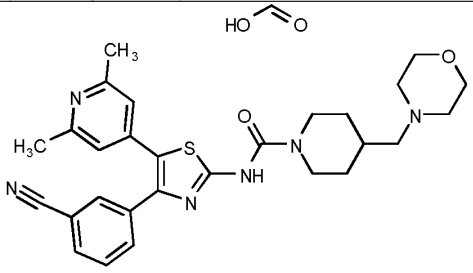
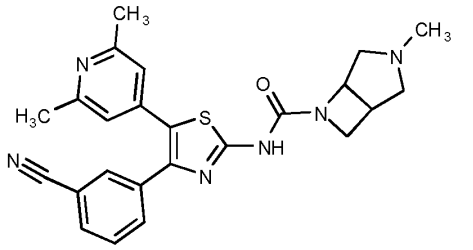
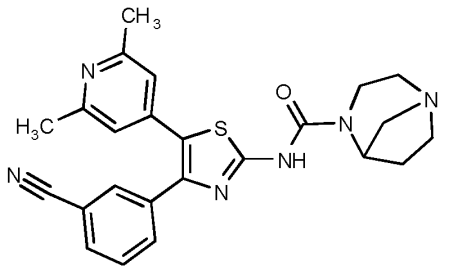
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.99	 N-[4-(3-Cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide (Prepared from Intermediate H)	LC-MS (Method 8B): Rt 4.39 mins; MS m/z 486.2 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.90 (d, J= 1.7 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.52 (t, J= 7.8 Hz, 1H), 7.44 (s, 1H), 7.36 (s, 1H), 4.82 (s, 4H), 4.31 (s, 4H), 2.55 (s, 3H). NH proton not observed.
6.100	 N-[5-(2-Chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide (Prepared from Intermediate D)	LC-MS (Method 8B): Rt 4.17 mins; MS m/z 452.1 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.44 (s, 1H), 7.90 (t, J= 1.5 Hz, 1H), 7.85 (dt, J= 7.8, 1.5 Hz, 1H), 7.71 (dt, J= 7.8, 1.5 Hz, 1H), 7.59 (t, J= 7.8 Hz, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 4.67 (s, 4H), 4.21 (s, 4H), 2.40 (s, 3H).
6.101	 (1R,4R)-5-Acetyl-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide	LC-MS (Method 8B): Rt 3.21 mins; MS m/z 473.2 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.91 – 7.89 (m, 1H), 7.73 – 7.67 (m, 2H), 7.49 (t, J= 7.8 Hz, 1H), 7.01 (s, 2H), 3.68 – 3.61 (m, 2H), 3.60 – 3.56 (m, 1H), 3.53 – 3.45 (m, 3H), 2.44 (s, 6H), 2.16 (s, 1H), 2.06 (s, 1H), 2.01 (s, 3H). NH proton not observed.

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.102	 (1S,4S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide	LC-MS (Method 8B): Rt 3.97 mins; MS m/z 445.3 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.92 (t, J = 1.7 Hz, 1H), 7.72 (ddt, J = 14.1, 7.8, 1.5 Hz, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.02 (s, 2H), 4.65 (s, 1H), 3.73 – 3.66 (m, 2H), 3.50 – 3.44 (m, 1H), 2.93 (d, J = 10.1 Hz, 1H), 2.88 (d, J = 10.3 Hz, 1H), 2.52 (s, 3H), 2.45 (s, 6H), 2.05 (d, J = 10.3 Hz, 1H), 1.91 (d, J = 10.4 Hz, 1H). NH proton not observed.
6.103	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 3.68 mins; MS m/z 502.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.27 (s, 1H), 7.89 (t, J= 1.7 Hz, 1H), 7.83 (dt, J= 7.8, 1.5 Hz, 1H), 7.71 (dt, J= 7.9, 1.5 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 6.92 (s, 1H), 3.68 – 3.49 (m, 4H), 3.16 (s, 2H), 2.63 (s, 3H), 2.37 (s, 6H), 1.68 – 1.52 (m, 4H).
6.104	 N-[5-[2,6-Bis(trideuteriomethyl)-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide (Prepared from Intermediate N)	LC-MS (Method 8B): Rt 2.83 mins; MS m/z 438.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.34 (br s, 1H), 7.87 (br t, J = 1.6 Hz, 1H), 7.81 (br dt, J = 7.7, 1.6 Hz, 1H), 7.69 (br dt, J = 8.0, 1.6 Hz, 1H), 7.55 (apr t, J = 7.8 Hz, 1H), 6.92 (s, 2H), 4.67 (s, 4H), 4.20 (s, 4H)

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.105	 N-[4-(3-Cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide (Prepared from Intermediate M)	LC-MS (Method 8B): Rt 3.02 mins; MS m/z 450.1 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.41 (s, 1H), 7.86 (d, J = 1.9 Hz, 1H), 7.80 (dd, J = 7.7, 1.7 Hz, 1H), 7.67 – 7.64 (m, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 5.0 Hz, 1H), 4.67 (s, 4H), 4.21 (s, 4H), 2.37 (s, 3H), 2.36 (d, J = 3.1 Hz, 3H).
6.106	 rac-(4aS,7aR)-N-[4-(3-Cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxamide (Prepared from Intermediate G)	LC-MS (Method 8B): Rt 3.44 mins; MS m/z 511.1 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.81 (t,J= 1.7 Hz, 1H), 7.61 (dt, J= 7.3, 1.5 Hz, 2H), 7.40 (t, J= 7.8 Hz, 1H), 7.24 (s, 1H), 7.20 (s, 1H), 6.50 (t, J= 55.2 Hz, 1H), 4.16 – 3.93 (m, 1H), 3.79 (dt, J= 11.6, 2.7 Hz, 1H), 3.68 – 3.27 (m, 6H), 2.65 (td, J= 11.6, 3.4 Hz, 1H), 2.42 (s, 3H), 2.39 (s, 1H), 2.34 (s, 3H). NH proton not observed.
6.107	 N-[4-(3-Cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-9-methyl-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxamide (Prepared from Intermediate G)	LC-MS (Method 8B): Rt 3.41 mins; MS m/z 525.4 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.17 (s, 1H), 7.91 (s, 1H), 7.86 (d, J= 7.8 Hz, 1H), 7.74 (d, J= 8.0 Hz, 1H), 7.59 (t, J= 7.8 Hz, 1H), 7.38 (s, 1H), 7.22 (s, 1H), 6.84 (t, J= 54.9 Hz, 1H), 3.78 – 3.38 (m, 6H), 2.49 (s, 3H), 2.44 – 2.20 (m, 5H), 2.17 (s, 3H), 1.91 (s, 1H).

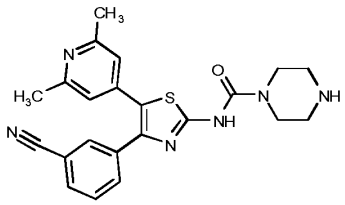
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.108	 N-[4-(3-Cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxamide (Prepared from Intermediate G)	LC-MS (Method 8B): Rt 2.81 mins; MS m/z 511.1 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.93 (t, J= 1.7 Hz, 1H), 7.73 (ddt, J= 7.8, 3.9, 1.3 Hz, 2H), 7.52 (t, J= 7.8 Hz, 1H), 7.36 (s, 1H), 7.32 (d, J= 1.6 Hz, 1H), 6.62 (t, J= 55.2 Hz, 1H), 3.84 – 3.72 (m, 3H), 3.71 – 3.58 (m, 2H), 3.44 (d, J= 11.4 Hz, 1H), 2.93 (q, J= 12.6 Hz, 2H), 2.86 (t, J= 4.9 Hz, 2H), 2.54 (s, 3H), 2.28 (s, 1H), 1.99 (s, 1H). 2 x NH protons not observed.
6.109	 rac-(4aS,7aS)-N-[4-(3-Cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxamide (Prepared from Intermediate G)	LC-MS (Method 8B): Rt 2.85 mins; MS m/z 511.1 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.20 (s, 1H), 7.91 (d, J= 2.0 Hz, 1H), 7.86 (d, J= 7.7 Hz, 1H), 7.74 (d, J= 8.0 Hz, 1H), 7.59 (t, J= 7.8 Hz, 1H), 7.38 (s, 1H), 7.22 (s, 1H), 6.84 (t, J= 54.9 Hz, 1H), 4.01 – 3.71 (m, 3H), 3.65 (td, J= 11.7, 2.7 Hz, 1H), 3.56 (s, 1H), 3.25 (d, J= 8.1 Hz, 1H), 3.13 (s, 1H), 2.97 (d, J= 18.3 Hz, 1H), 2.73 (d, J= 11.8 Hz, 1H), 2.49 (s, 3H), 2.17 (s, 3H), 2.14 – 2.05 (m, 1H).
6.110	 3-Cyano-N-[4-(3-cyanophenyl)-5-[2-methyl-6-(oxetan-3-yl)-4-pyridyl]thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide (Prepared from Intermediate L)	LC-MS (Method 8B): Rt 2.81 mins; MS m/z 485.1 = [M+H]+ (97% @ 254nm) 1H NMR (500 MHz, DMSO-d6) δ 11.26 (s, 1H), 7.90 (br t, J = 1.6 Hz, 1H), 7.83 (br dt, J = 7.7, 1.6 Hz, 1H), 7.73 (br dt, J = 7.9, 1.6 Hz, 1H), 7.57 (apr t, J = 7.8 Hz, 1H), 7.07 (s, 1H), 6.99 (s, 1H), 4.81 (dd, J = 8.5, 5.6 Hz, 2H), 4.66 (dd, J = 6.9, 5.6 Hz, 2H), 4.27 (tt, J = 8.5, 6.9 Hz, 1H), 3.97 – 3.89 (m, 1H), 3.71 – 3.64 (m, 1H), 3.64 – 3.56 (m, 1H), 3.45 – 3.38 (m, 1H), 2.45 (s, 3H), 2.42 – 2.37 (m, 1H), 2.11 – 2.03 (m, 1H), 1.47 (s, 3H).

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.111	 4-Cyano-N-[4-(3-cyanophenyl)-5-[2-methyl-6-(oxetan-3-yl)-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide (Prepared from Intermediate L)	LC-MS (Method 8B): Rt 3.05 mins; MS m/z 499.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.34 (s, 1H), 7.90 (t, J= 1.8 Hz, 1H), 7.84 (d, J= 7.7 Hz, 1H), 7.73 (dt, J= 8.0, 1.5 Hz, 1H), 7.58 (t, J= 7.8 Hz, 1H), 7.07 (s, 1H), 6.99 (s, 1H), 4.82 (dd, J= 8.5, 5.6 Hz, 2H), 4.66 (t, J= 6.2 Hz, 2H), 4.33 – 4.26 (m, 1H), 4.23 (d, J= 13.8 Hz, 2H), 3.04 (t, J= 13.1 Hz, 2H), 2.45 (s, 3H), 1.93 (d, J= 13.7 Hz, 2H), 1.54 (td, J= 13.0, 3.8 Hz, 2H), 1.38 (s, 3H).
6.112	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-morpholino-azetidine-1-carboxamide	LC-MS (Method 8B): Rt 2.72 mins; MS m/z 475.1 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.89 (s, 1H), 7.70 (d, J= 8.0 Hz, 1H), 7.68 (d, J= 7.7 Hz, 1H), 7.48 (t, J= 7.8 Hz, 1H), 7.00 (s, 2H), 4.17 (t, J= 8.1 Hz, 2H), 4.05 – 3.93 (m, 2H), 3.77 – 3.64 (m, 4H), 3.29 – 3.23 (m, 1H), 2.47 – 2.44 (m, 4H), 2.43 (s, 6H). NH proton not observed.
6.113	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-tetrahydropyran-4-yl-piperazine-1-carboxamide diformate salt	LC-MS (Method 7B): Rt 2.68 mins; MS m/z 503.4 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.27 (s, 1H), 8.14 (s, 2H), 7.89 (t, J = 1.5 Hz, 1H), 7.82 (dt, J = 7.7, 1.3 Hz, 1H), 7.70 (dt, J = 8.0, 1.4 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 3.88 (dd, J = 11.0, 3.5 Hz, 2H), 3.53 (s, 4H), 3.27 (t, J = 11.0 Hz, 2H), 2.43 (tt, J = 11.3, 3.6 Hz, 1H), 2.36 (s, 6H), 1.73 – 1.67 (m, 2H), 1.41 (qd, J = 12.2, 4.4 Hz, 2H). 2 x CH_2 signals not observed.
6.114	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-pyrrolidin-1-yl-azetidine-1-carboxamide	LC-MS (Method 7B): Rt 2.86 mins; MS m/z 459.4 = [M+H]+ 1H NMR (400 MHz, DMSO-d6) δ 11.29 (s, 1H), 7.87 (t, J = 1.6 Hz, 1H), 7.81 (dt, J = 7.8, 1.3 Hz, 1H), 7.70 (dt, J = 8.1, 1.5 Hz, 1H), 7.55 (dd, J = 7.8 Hz, 1H), 6.92 (s, 2H), 4.16 – 4.01 (m, 2H), 3.90 – 3.82 (m, 2H), 3.30 – 3.24 (m, 1H), 2.46 – 2.40 (m, 4H), 2.36 (s, 6H), 1.74 – 1.67 (m, 4H).

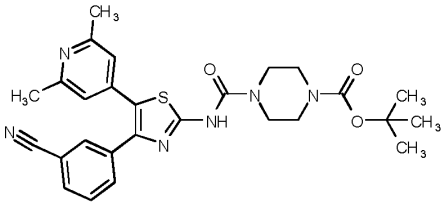
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
6.115	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(dimethylamino)azetidine-1-carboxamide	LC-MS (Method 7B): Rt 2.58 mins; MS m/z 433.3 = [M+H]+ 1H NMR (400 MHz, DMSO-d6) δ 11.30 (s, 1H), 7.87 (t, J = 1.5 Hz, 1H), 7.81 (dt, J = 7.7, 1.2 Hz, 1H), 7.70 (dt, J = 7.8, 1.3 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 4.10 – 4.01 (m, 2H), 3.86 – 3.78 (m, 2H), 3.13 – 3.06 (m, 1H), 2.36 (s, 6H), 2.10 (s, 6H).
6.116	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(morpholinomethyl)piperidine-1-carboxamide formate salt	LC-MS (Method 7B): Rt 3.38 mins; MS m/z 517.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.16 (s, 1H), 8.14 (s, 1H), 7.89 (t, J = 1.5 Hz, 1H), 7.82 (dt, J = 7.7, 1.3 Hz, 1H), 7.70 (dt, J = 8.0, 1.3 Hz, 1H), 7.56 (dd, J = 7.8 Hz, 1H), 6.92 (s, 2H), 4.22 – 4.15 (m, 2H), 3.61 – 3.53 (m, 4H), 2.89 – 2.79 (m, 2H), 2.36 (s, 6H), 2.35 – 2.27 (m, 4H), 2.16 – 2.11 (m, 2H), 1.81 – 1.69 (m, 3H), 1.07 – 0.97 (m, 2H).
6.120	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-3,6-diazabicyclo[3.2.0]heptane-6-carboxamide	LC-MS (Method 7A): Rt 0.95 mins; MS m/z 445.0 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.89 (t, J = 1.7 Hz, 1H), 7.71 (dt, J = 7.9, 1.4 Hz, 1H), 7.68 (dt, J = 7.8, 1.4 Hz, 1H), 7.48 (dd, J = 7.9, 7.9 Hz, 1H), 7.00 (s, 2H), 4.22 – 4.15 (m, 1H), 3.87 – 3.82 (m, 1H), 3.40 (d, J = 11.3 Hz, 1H), 3.18 – 3.12 (m, 1H), 3.08 (d, J = 10.3 Hz, 1H), 2.45 (s, 3H), 2.43 (s, 6H), 2.18 (dd, J = 10.4, 5.9 Hz, 1H), 2.11 (dd, J = 11.3, 4.0 Hz, 1H). NH proton and 1 x CH proton not observed.
6.121	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,4-diazabicyclo[3.2.1]octane-4-carboxamide	LC-MS (Method 7A): Rt 0.91 mins; MS m/z 445.3 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.90 (t, J = 1.8 Hz, 1H), 7.71 (dt, J = 7.9, 1.5 Hz, 1H), 7.68 (dt, J = 7.8, 1.4 Hz, 1H), 7.48 (dd, J = 7.8, 7.8 Hz, 1H), 6.99 (s, 2H), 4.82 – 4.79 (m, 1H), 3.81 (dd, J = 13.6, 5.6 Hz, 1H), 3.38 – 3.32 (m, 1H), 3.14 – 3.07 (m, 1H), 3.06 – 2.97 (m, 3H), 2.79 (dd, J = 13.5, 4.8 Hz, 1H), 2.68 – 2.63 (m, 1H), 2.43 (s, 6H), 2.16 – 2.08 (m, 1H), 2.02 – 1.94 (m, 1H). NH proton not observed.

Example 7

N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide



Step 1: *tert*-Butyl 4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]piperazine-1-carboxylate



[00275] A solution of 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) (50 mg, 0.16 mmol) and CDI (40 mg, 0.24 mmol) in DMA (0.5 mL) was stirred at 50 °C for 18 h. The resulting mixture was treated with *tert*-butyl piperazine-1-carboxylate (61 mg, 0.33 mmol) and stirring continued at 50 °C for 1 h. After cooling to room temperature, the crude mixture was diluted with water (10 mL) and the precipitate was collected by vacuum filtration. The solid was dissolved in DCM, filtered through a phase separating cartridge and concentrated *in vacuo*. Purification of the crude product by chromatography on silica eluting with 0-100% EtOAc in DCM afforded the title compound.
LC-MS (Method 7A): Rt 2.16 mins; MS m/z 519.3 = [M+H]+

^{1}H NMR (500 MHz, DMSO-d6) δ 11.30 (s, 1H), 7.89 (t, *J* = 1.4 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.71 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 3.55 – 3.49 (m, 4H), 3.39 – 3.34 (m, 4H), 2.36 (s, 6H), 1.42 (s, 9H).

Step 2: N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide

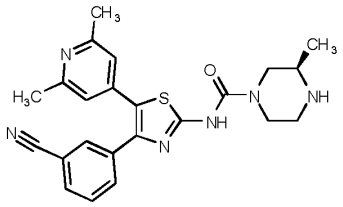
[00276] A solution of *tert*-butyl 4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]piperazine-1-carboxylate (step 1)(70 mg, 0.14 mmol) in DCM (2 mL), MeOH (2 drops) and 4M HCl in 1,4-dioxane (338 µL, 1.35 mmol) was stirred at room temperature for 22 h. The resulting mixture was concentrated *in vacuo* and purification of the crude product by preparative HPLC using basic conditions, early elution method to afford the title compound.

LC-MS (Method 7A): Rt 0.94 mins; MS m/z 419.2 = [M+H]+

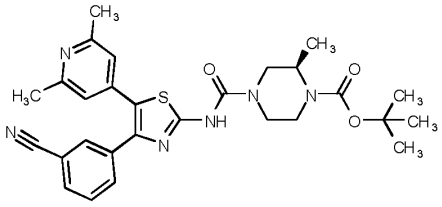
^{1}H NMR (400 MHz, DMSO-d6) δ 7.88 (s, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.92 (s, 2H), 3.50 – 3.43 (m, 4H), 2.74 – 2.68 (m, 4H), 2.36 (s, 6H). 2 x NH protons not observed.

Example 7.1

(3R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide



Step 1: *tert*-Butyl (2R)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2-methyl-piperazine-1-carboxylate



[00277] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl (2R)-2-methylpiperazine-1-carboxylate analogously to Example 7 step 1.
LC-MS (Method 2A): Rt 1.07 mins; MS m/z 533.3 = [M+H]+

^{1}H NMR (400 MHz, DMSO-d6) δ 11.30 (s, 1H), 7.89 (t, *J* = 1.5 Hz, 1H), 7.82 (dt, *J* = 7.7, 1.7 Hz, 1H), 7.71 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 4.20 – 4.09 (m, 2H), 4.02 (d, *J* = 13.7 Hz, 1H), 3.78 – 3.69 (m, 1H), 3.14 (dd, *J* = 13.7, 4.1 Hz, 1H), 3.09 – 3.00 (m, 1H), 2.99 – 2.89 (m, 1H), 2.36 (s, 6H), 1.42 (s, 9H), 1.07 (d, *J* = 6.7 Hz, 3H).

Step 2: (3R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide

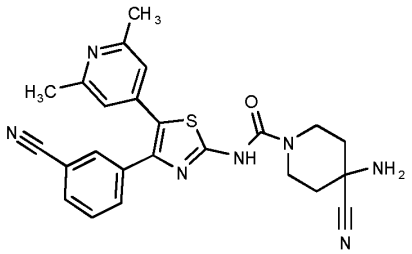
[00278] The title compound was prepared from *tert*-butyl (2R)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2-methyl-piperazine-1-carboxylate and 4M HCl in 1,4-dioxane analogously to Example 7 step 2.

LC-MS (Method 7A): Rt 1.00 mins; MS m/z 433.2 = [M+H]+

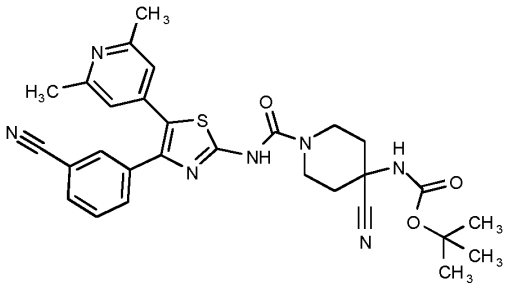
^{1}H NMR (400 MHz, DMSO-d6) δ 7.89 (t, *J* = 1.5 Hz, 1H), 7.82 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 2H), 4.18 – 4.08 (m, 2H), 3.06 (d, *J* = 11.6 Hz, 1H), 3.02 – 2.91 (m, 2H), 2.88 (s, 1H), 2.82 – 2.73 (m, 1H), 2.36 (s, 6H), 1.08 (d, *J* = 6.3 Hz, 3H). 2x NH protons not observed.

Example 7.2

4-Amino-4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide



Step 1: *tert*-Butyl N-[4-cyano-1-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-4-piperidyl]carbamate



[00279] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl N-(4-cyano-4-piperidyl)carbamate analogously to Example 7 step 1.
LC-MS (Method 5B): Rt 2.95 mins; MS m/z 558.2 = [M+H]+

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.34 (s, 1H), 7.88 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.77 (s, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 6.92 (s, 2H), 3.94 – 3.86 (m, 2H), 2.36 (s, 6H), 2.23 – 2.17 (m, 2H), 1.87 – 1.81 (m, 2H), 1.43 (s, 9H). 1 x CH_2 signal not observed.

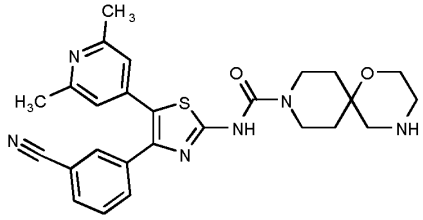
Step 2: 4-Amino-4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide

[00280] The title compound was prepared from *tert*-butyl N-[4-cyano-1-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-4-piperidyl]carbamate and 4M HCl in 1,4-dioxane analogously to Example 7 step 2.
LC-MS (Method 8B): Rt 3.30 mins; MS m/z 458.3 = [M+H]+

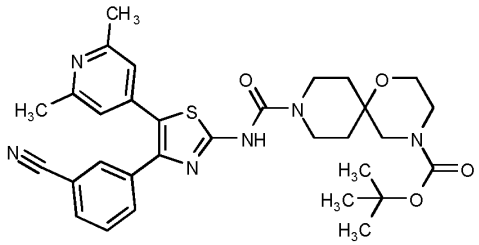
^{1}H NMR (500 MHz, DMSO-d_6) δ 11.31 (s, 1H), 7.88 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 6.92 (s, 2H), 3.97 – 3.77 (m, 3H), 2.77 – 2.65 (m, 2H), 2.46 – 2.40 (m, 1H), 2.36 (s, 6H), 2.02 – 1.86 (m, 2H), 1.70 – 1.53 (m, 2H).

Example 7.3

N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxamide



Step 1: *tert*-Butyl 9-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate



[00281] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate analogously to Example 7 step 1.
LC-MS (Method 2A): Rt 0.77 mins; MS m/z 589.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.22 (s, 1H), 7.89 (t, J = 1.5 Hz, 1H), 7.82 (dt, J = 7.7, 1.3 Hz, 1H), 7.70 (dt, J = 8.0, 1.3 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 6.92 (s, 2H), 3.86 – 3.78 (m, 2H), 3.64 – 3.59 (m, 2H), 3.36 – 3.32 (m, 2H), 3.28 – 3.16 (m, 4H), 2.36 (s, 6H), 1.75 – 1.69 (m, 2H), 1.52 – 1.44 (m, 2H), 1.41 (s, 9H).

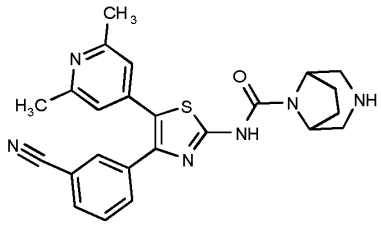
Step 2: N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxamide

[00282] The title compound was prepared from *tert*-butyl 9-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (step 1) and 4M HCl in 1,4-dioxane analogously to Example 7 step 2.
LC-MS (Method 7B): Rt 2.68 mins; MS m/z 489.4 = [M+H]+

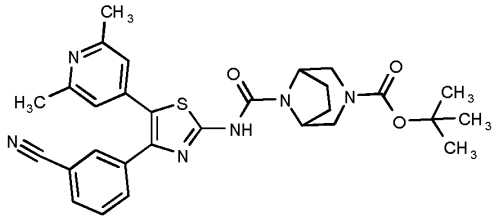
1H NMR (500 MHz, DMSO-d6) δ 7.88 (t, J = 1.7 Hz, 1H), 7.81 (dt, J = 7.9, 1.4 Hz, 1H), 7.70 (dt, J = 8.2, 1.4 Hz, 1H), 7.55 (dd, J = 7.8, 7.8 Hz, 1H), 6.91 (s, 2H), 3.83 (dt, J = 13.2, 4.1 Hz, 2H), 3.56 – 3.52 (m, 2H), 3.23 – 3.15 (m, 2H), 2.64 (td, J = 3.9, 2.1 Hz, 2H), 2.54 (s, 2H), 2.35 (s, 6H), 1.89 – 1.83 (m, 2H), 1.45 – 1.37 (m, 2H). 2 x NH protons not observed

Example 7.4

N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxamide



Step 1: *tert*-Butyl 8-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[00283] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate analogously to Example 7 step 1.
LC-MS (Method 2A): Rt 0.77 mins; MS m/z 545.3 = [M+H]+

1H NMR (400 MHz, DMSO-D6) δ 11.37 (s, 1H), 7.88 (d, J = 1.7 Hz, 1H), 7.82 (dt, J = 7.8, 1.4 Hz, 1H), 7.70 (dt, J = 8.1, 1.4 Hz, 1H), 7.56 (dd, J = 7.8, 7.8 Hz, 1H), 6.93 (s, 2H), 4.60 – 4.49 (m, 2H), 3.80 – 3.66 (m, 2H), 3.09 – 3.02 (m, 1H), 2.96 – 2.89 (m, 1H), 2.36 (s, 6H), 1.89 – 1.80 (m, 2H), 1.62 (q, J = 7.0 Hz, 2H), 1.41 (s, 9H).

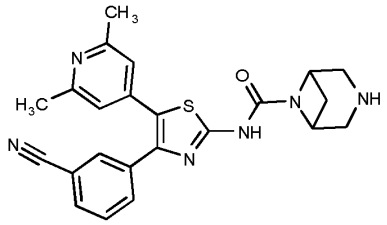
Step 2: N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxamide

[00284] The title compound was prepared from *tert*-butyl 8-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (step 1) and 4M HCl in 1,4-dioxane analogously to Example 7 step 2.
LC-MS (Method 7B): Rt 2.57 mins; MS m/z 445.4 = [M+H]+

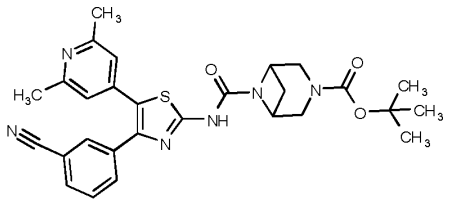
1H NMR (500 MHz, Methanol-d4) δ 7.91 (t, J = 1.7 Hz, 1H), 7.72 (dt, J = 7.9, 1.4 Hz, 1H), 7.68 (dt, J = 7.8, 1.4 Hz, 1H), 7.48 (dd, J = 7.8, 7.8 Hz, 1H), 7.01 (s, 2H), 4.43 – 4.37 (m, 2H), 2.98 (dd, J = 13.1, 2.0 Hz, 2H), 2.74 (dd, J = 13.1, 2.1 Hz, 2H), 2.44 (s, 6H), 2.05 – 1.98 (m, 4H). 2 x NH protons not observed.

Example 7.5

N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,6-diazabicyclo[3.1.1]heptane-6-carboxamide



Step 1: *tert*-Butyl 6-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate



[00285] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate analogously to Example 7 step 1.
LC-MS (Method 2A): Rt 0.70 mins; MS m/z 531.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.59 (s, 1H), 7.87 (t, J = 1.7 Hz, 1H), 7.82 (dt, J = 7.7, 1.4 Hz, 1H), 7.69 (dt, J = 8.0, 1.4 Hz, 1H), 7.56 (dd, J = 7.8, 7.8 Hz, 1H), 6.92 (s, 2H), 4.53 –

4.35 (m, 2H), 3.87 – 3.70 (m, 2H), 3.42 – 3.34 (m, 2H), 2.59 (q, J = 7.1 Hz, 1H), 2.35 (s, 6H), 1.45 (d, J = 8.9 Hz, 1H), 1.38 (s, 9H).

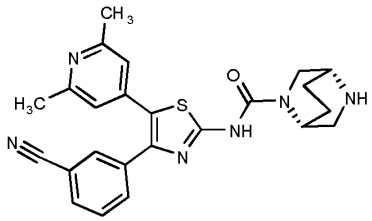
Step 2: N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,6-diazabicyclo[3.1.1]heptane-6-carboxamide

[00286] The title compound was prepared from *tert*-butyl 6-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (step 1) and 4M HCl in 1,4-dioxane analogously to Example 7 step 2.
LC-MS (Method 7A): Rt 0.98 mins; MS m/z 431.3 = [M+H]+

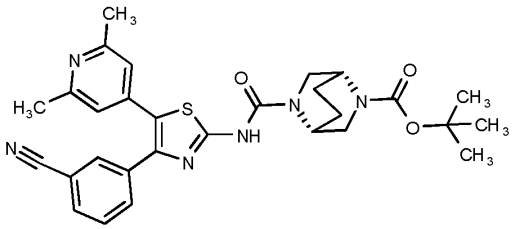
1H NMR (500 MHz, Methanol-d4) δ 7.90 (t, J = 1.7 Hz, 1H), 7.71 (dt, J = 8.0, 1.4 Hz, 1H), 7.68 (dt, J = 7.8, 1.4 Hz, 1H), 7.51 – 7.45 (m, 1H), 7.01 (s, 2H), 4.43 – 4.38 (m, 2H), 3.48 (d, J = 13.2 Hz, 2H), 2.99 (dd, J = 13.0, 1.9 Hz, 2H), 2.76 – 2.70 (m, 1H), 2.44 (s, 6H), 1.84 (d, J = 8.8 Hz, 1H). 2 x NH protons not observed

Example 7.6

(1R,4R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide



Step 1: *tert*-Butyl (1R,4R)-5-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,5-diazabicyclo[2.2.2]octane-2-carboxylate



[00287] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl (2R,5R)-5-ethyl-2-methyl-piperazine-1-carboxylate analogously to Example 7 step 1.

LC-MS (Method 2A): Rt 0.76 mins; MS m/z 545.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.07 (s, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.82 (dt, J = 7.8, 1.5 Hz, 1H), 7.71 (dt, J = 8.0, 1.4 Hz, 1H), 7.56 (dd, J = 7.8, 7.8 Hz, 1H), 6.93 (s, 2H), 4.50 – 4.37 (m, 1H), 4.23 – 4.13 (m, 1H), 3.68 – 3.38 (m, 4H), 2.36 (s, 6H), 1.91 – 1.73 (m, 4H), 1.41 (d, J = 3.3 Hz, 9H).

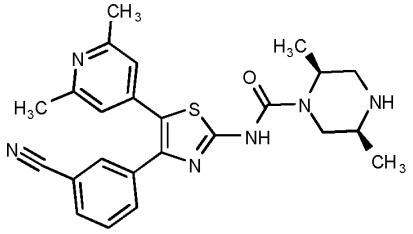
Step 2: (1R,4R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide

[00288] The title compound was prepared from *tert*-butyl (1R,4R)-5-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,5-diazabicyclo[2.2.2]octane-2-carboxylate (step 1) and 4M HCl in 1,4-dioxane analogously to Example 7 step 2.
LC-MS (Method 7A): Rt 0.99 mins; MS m/z 445.3 = [M+H]+

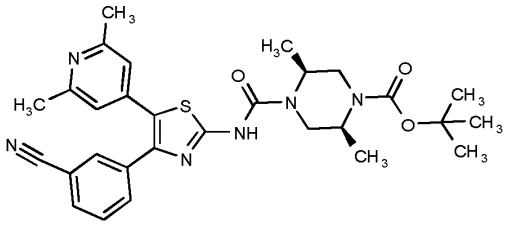
1H NMR (500 MHz, Methanol-d4) δ 7.91 (t, J = 1.7 Hz, 1H), 7.72 (dt, J = 8.0, 1.5 Hz, 1H), 7.68 (dt, J = 7.8, 1.4 Hz, 1H), 7.49 (dd, J = 7.8, 7.8 Hz, 1H), 7.00 (s, 2H), 4.27 (s, 1H), 3.78 (d, J = 10.7 Hz, 1H), 3.64 (d, J = 10.7 Hz, 1H), 3.28 – 3.23 (m, 1H), 3.22 – 3.18 (m, 1H), 3.11 (dd, J = 11.5, 1.9 Hz, 1H), 2.43 (s, 6H), 2.08 – 1.98 (m, 2H), 1.97 – 1.89 (m, 1H), 1.88 – 1.80 (m, 1H). 2 x NH protons not observed.

Example 7.7

(2S,5S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-dimethyl-piperazine-1-carboxamide



Step 1: *tert*-Butyl (2S,5S)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,5-dimethyl-piperazine-1-carboxylate



[00289] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-

pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl cis-(2S,5S)-2,5-dimethylpiperazine-1-carboxylate analogously to Example 7 step 1.
LC-MS (Method 7A): Rt 0.80 mins; MS m/z 547.4 = [M+H]+

1H NMR (400 MHz, DMSO-d6) δ 11.19 (s, 1H), 7.89 (t, J = 1.7 Hz, 1H), 7.82 (dt, J = 7.8, 1.4 Hz, 1H), 7.70 (dt, J = 8.0, 1.4 Hz, 1H), 7.56 (dd, J = 7.8, 7.8 Hz, 1H), 6.93 (s, 2H), 4.20 – 4.08 (m, 2H), 3.95 – 3.84 (m, 2H), 2.96 (dd, J = 14.6, 11.2 Hz, 1H), 2.88 (dd, J = 14.2, 10.7 Hz, 1H), 2.36 (s, 6H), 1.39 (s, 9H), 1.10 (d, J = 6.1 Hz, 3H), 1.06 (d, J = 6.1 Hz, 3H).

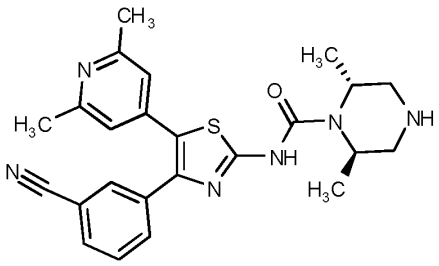
Step 2: (2S,5S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-dimethyl-piperazine-1-carboxamide

[00290] The title compound was prepared from *tert*-butyl (2S,5S)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,5-dimethyl-piperazine-1-carboxylate (step 1) and 4M HCl in 1,4-dioxane analogously to Example 7 step 2.
LC-MS (Method 7B): Rt 2.72 mins; MS m/z 447.3 = [M+H]+

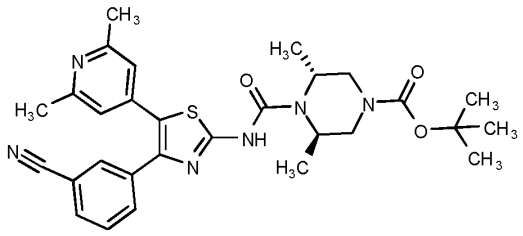
1H NMR (500 MHz, Methanol-d4) δ 7.91 (t, J = 1.7 Hz, 1H), 7.71 (dt, J = 7.9, 1.4 Hz, 1H), 7.69 (dt, J = 7.8, 1.4 Hz, 1H), 7.49 (dd, J = 7.8, 7.8 Hz, 1H), 7.00 (s, 2H), 4.37 – 4.29 (m, 1H), 3.98 – 3.90 (m, 1H), 2.99 (dd, J = 12.9, 4.2 Hz, 1H), 2.90 (dd, J = 12.9, 1.5 Hz, 1H), 2.78 – 2.69 (m, 2H), 2.43 (s, 6H), 1.31 (d, J = 6.9 Hz, 3H), 1.16 (d, J = 5.8 Hz, 3H). 2 x NH protons not observed.

Example 7.8

(2R,6R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,6-dimethyl-piperazine-1-carboxamide



Step 1: *tert*-Butyl (3R,5R)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3,5-dimethyl-piperazine-1-carboxylate



[00291] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl (3R,5R)-3,5-dimethylpiperazine-1-carboxylate analogously to Example 7 step 1.
LC-MS (Method 2A): Rt 0.81 mins; MS m/z 547.3 = [M+H]+

1H NMR (400 MHz, DMSO-d6) δ 11.16 (s, 1H), 7.90 (t, J = 1.7 Hz, 1H), 7.82 (dt, J = 7.8, 1.2 Hz, 1H), 7.71 (dt, J = 8.3, 1.2 Hz, 1H), 7.56 (dd, J = 7.8, 7.8 Hz, 1H), 6.92 (s, 2H), 4.39 – 4.29 (m, 2H), 3.61 – 3.45 (m, 4H), 2.35 (s, 6H), 1.43 (s, 9H), 1.23 – 1.17 (m, 6H).

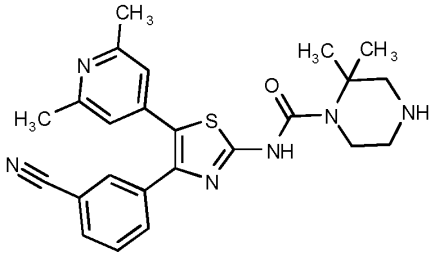
Step 2: (2R,6R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,6-dimethyl-piperazine-1-carboxamide

[00292] The title compound was prepared from *tert*-butyl rac-(3R,5R)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3,5-dimethyl-piperazine-1-carboxylate (step 1) and 4M HCl in 1,4-dioxane analogously to Example 7 step 2.
LC-MS (Method 7B): Rt 2.73 mins; MS m/z 447.4 = [M+H]+

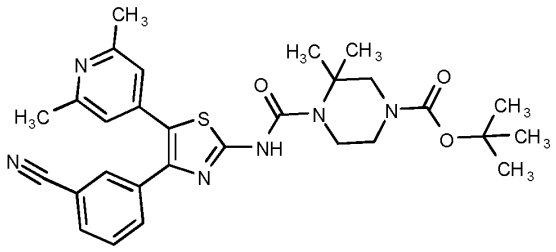
1H NMR (400 MHz, Methanol-d4) δ 7.91 (t, J = 1.7 Hz, 1H), 7.72 (dt, J = 8.0, 1.5 Hz, 1H), 7.69 (dt, J = 7.8, 1.4 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.01 (s, 2H), 4.02 – 3.95 (m, 2H), 3.21 (dd, J = 13.0, 3.9 Hz, 2H), 2.78 (dd, J = 13.1, 4.5 Hz, 2H), 2.44 (s, 6H), 1.34 (d, J = 6.5 Hz, 6H). - 2 x NH protons not observed

Example 7.9

N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,2-dimethyl-piperazine-1-carboxamide



Step 1: *tert*-Butyl 4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3,3-dimethyl-piperazine-1-carboxylate



[00293] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate analogously to Example 7 step 1.
LC-MS (Method 2A): Rt 0.83 mins; MS m/z 547.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.24 (s, 1H), 7.87 (t, J = 1.7 Hz, 1H), 7.82 (dt, J = 7.7, 1.5 Hz, 1H), 7.70 (dt, J = 8.1, 1.4 Hz, 1H), 7.56 (dd, J = 7.8, 7.8 Hz, 1H), 6.92 (s, 2H), 3.71 – 3.65 (m, 2H), 3.45 – 3.36 (m, 4H), 2.35 (s, 6H), 1.42 (s, 9H), 1.39 (s, 6H).

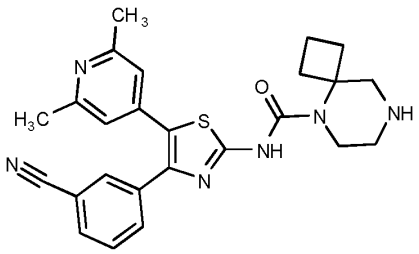
Step 2: N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,2-dimethyl-piperazine-1-carboxamide

[00294] The title compound was prepared from *tert*-butyl 4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3,3-dimethyl-piperazine-1-carboxylate (step 1) and 4M HCl in 1,4-dioxane analogously to Example 7 step 2.
LC-MS (Method 7B): Rt 2.88 mins; MS m/z 447.4 = [M+H]+

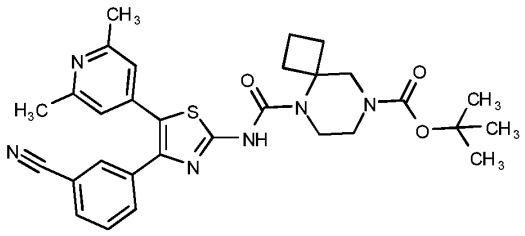
1H NMR (400 MHz, Methanol-d4) δ 7.89 (t, J = 1.5 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.49 (dd, J = 7.8, 7.8 Hz, 1H), 7.00 (s, 2H), 3.50 – 3.45 (m, 2H), 2.99 – 2.93 (m, 2H), 2.69 (s, 2H), 2.44 (s, 6H), 1.47 (s, 6H). 2 x NH protons not observed.

Example 7.10

N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5,8-diazaspiro[3.5]nonane-5-carboxamide



Step 1: *tert*-Butyl 5-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-5,8-diazaspiro[3.5]nonane-8-carboxylate



[00295] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl 5,8-diazaspiro[3.5]nonane-8-carboxylate analogously to Example 7 step 1.
LC-MS (Method 2A): Rt 0.83 mins; MS m/z 559.3 = [M+H]+

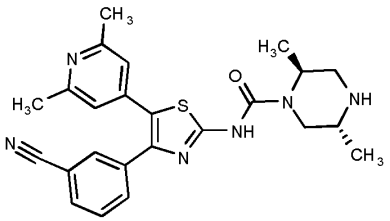
1H NMR (400 MHz, DMSO-d6) δ 11.40 (s, 1H), 7.87 (t, J = 1.7 Hz, 1H), 7.82 (dt, J = 7.8, 1.5 Hz, 1H), 7.70 (dt, J = 8.0, 1.4 Hz, 1H), 7.56 (dd, J = 7.8, 7.8 Hz, 1H), 6.93 (s, 2H), 3.53 (s, 2H), 3.50 – 3.44 (m, 2H), 3.29 – 3.25 (m, 2H), 2.35 (s, 6H), 2.28 – 2.16 (m, 3H), 2.04 – 1.97 (m, 2H), 1.81 – 1.75 (m, 1H), 1.42 (s, 9H).

Step 2: N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5,8-diazaspiro[3.5]nonane-5-carboxamide

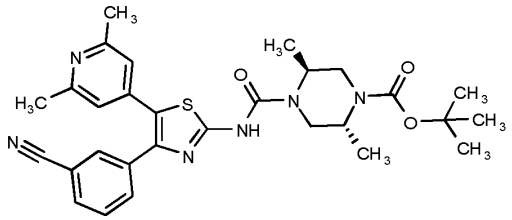
[00296] The title compound was prepared from *tert*-butyl 5-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-5,8-diazaspiro[3.5]nonane-8-carboxylate (step 1) and 4M HCl in 1,4-dioxane analogously to Example 7 step 2.
LC-MS (Method 7B): Rt 2.48 mins; MS m/z 459.3 = [M+H]+

1H NMR (400 MHz, Methanol-d4) δ 7.89 (t, J = 1.7 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.48 (dd, J = 7.8, 0.6 Hz, 1H), 6.99 (s, 2H), 3.51 – 3.47 (m, 2H), 3.01 (s, 2H), 2.73 – 2.69 (m, 2H), 2.43 (s, 6H), 2.33 – 2.25 (m, 4H), 1.88 – 1.69 (m, 2H). 2 x NH protons not observed.

Example 7.11
***trans*-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-dimethyl-piperazine-1-carboxamide**



Step 1: *tert*-Butyl trans-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,5-dimethyl-piperazine-1-carboxylate



[00297] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl trans-2,5-dimethylpiperazine-1-carboxylate analogously to Example 7 step 1

LC-MS (Method 2A): Rt 0.81 mins; MS m/z 547.3 = [M+H]+

1H NMR (400 MHz, DMSO-d6) δ 11.29 (s, 1H), 7.89 (t, J = 1.7 Hz, 1H), 7.85 – 7.78 (m, 1H), 7.70 (dt, J = 8.2, 1.6 Hz, 1H), 7.56 (dd, J = 7.8, 7.8 Hz, 1H), 6.92 (s, 2H), 4.44 (d, J = 21.6 Hz, 2H), 4.31 – 4.21 (m, 1H), 4.21 – 4.11 (m, 1H), 3.92 – 3.85 (m, 1H), 3.65 – 3.56 (m, 1H), 2.36 (s, 6H), 1.42 (s, 9H), 1.15 – 1.01 (m, 6H).

Step 2: *trans*-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-dimethyl-piperazine-1-carboxamide

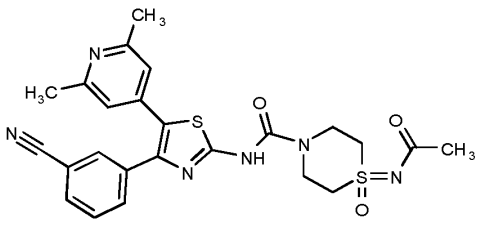
[00298] The title compound was prepared from *tert*-butyl trans-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,5-dimethyl-piperazine-1-carboxylate (step 1) and 4M HCl in 1,4-dioxane analogously to Example 7 step 2.

LC-MS (Method 7A): Rt 1.10 mins; MS m/z 447.3 = [M+H]+

1H NMR (400 MHz, Methanol-d4) δ 7.91 (t, J = 1.7 Hz, 1H), 7.74 – 7.67 (m, 2H), 7.49 (dd, J = 7.8, 7.8 Hz, 1H), 7.00 (s, 2H), 4.33 – 4.26 (m, 1H), 3.74 (dd, J = 14.0, 2.2 Hz, 1H), 3.40 (dd, J = 13.6, 4.0 Hz, 1H), 3.26 – 3.17 (m, 2H), 2.60 (dd, J = 13.5, 2.9 Hz, 1H), 2.43 (s, 6H), 1.33 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H). 2 x NH protons not observed.

Example 8

1-Acetylimino-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide



[00299] To a suspension of N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide (Example 4.2) (50 mg, 0.11 mmol) in DCM

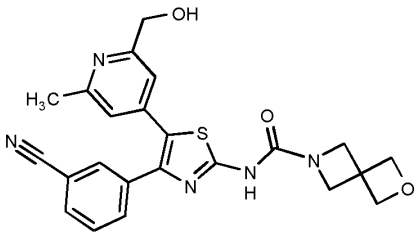
(2.5 mL) at 0 °C was added triethylamine (37 µL, 0.27 mmol) followed by acetyl chloride (10 µL, 0.14 mmol) and the mixture was stirred for 1 h. A further portion of acetyl chloride (10 µL, 0.14 mmol) was added and the reaction mixture was stirred at 0 °C for 30 mins after which time additional acetyl chloride (4 µL, 0.05 mmol) was added and the reaction mixture was stirred at 0 °C for 15 mins. The resulting mixture was concentrated *in vacuo* then partitioned between 10% MeOH in EtOAc (20 mL) and water (20 mL). The layers were separated and the aqueous layer was further extracted with 10% MeOH in EtOAc (2 x 20 mL). The combined organic extracts were concentrated *in vacuo* and purification of the crude material by C18 reverse phase chromatography eluting with 5-15% MeCN in water (+0.1% ammonium hydroxide modifier) afforded the title compound as an off-white solid.

LC-MS (Method 8B): Rt 2.16 mins; MS m/z 509.3 = [M+H]+

^{1}H NMR (500 MHz, DMSO-d6) δ 11.58 (s, 1H), 7.88 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.92 (s, 2H), 4.26 – 4.18 (m, 2H), 3.77 – 3.65 (m, 4H), 3.53 – 3.47 (m, 2H), 2.36 (s, 6H), 1.99 (s, 3H).

Example 9

N-[4-(3-Cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



[00300] A solution of 3-[2-amino-5-[2-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate I) (60 mg, 0.13 mmol) and CDI (49 mg, 0.30 mmol) in DMA (0.5 mL) was stirred at 50 °C overnight. The resulting mixture was treated with 2-oxa-6-azaspiro[3.3]heptane (30 mg, 0.30 mmol) in DMA (0.1 mL) and DIPEA (78 µL, 0.45 mmol) and stirring continued at 50 °C for 30 mins. The reaction mixture was cooled to room temperature and 1M TBAF in THF (211 µL, 0.21 mmol) was added. After stirring for 15 mins, the resulting mixture was purified by C18 reverse phase chromatography eluting with a gradient of 5 to 15% MeCN in water (+0.1% ammonium hydroxide modifier). The product fractions were combined, concentrated and loaded onto an Isolute® SCX cartridge. The column was flushed with MeOH (30 mL) and the product was eluted with 0.7 M NH_3 in MeOH (30 mL). The solvent was removed *in vacuo* and the resulting material was triturated in 2:1

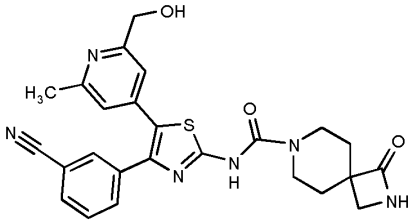
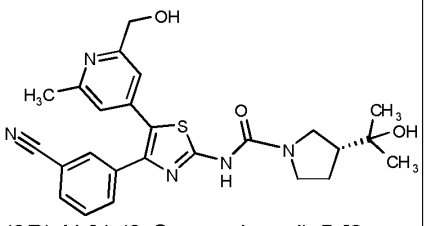
hexane/diethyl ether (1 mL) to yield a solid. The solid was purified further by chromatography on silica eluting with a gradient of 0 to 4% MeOH in DCM to afford the title compound as a yellow solid.

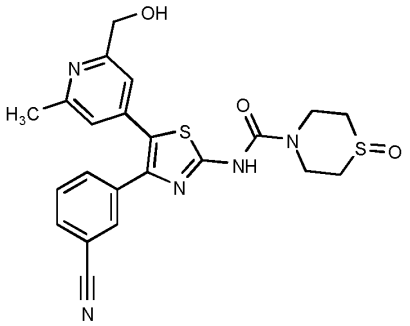
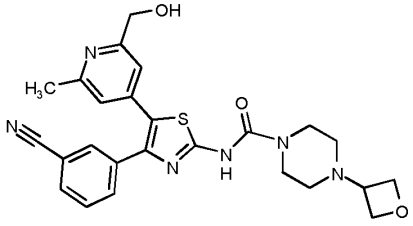
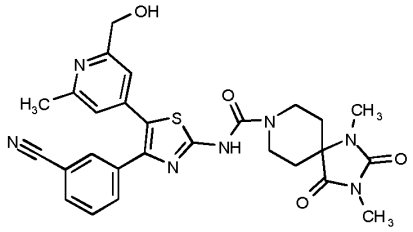
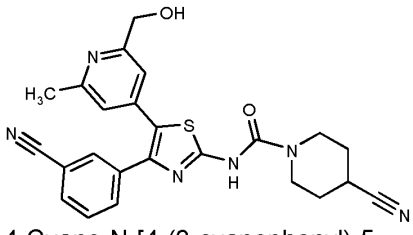
LC-MS (Method 8B): Rt 2.93 mins; MS m/z 448.3 = [M+H]+

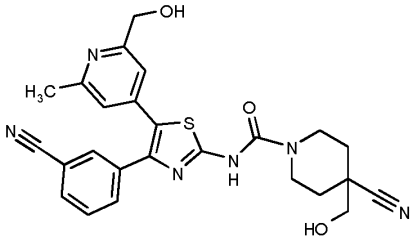
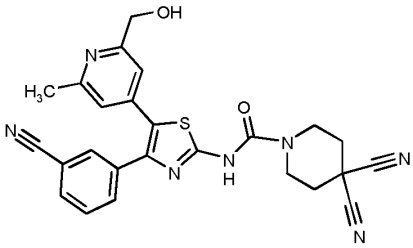
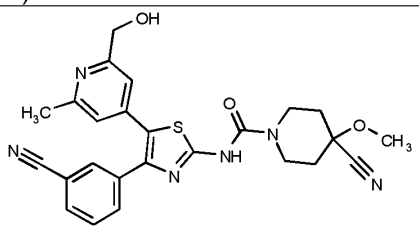
1H NMR (500 MHz, DMSO-d6) δ 11.36 (s, 1H), 7.87 (d, J = 1.5 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.71 (dt, J = 7.8, 1.5 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.13 (s, 1H), 6.96 (s, 1H), 5.32 (t, J = 5.8 Hz, 1H), 4.67 (s, 4H), 4.46 (d, J = 5.8 Hz, 2H), 4.19 (s, 4H), 2.36 (s, 3H).

[00301] The compounds of the following tabulated Examples (Table Ex9) were prepared analogously to Example 9 from 3-[2-amino-5-[2-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate I) and the appropriate amine.

Table Ex9

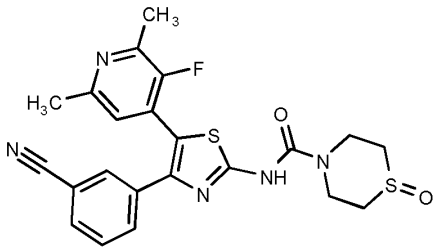
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
9.1	 N-[4-(3-Cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3-oxo-2,7-diazaspiro[3.5]nonane-7-carboxamide	LC-MS (Method 8B): Rt 3.02 mins; MS m/z 489.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.28 (s, 1H), 7.90 (d, J= 1.5 Hz, 1H), 7.85 – 7.77 (m, 2H), 7.73 (dt, J= 8.0, 1.5 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 7.15 (s, 1H), 6.98 (s, 1H), 5.32 (t, J= 5.8 Hz, 1H), 4.47 (d, J= 5.8 Hz, 2H), 3.87 (dt, J= 13.4, 5.0 Hz, 2H), 3.40 – 3.36 (m, 2H), 3.09 (s, 2H), 2.38 (s, 3H), 1.81 – 1.69 (m, 4H).
9.2	 (3R)-N-[4-(3-Cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide	LC-MS (Method 8B): Rt 3.66 mins; MS m/z 478.3 = [M+H]+ ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.91 (t, *J* = 1.5 Hz, 1H), 7.73 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.68 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.29 (s, 1H), 7.07 (s, 1H), 4.61 (s, 2H), 3.72 (t, *J* = 9.3 Hz, 1H), 3.68 – 3.63 (m, 1H), 3.46 – 3.41 (m, 1H), 3.41 – 3.35 (m, 1H), 2.45 (s, 3H), 2.43 – 2.34 (m, 1H), 2.09 – 1.98 (m, 1H), 1.98 – 1.85 (m, 1H), 1.26 (d, *J* = 1.8 Hz, 6H). NH and 2 x OH protons not observed.

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
9.3	 N-[4-(3-Cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide	LC-MS (Method 8B): Rt 2.71 mins; MS m/z 468.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.45 (s, 1H), 7.89 (t, J = 1.5 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.72 (dt, J = 7.8, 1.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.14 (s, 1H), 6.98 (s, 1H), 5.32 (t, J = 5.8 Hz, 1H), 4.47 (d, J = 5.8 Hz, 2H), 4.16 – 4.07 (m, 2H), 3.79 (t, J = 13.1 Hz, 2H), 2.93 (t, J = 12.5 Hz, 2H), 2.75 (d, J = 13.7 Hz, 2H), 2.37 (s, 3H).
9.4	 N-[4-(3-Cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide	LC-MS (Method 8B): Rt 2.97 mins; MS m/z 491.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.27 (s, 1H), 7.89 (t, J= 1.5 Hz, 1H), 7.82 (dt, J= 7.8, 1.5 Hz, 1H), 7.72 (dt, J= 7.8, 1.5 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 7.14 (s, 1H), 6.98 (s, 1H), 5.32 (t, J= 5.8 Hz, 1H), 4.54 (t, J= 6.5 Hz, 2H), 4.51 – 4.40 (m, 4H), 3.57 (t, J= 4.9 Hz, 4H), 3.45 – 3.40 (m, 1H), 2.37 (s, 3H), 2.28 (t,J= 4.9 Hz, 4H).
9.5	 N-[4-(3-Cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-1,3-dimethyl-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide	LC-MS (Method 8B): Rt 3.44 mins; MS m/z 546.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.32 (s, 1H), 7.89 (d, J= 1.5 Hz, 1H), 7.82 (d, J= 7.9 Hz, 1H), 7.72 (dt, J= 7.9, 1.5 Hz, 1H), 7.56 (t, J= 7.9 Hz, 1H), 7.15 (s, 1H), 6.98 (s, 1H), 5.32 (t, J= 5.8 Hz, 1H), 4.47 (d, J= 5.8 Hz, 2H), 4.25 (d, J= 13.1 Hz, 2H), 3.49 (d, J= 13.1 Hz, 2H), 2.87 (s, 3H), 2.76 (s, 3H), 2.37 (s, 3H), 1.92 (td, J= 13.1, 4.6 Hz, 2H), 1.72 (d, J= 13.1 Hz, 2H).
9.6	 4-Cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]piperidine-1-carboxamide	LC-MS (Method 8B): Rt 3.60 mins; MS m/z 459.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.30 (s, 1H), 7.89 (t, J = 1.5 Hz, 1H), 7.82 (dt, J = 7.8, 1.5 Hz, 1H), 7.72 (dt, J = 7.8, 1.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.14 (s, 1H), 6.97 (s, 1H), 5.32 (t, J = 5.8 Hz, 1H), 4.47 (d, J = 5.8 Hz, 2H), 3.85 – 3.73 (m, 2H), 3.41 – 3.34 (m, 2H), 3.14 – 3.08 (m, 1H), 2.37 (s, 3H), 1.95 – 1.86 (m, 2H), 1.75 – 1.65 (m, 2H).

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
9.7	 4-Cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-(hydroxymethyl)piperidine-1-carboxamide (Prepared from amine Intermediate E)	LC-MS (Method 8B): Rt 3.00 mins; MS m/z 489.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.33 (s, 1H), 7.90 (s, 1H), 7.83 (d, J= 7.8 Hz, 1H), 7.72 (d, J= 7.8 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 7.15 (s, 1H), 6.98 (s, 1H), 5.49 (t, J= 5.8 Hz, 1H), 5.33 (t, J= 5.8 Hz, 1H), 4.47 (d, J= 5.8 Hz, 2H), 4.28 (d, J= 14.0 Hz, 2H), 3.51 (d, J= 5.8 Hz, 2H), 3.02 (t, J= 13.0 Hz, 2H), 2.38 (s, 3H), 1.90 (d, J= 13.7 Hz, 2H), 1.51 (td, J= 13.4, 4.0 Hz, 2H).
9.8	 4,4-Dicyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]piperidine-1-carboxamide (Prepared from amine Intermediate F)	LC-MS (Method 8B): Rt 3.51 mins; MS m/z 484.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.43 (s, 1H), 7.90 (t, J= 1.8 Hz, 1H), 7.84 (dt, J= 7.7, 1.5 Hz, 1H), 7.73 (dt, J= 8.0, 1.4 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 7.15 (s, 1H), 6.99 (s, 1H), 5.33 (t, J= 5.8 Hz, 1H), 4.48 (d, J= 6.1 Hz, 2H), 3.70 (t, J= 5.4 Hz, 4H), 2.37 (d, J= 10.5 Hz, 7H).
9.9	 4-Cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methoxy-piperidine-1-carboxamide	LC-MS (Method 8B): Rt 3.92 mins; MS m/z 489.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.37 (s, 1H), 7.90 (t, J= 1.7 Hz, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.72 (dt, J= 8.1, 1.4 Hz, 1H), 7.57 (t, J= 7.9 Hz, 1H), 7.17 – 7.13 (m, 1H), 6.99 (s, 1H), 5.33 (t, J= 5.8 Hz, 1H), 4.47 (d, J= 5.9 Hz, 2H), 3.70 (s, 2H), 3.57 – 3.49 (m, 2H), 3.41 (s, 3H), 2.38 (s, 3H), 2.18 – 2.10 (m, 2H), 1.94 – 1.87 (m, 2H).

Example 10

N-[4-(3-Cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide



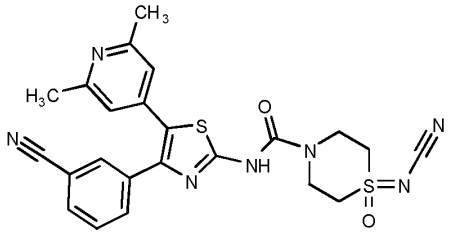
[00302] The title compound was prepared from 3-[2-amino-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate M) and 1,4-thiazinane 1-oxide hydrochloride analogously to Example 6.

LC-MS (Method 8A): Rt 2.64 mins; MS m/z 470.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.51 (s, 1H), 7.89 (s, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.11 (d, J = 4.9 Hz, 1H), 4.12 (d, J = 14.7 Hz, 2H), 3.79 (t, J = 13.1 Hz, 2H), 2.94 (t, J = 12.5 Hz, 2H), 2.75 (d, J = 13.6 Hz, 2H), 2.41 – 2.32 (m, 6H).

Example 11

1-Cyanoimino-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide



[00303] To a suspension of N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide (Example 4.2)(50 mg, 0.11 mmol) in DCM (2 mL) at 0 °C was added DMAP (14 mg, 0.12 mmol) followed by cyanogen bromide (23 mg, 0.21 mmol) and the mixture was stirred at 0 °C for 1h 10 mins. Further cyanogen bromide (3 mg, 0.03 mmol) and DMAP (2 mg, 0.02 mmol) were added and stirring continued at 0 °C for 1 h. Additional cyanogen bromide (6 mg, 0.05 mmol) and DMAP (3 mg, 0.03 mmol) were added and after stirring for 45 mins, the mixture was concentrated *in vacuo*. The crude product was purified by C18 reverse phase chromatography eluting with 5 to 40% MeCN in water with (0.1% ammonium hydroxide modifier) and further purified by chromatography on silica eluting with a gradient of 0 to 5% MeOH in DCM followed by purification by chromatography on silica

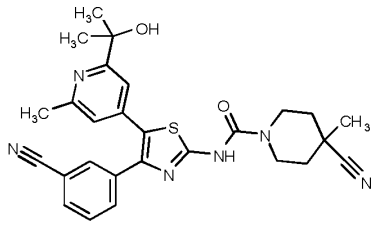
eluting with a gradient of 0 to 80% EtOAc in DCM to afford the title compound as a yellow solid.

LC-MS (Method 8B): Rt 4.70 mins; MS m/z 492.0 = [M+H]+

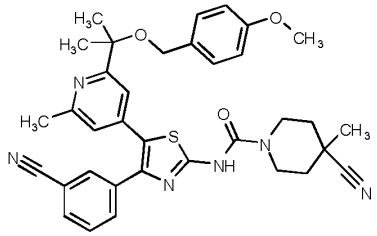
1H NMR (500 MHz, DMSO-d6) δ 11.64 (s, 1H), 7.89 (s, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 4.40 (d, J = 13.7 Hz, 2H), 3.82 – 3.73 (m, 4H), 3.70 – 3.63 (m, 2H), 2.36 (s, 6H).

Example 12

4-Cyano-N-[4-(3-cyanophenyl)-5-[2-(1-hydroxy-1-methyl-ethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide



Step 1: 4-Cyano-N-[4-(3-cyanophenyl)-5-[2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide



[00304] The title compound was prepared from 3-[2-amino-5-[2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate J) and 4-methylpiperidine-4-carbonitrile analogously to Example 6.

LC-MS (Method 3B): Rt 2.37 mins; MS m/z 621.4 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.34 (s, 1H), 7.84 (t, J = 1.8 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.52 (t, J = 7.9 Hz, 1H), 7.18 – 7.13 (m, 2H), 7.00 – 6.95 (m, 2H), 6.86 – 6.80 (m, 2H), 4.25 – 4.18 (m, 2H), 4.11 (s, 2H), 3.75 (s, 3H), 3.08 – 2.99 (m, 2H), 2.48 (s, 3H), 1.95 – 1.88 (m, 2H), 1.57 – 1.50 (m, 2H), 1.45 (s, 6H), 1.37 (s, 3H).

Step 2: 4-Cyano-N-[4-(3-cyanophenyl)-5-[2-(1-hydroxy-1-methyl-ethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide

[00305] To a solution of 4-cyano-N-[4-(3-cyanophenyl)-5-[2-[1-[(4-

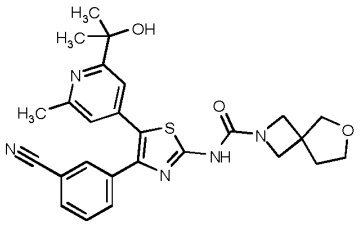
methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide (step 1) (77 mg, 0.12 mmol) in DCM (3.6 mL) was added trifluoroacetic acid (0.38 mL, 4.96 mmol) and the mixture stirred at room temperature for 45 mins. The reaction mixture was diluted with DCM (15 mL) and washed with sat. $NaHCO_3$ solution (2 x 20 mL) before being dried over Na_2SO_4 and the solvent removed *in vacuo*. Purification by chromatography on silica eluting with 3% MeOH in DCM afforded an oil which was suspended in 10% Et_2O/hexane causing a precipitate to form which was collected by filtration and dried to afford the title compound as an off-white solid.

LC-MS (Method 8B): Rt 4.20 mins; MS m/z 501.2 = [M+H]+

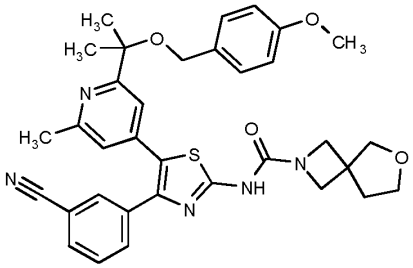
1H NMR (500 MHz, DMSO-d6) δ 11.33 (s, 1H), 7.85 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.29 (s, 1H), 7.03 (s, 1H), 5.09 (s, 1H), 4.23 (apr d, J = 14.1 Hz, 2H), 3.04 (apr t, J = 13.1 Hz, 2H), 2.43 (s, 3H), 1.93 (apr d, J = 13.6 Hz, 2H), 1.58 – 1.50 (m, 2H), 1.38 (s, 3H), 1.36 (s, 6H).

Example 12.1

N-[4-(3-Cyanophenyl)-5-[2-(1-hydroxy-1-methyl-ethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-6-oxa-2-azaspiro[3.4]octane-2-carboxamide



Step 1: N-[4-(3-Cyanophenyl)-5-[2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-6-oxa-2-azaspiro[3.4]octane-2-carboxamide



[00306] The title compound was prepared from 3-[2-amino-5-[2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate J) and 6-oxa-2-azaspiro[3.4]octane analogously to Example 6.

LC-MS (Method 3B): Rt 2.17 mins; MS m/z 610.3 = [M+H]+

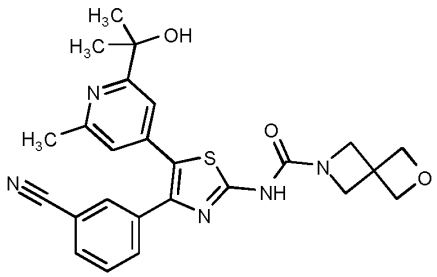
1H NMR (500 MHz, Methanol-d4) δ 7.82 (t, J = 1.6 Hz, 1H), 7.69 (dt, J = 7.8, 1.6 Hz, 1H), 7.51 (dt, J = 7.8, 1.6 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.26 (d, J = 1.6 Hz, 1H), 7.15 (d, J = 1.6 Hz, 1H), 7.05 – 7.01 (m, 2H), 6.86 – 6.80 (m, 2H), 4.16 (s, 2H), 4.11 (s, 4H), 3.89 (s, 2H), 3.86 (t, J = 7.0 Hz, 2H), 3.80 (s, 3H), 2.54 (s, 3H), 2.23 (t, J = 7.0 Hz, 2H), 1.54 (s, 6H). 1 x NH proton not observed.

Step 2: N-[4-(3-Cyanophenyl)-5-[2-(1-hydroxy-1-methyl-ethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-6-oxa-2-azaspiro[3.4]octane-2-carboxamide

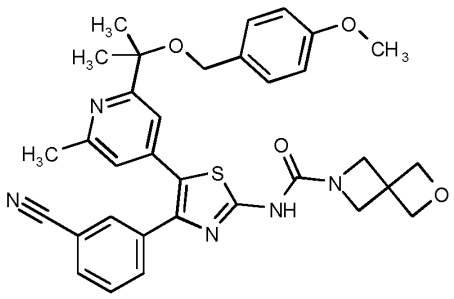
The title compound was prepared from N-[4-(3-cyanophenyl)-5-[2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-6-oxa-2-azaspiro[3.4]octane-2-carboxamide (step 1) and TFA analogously to Example 12 step 2.
LC-MS (Method 8B): Rt 3.18 mins; MS m/z 490.1 = [M+H]+
1H NMR (500 MHz, DMSO-d6) δ 11.36 (s, 1H), 7.85 – 7.81 (m, 2H), 7.76 (dt, J = 7.8, 1.6 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.29 (d, J = 1.6 Hz, 1H), 7.02 (d, J = 1.6 Hz, 1H), 5.09 (s, 1H), 4.02 (s, 4H), 3.78 (s, 2H), 3.72 (t, J = 7.0 Hz, 2H), 2.42 (s, 3H), 2.13 (t, J = 7.0 Hz, 2H), 1.36 (s, 6H).

Example 12.2

N-[4-(3-Cyanophenyl)-5-[2-(1-hydroxy-1-methyl-ethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



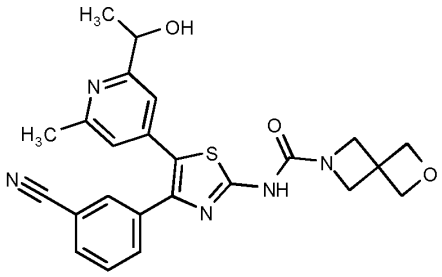
Step 1: N-[4-(3-Cyanophenyl)-5-[2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



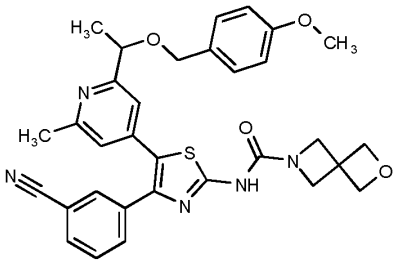
[00307] The title compound was prepared from 3-[2-amino-5-[2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate J) and 2-oxa-6-azaspiro[3.3]heptane analogously to Example 6.
LC-MS (Method 3B): Rt 2.06 mins; MS m/z 596.3 = [M+H]+
1H NMR (500 MHz, DMSO-d6) δ 11.37 (br s, 1H), 7.83 (br t, J = 1.7 Hz, 1H), 7.74 – 7.71 (m, 1H), 7.73 – 7.68 (m, 1H), 7.52 (apr t, J = 7.8 Hz, 1H), 7.16 – 7.12 (m, 2H), 6.99 – 6.95 (m, 2H), 6.85 – 6.81 (m, 2H), 4.67 (s, 4H), 4.20 (s, 4H), 4.10 (s, 2H), 3.75 (s, 3H), 2.48 (s, 3H), 1.45 (s, 6H).
Step 2: N-[4-(3-Cyanophenyl)-5-[2-(1-hydroxy-1-methyl-ethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

[00308] The title compound was prepared from N-[4-(3-cyanophenyl)-5-[2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide (step 1) and TFA analogously to Example 12 step 2.
LC-MS (Method 8B): Rt 3.68 mins; MS m/z 476.2 = [M+H]+
1H NMR (500 MHz, DMSO-d6) δ 11.35 (s, 1H), 7.85 – 7.79 (m, 2H), 7.75 (dt, J = 7.9, 1.4 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.27 (d, J = 1.6 Hz, 1H), 7.01 (d, J = 1.6 Hz, 1H), 5.08 (s, 1H), 4.67 (s, 4H), 4.20 (s, 4H), 2.41 (s, 3H), 1.35 (s, 6H).

Example 12.3
N-[4-(3-Cyanophenyl)-5-[2-(1-hydroxyethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



Step 1: N-[4-(3-Cyanophenyl)-5-[2-[1-[(4-methoxyphenyl)methoxy]ethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



[00309] The title compound was prepared from 3-[2-amino-5-[2-[1-[(4-methoxyphenyl)methoxy]ethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate PA) and 2-oxa-6-azaspiro[3.3]heptane analogously to Example 6.

LC-MS (Method 3B): Rt 1.81 mins; MS m/z 580.4 = [M-H]-

1H NMR (500 MHz, DMSO-d6) δ 11.38 (br s, 1H), 7.85 (t, J = 1.7 Hz, 1H), 7.75 – 7.71 (m, 2H), 7.53 (apr t, J = 7.8 Hz, 1H), 7.16 (br d, J = 1.6 Hz, 1H), 7.06 – 7.02 (m, 2H), 6.98 (br d, J = 1.6 Hz, 1H), 6.88 – 6.84 (m, 2H), 4.67 (s, 4H), 4.42 (q, J = 6.5 Hz, 1H), 4.23 – 4.18 (m, 5H), 4.16 (d, J = 11.5 Hz, 1H), 3.75 (s, 3H), 2.46 (s, 3H), 1.27 (d, J = 6.5 Hz, 3H).

Step 2: N-[4-(3-Cyanophenyl)-5-[2-(1-hydroxyethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

[00310] The title compound was prepared from N-[4-(3-cyanophenyl)-5-[2-[1-[(4-methoxyphenyl)methoxy]ethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide (step 1) and TFA analogously to Example 12 step 2.

LC-MS (Method 8B): Rt 3.67 mins; MS m/z 462.2 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.36 (s, 1H), 7.84 (br t, J = 1.5 Hz, 1H), 7.82 (br dt, J = 7.7, 1.5 Hz, 1H), 7.74 (br dt, J = 8.0, 1.5 Hz, 1H), 7.57 (apr t, J = 7.8 Hz, 1H), 7.12 (s, 1H), 7.01 (s, 1H), 5.23 (d, J = 4.5 Hz, 1H), 4.67 (s, 4H), 4.65 – 4.56 (m, 1H), 4.21 (s, 4H), 2.40 (s, 3H), 1.26 (d, J = 6.6 Hz, 3H).

Example 12.3a and Example 12.3b

[00311] Racemic N-[4-(3-Cyanophenyl)-5-[2-(1-hydroxyethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide (Example 12.3) was dissolved to 50 mg/mL in EtOH/DCM (4:1) and purified by SFC to afford the individual enantiomers:

Purification Conditions;

Column Details	Lux iC5 (21.2mm x 250mm, 5um)
Column Temp	40 °C
Flow Rate	50 mL/min
BPR	100 BarG
Detector Wavelength	218 nm
Injection Volume	250 uL (2 mg)
Isocratic Conditions	50:50 EtOH:CO_2

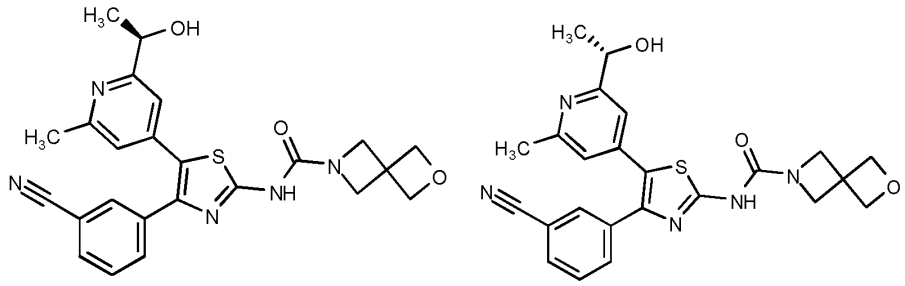
Chiral Purity Analysis Conditions;

Column Details	Lux iC5 (4.6mm x 250mm, 5um)

Column Temp	40 °C
Flow Rate	4 mL/min
Detector Wavelength	210-400 nm
Injection Volume	1.0 uL
BPR	125 BarG
Isocratic Conditions	50:50 EtOH:CO_2 (0.2% v/v NH_3)

Example 12.3a

N-[4-(3-Cyanophenyl)-5-[2-[(1R)-1-hydroxyethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide or N-[4-(3-cyanophenyl)-5-[2-[(1S)-1-hydroxyethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



(*R*)-Isomer or (*S*)-Isomer

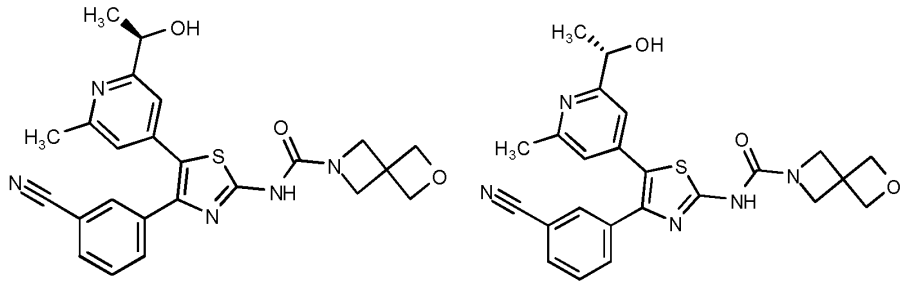
First Eluted Peak: Chiral LCMS retention time: = 3.12 mins

LC-MS (Method 8B): Rt 2.56 mins; MS m/z 462.1 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.36 (s, 1H), 7.84 (t, J = 1.6 Hz, 1H), 7.82 (dt, J = 7.8, 1.6 Hz, 1H), 7.74 (dt, J = 7.8, 1.6 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 1.7 Hz, 1H), 7.01 (d, J = 1.7 Hz, 1H), 5.23 (d, J = 4.5 Hz, 1H), 4.67 (s, 4H), 4.60 (td, J = 6.5, 4.5 Hz, 1H), 4.21 (s, 4H), 2.40 (s, 3H), 1.26 (d, J = 6.5 Hz, 3H).

Example 12.3b

N-[4-(3-Cyanophenyl)-5-[2-[(1R)-1-hydroxyethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide or N-[4-(3-cyanophenyl)-5-[2-[(1S)-1-hydroxyethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



(*R*)-Isomer or (*S*)-Isomer

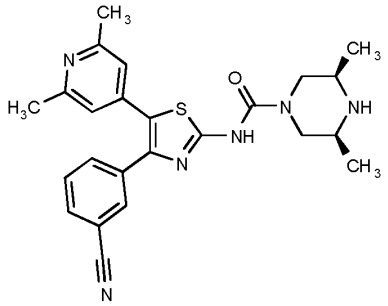
Second Eluted Peak: Chiral LCMS retention time: = 4.12 mins

LC-MS (Method 8B): Rt 2.74 mins; MS m/z 462.1 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.36 (s, 1H), 7.84 (t, J = 1.6 Hz, 1H), 7.82 (dt, J = 7.8, 1.6 Hz, 1H), 7.74 (dt, J = 7.8, 1.6 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 1.7 Hz, 1H), 7.01 (d, J = 1.7 Hz, 1H), 5.23 (d, J = 4.4 Hz, 1H), 4.67 (s, 4H), 4.63 – 4.58 (m, 1H), 4.21 (s, 4H), 2.40 (s, 3H), 1.26 (d, J = 6.5 Hz, 3H).

Example 13

(3S,5R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,5-dimethyl-piperazine-1-carboxamide



Step 1: *tert*-Butyl rac-(2S,6R)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,6-dimethyl-piperazine-1-carboxylate

[00312] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and (2R,6S)-*tert*-butyl 2,6-dimethylpiperazine-1-carboxylate analogously to Example 6.

LC-MS (Method 2B): Rt 1.69 mins; MS m/z 547.2 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.39 (s, 1H), 7.90 (d, J = 1.8 Hz, 1H), 7.83 (dt, J = 7.8, 1.5 Hz, 1H), 7.72 (dt, J = 8.0, 1.5 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 4.17 (d, J = 13.4

Hz, 2H), 4.13 – 4.01 (m, 2H), 3.12 – 3.04 (m, 2H), 2.37 (s, 6H), 1.43 (s, 9H), 1.15 (d, J = 2.5 Hz, 6H).

Step 2: (3S,5R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,5-dimethyl-piperazine-1-carboxamide

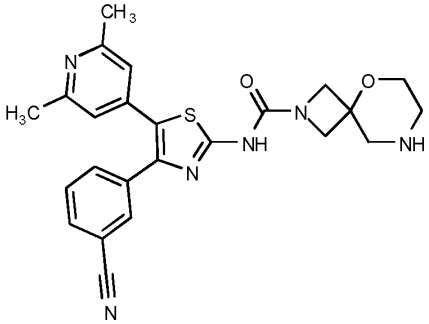
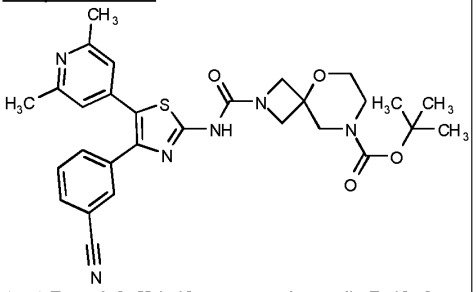
[00313] To a stirred solution of *tert*-butyl (2S,6R)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,6-dimethyl-piperazine-1-carboxylate (step 1) (100 mg, 0.14 mmol) in chloroform (2 mL) was added dropwise trimethylsilyl iodide (0.08 mL, 0.58 mmol) and the reaction mixture was stirred at room temperature for 30 mins. The resulting mixture was concentrated under a flow of nitrogen, chloroform (2 mL) was added and concentrated once again. Purification by C18 reverse phase chromatography eluting with a gradient of 15 to 40% MeCN in water (+0.1% ammonium hydroxide modifier) followed by freeze drying of the product fractions afforded the title compound as a white solid.

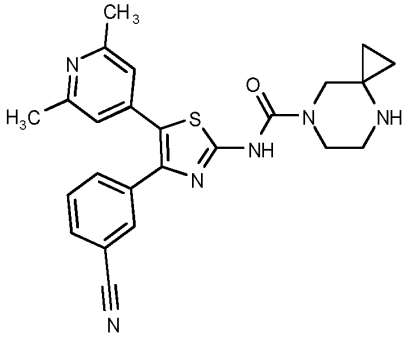
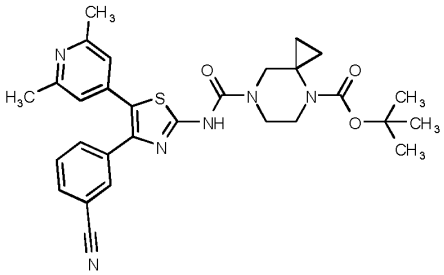
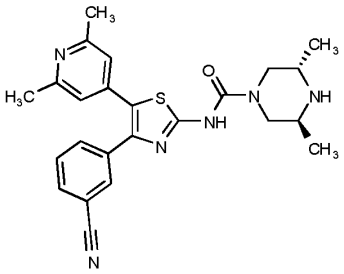
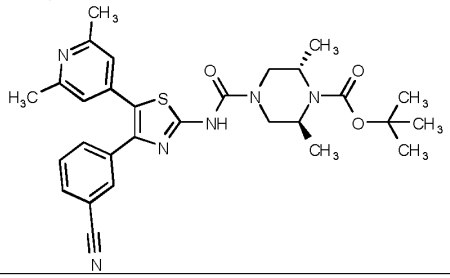
LC-MS (Method 8B): Rt 3.04 mins; MS m/z 447.2 = [M+H]+

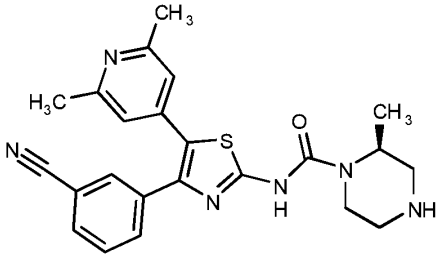
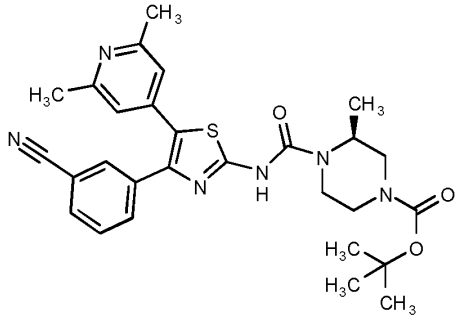
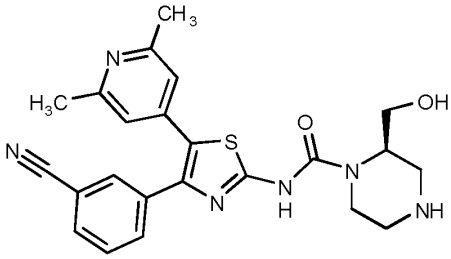
1H NMR (500 MHz, DMSO-d6) δ 11.16 (s, 1H), 7.90 (t, J = 1.8 Hz, 1H), 7.82 (dt, J = 7.7, 1.5 Hz, 1H), 7.71 (dt, J = 8.0, 1.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 4.10 (d, J = 12.5 Hz, 2H), 2.74 – 2.57 (m, 2H), 2.37 (s, 6H), 2.35 – 2.27 (m, 2H), 0.99 (d, J = 6.2 Hz, 6H). 1 x NH proton not observed.

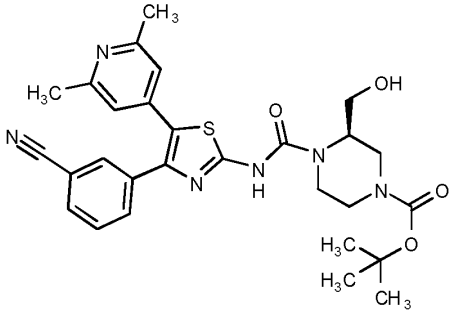
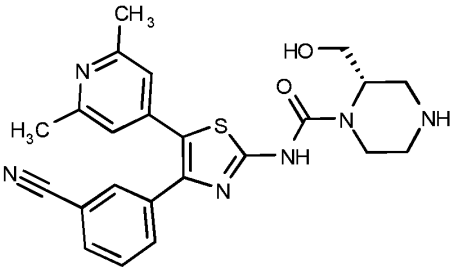
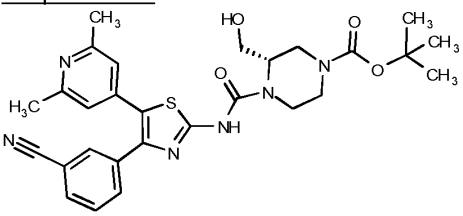
[00314] The compounds of the following tabulated Examples (Table Ex13) were prepared analogously to Example 13 from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C)) and the appropriate amine (step 1) followed by deprotection using trimethylsilyl iodide (step 2).

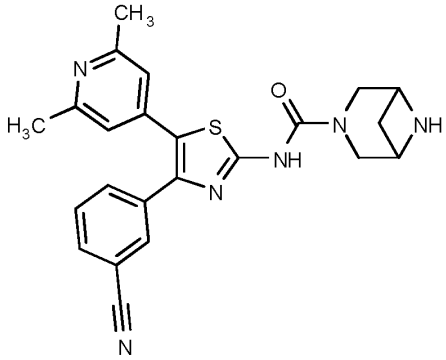
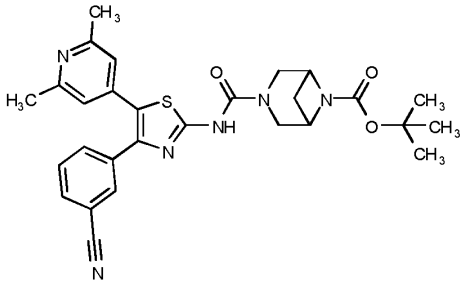
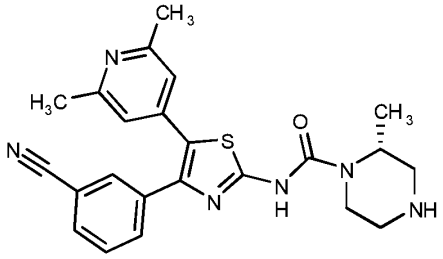
Table Ex13

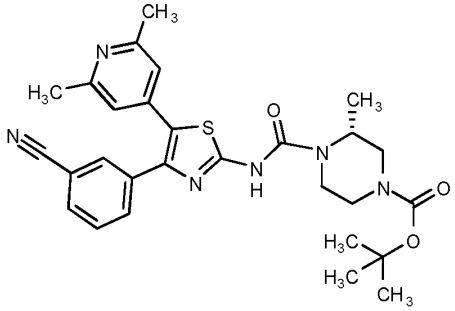
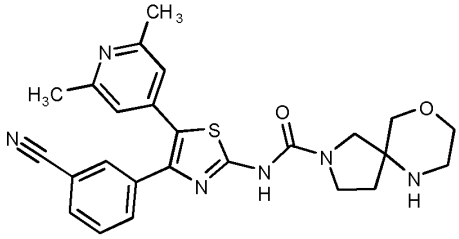
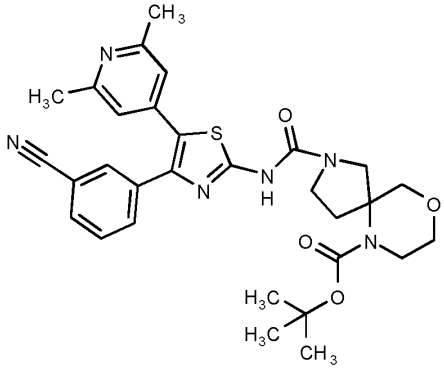
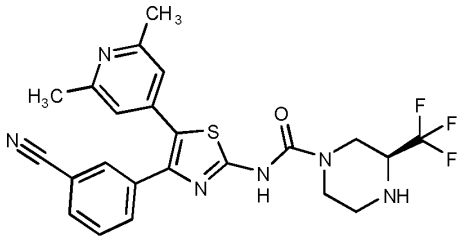
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
13.1	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxamide Prepared via:  *tert*-Butyl 2-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-5-oxa-2,8-diazaspiro[3.5]nonane-8-carboxylate	LC-MS (Method 8B): Rt 2.75 mins; MS m/z 461.1 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.37 (s, 1H), 7.88 (t, J = 1.7 Hz, 1H), 7.82 (dt, J = 7.7, 1.4 Hz, 1H), 7.71 (dt, J = 8.0, 1.5 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 3.99 – 3.88 (m, 2H), 3.88 – 3.65 (m, 2H), 3.54 (t, J = 4.6 Hz, 2H), 2.80 (s, 2H), 2.73 – 2.57 (m, 2H), 2.37 (s, 6H).1 x NH proton not observed. Intermediate Data: LC-MS (Method 2B): Rt 1.56 mins; MS m/z 561.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.43 (s, 1H), 7.88 (s, 1H), 7.82 (dt, J = 7.7, 1.5 Hz, 1H), 7.71 (dt, J = 8.0, 1.5 Hz, 1H), 7.61 – 7.49 (m, 1H), 6.94 (s, 2H), 4.02 – 3.82 (m, 4H), 3.71 (d, J = 1.7 Hz, 1H), 3.59 (tt, J = 19.4, 4.9 Hz, 3H), 3.51 (s, 2H), 2.37 (s, 6H), 1.43 (s, 9H).

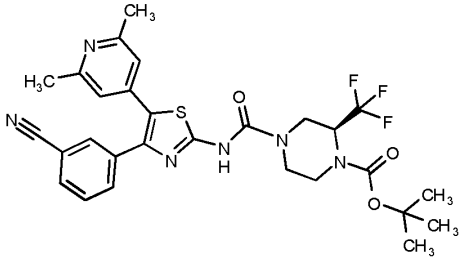
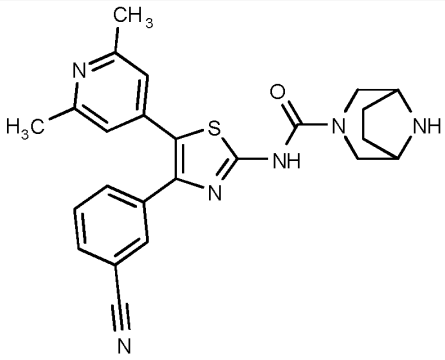
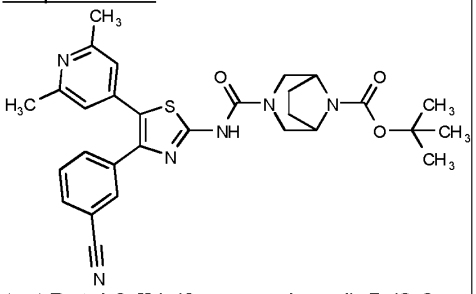
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
13.2	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4,7-diazaspiro[2.5]octane-7-carboxamide Prepared via:  *tert*-Butyl 7-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-4,7-diazaspiro[2.5]octane-4-carboxylate	LC-MS (Method 8A): Rt 1.82 mins; MS m/z 445.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.10 (s, 1H), 7.89 (t, J = 1.9 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 3.53 – 3.42 (m, 2H), 3.43 – 3.38 (m, 2H), 2.76 (t, J = 5.0 Hz, 2H), 2.37 (s, 6H), 0.52 – 0.42 (m, 4H). 1 x NH proton not observed. Intermediate Data: LC-MS (Method 2B): Rt 1.72 mins; MS m/z 545.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.22 (s, 1H), 7.89 (s, 1H), 7.83 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 8.0 Hz, 1H), 7.57 (t, J= 7.9 Hz, 1H), 6.93 (s, 2H), 3.53 (s, 2H), 3.44 (d, J= 16.6 Hz, 4H), 2.36 (s, 6H), 1.43 (s, 9H), 0.91 (s, 2H), 0.84 (s, 2H).
13.3	 (3S,5S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,5-dimethyl-piperazine-1-carboxamide Prepared via: 	LC-MS (Method 8A): Rt 1.80 mins; MS m/z 447.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 7.89 (s, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 6.92 (s, 2H), 3.60 – 3.47 (m, 2H), 3.18 (dd, J = 13.0, 6.3 Hz, 2H), 3.12 – 3.03 (m, 2H), 2.36 (s, 6H), 1.01 (d, J = 6.4 Hz, 6H) 2 x NH protons not observed. Intermediate Data: LC-MS (Method 2B): Rt 1.70 mins; MS m/z 547.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.19 (s, 1H), 7.90 (s, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 4.18 – 3.92 (m, 2H), 3.81 – 3.66 (m, 2H), 3.67 – 3.49 (m, 2H), 2.37 (s, 6H), 1.43 (s, 9H), 1.19 (s, 6H).

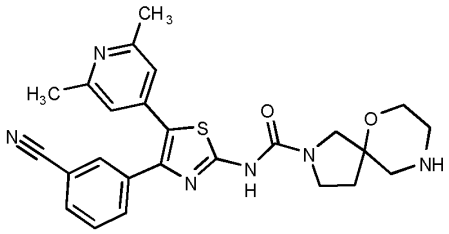
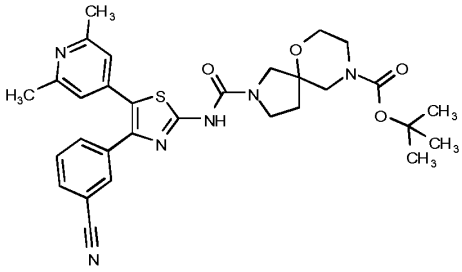
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
	tert-Butyl (2S,6S)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,6-dimethyl-piperazine-1-carboxylate	
13.4	 (2S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-piperazine-1-carboxamide Prepared via:  *tert*-Butyl (3S)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3-methyl-piperazine-1-carboxylate	LC-MS (Method 8B): Rt 3.84 mins; MS m/z 433.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 7.90 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 4.41 – 4.34 (m, 1H), 3.95 (d, J = 13.3 Hz, 1H), 3.05 (t, J = 12.5 Hz, 1H), 2.98 (d, J = 12.5 Hz, 1H), 2.87 – 2.80 (m, 1H), 2.65 – 2.59 (m, 2H), 2.36 (s, 6H), 1.23 (d, J = 6.9 Hz, 3H). 2 x NH protons not observed. Intermediate Data: LC-MS (Method 5B): Rt 3.32 mins; MS m/z 533.5 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.28 (s, 1H), 7.89 (s, 1H), 7.82 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 8.0 Hz, 1H), 7.56 (t, J= 7.9 Hz, 1H), 6.92 (s, 2H), 4.50 – 4.40 (m, 1H), 4.01 – 3.96 (m, 1H), 3.79 – 3.71 (m, 1H), 3.12 – 3.03 (m, 2H), 2.36 (s, 6H), 1.43 (s, 9H), 1.11 (d, J= 6.5 Hz, 3H). 2 x CH protons not observed.
13.5	 (2R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)piperazine-1-carboxamide Prepared via:	LC-MS (Method 15B): Rt 5.62 mins; MS m/z 449.3 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.89 (s, 1H), 7.75 – 7.65 (m, 2H), 7.49 (t,J= 7.9 Hz, 1H), 6.99 (s, 2H), 4.25 – 4.18 (m, 1H), 4.02 (d,J= 13.1 Hz, 1H), 3.90 (t,J= 11.1, 7.8 Hz, 1H), 3.81 (dd,J= 11.1, 6.6 Hz, 1H), 3.20 – 3.10 (m, 2H), 3.02 (d,J= 13.1 Hz, 1H), 2.88 (dd,J= 13.1, 4.5 Hz, 1H), 2.73 (td,J= 12.6, 3.7 Hz, 1H), 2.43 (s, 6H). OH and 2 x NH protonsnot observed. Intermediate Data: LC-MS (Method 5B): Rt 2.61 mins; MS m/z 549.5 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.13 (s, 1H), 7.88 (s, 1H), 7.82 (d,J= 7.7 Hz, 1H), 7.70 (d,J= 8.0 Hz, 1H), 7.56 (t,J= 7.8 Hz, 1H), 6.92 (s, 2H), 4.93 (s, 1H), 4.33 – 4.23 (m, 1H), 4.00 – 3.91 (m, 2H), 3.89 – 3.75 (m, 2H), 3.46 (d,J= 7.2

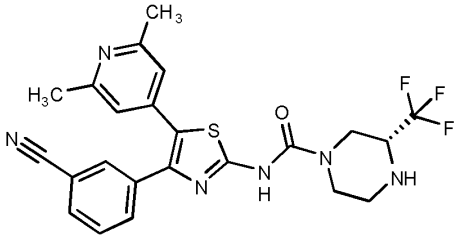
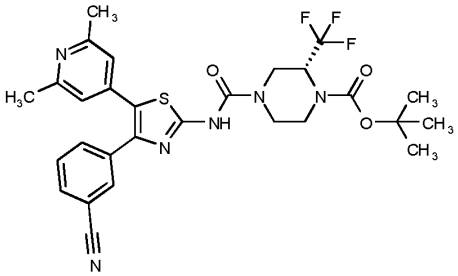
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
	 *tert*-Butyl (3R)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3-(hydroxymethyl)piperazine-1-carboxylate	Hz, 2H), 3.06 – 2.97 (m, 2H), 2.36 (s, 6H), 1.41 (s, 9H).
13.6	 (2S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)piperazine-1-carboxamide Prepared via:  *tert*-Butyl (3S)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3-(hydroxymethyl)piperazine-1-carboxylate	LC-MS (Method 8B): Rt 3.48 mins; MS m/z 449.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 10.77 (br s, 1H), 7.88 (s, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.55 (apr t, J = 7.8 Hz, 1H), 6.92 (s, 2H), 4.78 (br s, 1H), 4.15 – 4.07 (m, 1H), 3.90 (d, J = 13.0 Hz, 1H), 3.69 – 3.58 (m, 2H), 3.00 – 2.90 (m, 2H), 2.87 (d, J = 12.4 Hz, 1H), 2.67 – 2.62 (m, 1H), 2.56 – 2.51 (m, 1H), 2.36 (s, 6H). 1 x NH not observed. Intermediate Data: LC-MS (Method 3B): Rt 1.66 mins; MS m/z 549.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.11 (br s, 1H), 7.88 (t, J = 1.5 Hz, 1H), 7.82 (dt, J = 7.7, 1.5 Hz, 1H), 7.70 (dt, J = 8.1, 1.5 Hz, 1H), 7.56 (apr t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 4.92 (br s, 1H), 4.28 (br s, 1H), 3.96 (dd, J = 24.8, 13.4 Hz, 2H), 3.86 (br s, 1H), 3.47 (d, J = 7.2 Hz, 2H), 3.10 – 2.97 (m, 2H), 2.87 (br s, 1H), 2.36 (s, 6H), 1.41 (s, 9H)

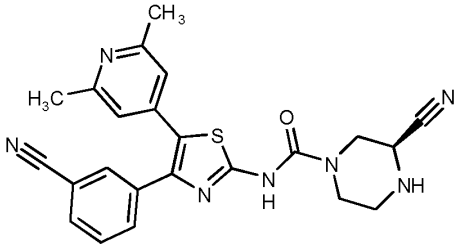
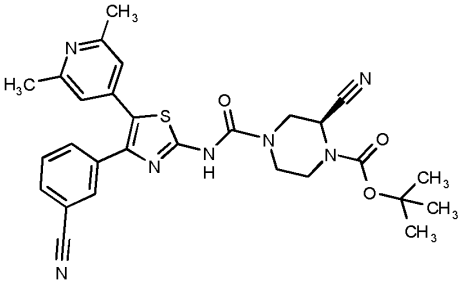
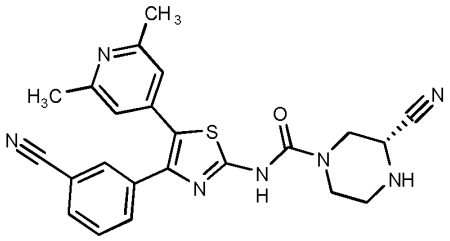
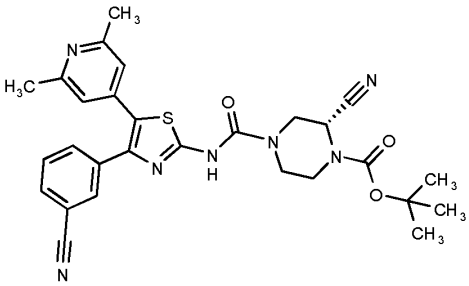
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
13.7	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxamide Prepared via:  *tert*-Butyl 3-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate	LC-MS (Method 8B): Rt 3.64 mins; MS m/z 431.3 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.92 (t, J = 1.5 Hz, 1H), 7.72 (dt, J = 8.0, 1.5 Hz, 1H), 7.69 (dt, J = 7.9, 1.5 Hz, 1H), 7.49 (apr t, J = 7.8 Hz, 1H), 7.01 (s, 2H), 3.86 – 3.74 (m, 6H), 2.79 – 2.71 (m, 1H), 2.44 (s, 6H), 1.63 (d, J = 9.4 Hz, 1H). 2 x NH protons not observed. Intermediate Data: LC-MS (Method 3B): Rt 1.85 mins; MS m/z 529.4 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.17 (s, 1H), 7.91 (d, J = 1.8 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 4.13 (d, J = 6.4 Hz, 3H), 3.96 (d, J = 12.1 Hz, 1H), 3.55 (s, 1H), 2.37 (s, 6H), 1.44 (d, J = 8.9 Hz, 1H), 1.36 (s, 9H). 2 x CH protons not observed.
13.8	 (2R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-piperazine-1-carboxamide	LC-MS (Method 8B): Rt 3.89 mins; MS m/z 433.3 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.92 (t, J = 1.5 Hz, 1H), 7.73 (dt, J = 7.9, 1.5 Hz, 1H), 7.71 (dt, J = 7.9, 1.5 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.02 (s, 2H), 4.39 – 4.33 (m, 1H), 3.94 (d, J = 13.6 Hz, 1H), 3.20 (td, J = 12.9, 3.3 Hz, 1H), 3.04 (d, J = 12.5 Hz, 1H), 2.95 (dd, J = 12.9, 4.1 Hz, 1H), 2.89 (d, J = 12.9 Hz, 1H), 2.72 (td, J = 12.6, 3.7 Hz, 1H), 2.45 (s, 6H), 1.35 (d, J = 6.8 Hz, 3H). 2 x NH protons not observed. Intermediate Data: LC-MS (Method 3B): Rt 1.94 mins; MS m/z 531.4 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.27 (s, 1H), 7.88 (t, J= 1.5 Hz, 1H), 7.81 (d, J= 7.8 Hz, 1H), 7.70 (dt, J= 7.8, 1.5 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.91 (s, 2H), 4.44 (s, 1H), 3.99 (d, J= 13.5 Hz, 1H), 3.96-3.82 (m, 2H), 3.74 (d, J= 13.5

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
	Prepared via:  *tert*-Butyl (3R)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3-methyl-piperazine-1-carboxylate	Hz, 1H), 3.12 – 3.02 (m, 2H), 2.35 (s, 6H), 1.42 (s, 9H), 1.10 (d, J= 6.7 Hz, 3H).
13.9	 Prepared via:  *tert*-Butyl 2-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-9-oxa-2,6-diazaspiro[4.5]decane-6-carboxylate	LC-MS (Method 8B): Rt 3.67 mins; MS m/z 475.2 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.91 (t, J= 1.5 Hz, 1H), 7.72 (dt, J= 7.9, 1.5 Hz, 1H), 7.69 (dt, J= 7.9, 1.5 Hz, 1H), 7.49 (t, J= 7.9 Hz, 1H), 7.00 (s, 2H), 3.78 – 3.43 (m, 8H), 2.99 – 2.81 (m, 2H), 2.43 (s, 6H), 2.12 – 2.02 (m, 1H), 1.99 – 1.88 (m, 1H). 2 x NH protons not observed. Intermediate Data: LC-MS (Method 3B): Rt 1.96 mins; MS m/z 575.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.06 (s, 1H), 7.89 (t, J = 1.5 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.71 (dt, J = 7.8, 1.5 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 6.92 (s, 2H), 3.81 – 3.73 (m, 1H), 3.71 – 3.60 (m, 4H), 3.54 – 3.43 (m, 5H), 2.42 – 2.32 (m, 7H), 2.14 – 2.04 (m, 1H), 1.41 (s, 9H).
13.10	 (3S)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-	LC-MS (Method 8B): Rt 4.13 mins; MS m/z 487.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.40 (s, 1H), 7.89 (t, J = 1.5 Hz, 1H), 7.82 (dt, J = 7.8, 1.5 Hz, 1H), 7.71 (dt, J = 7.8, 1.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.92 (s, 2H), 4.15 (d, J = 12.9 Hz, 1H), 3.91 (d, J = 12.9 Hz, 1H), 3.45 – 3.37 (m, 1H), 3.15 – 3.04 (m, 2H), 3.03

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
	(trifluoromethyl)piperazine-1-carboxamide Prepared via:  tert-Butyl (2S)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2-(trifluoromethyl)piperazine-1-carboxylate	– 2.97 (m, 1H), 2.92 (d, J = 12.6 Hz, 1H), 2.70 – 2.63 (m, 1H), 2.36 (s, 6H). Intermediate Data: LC-MS (Method 3B): Rt 1.92 mins; MS m/z 585.4 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.51 (s, 1H), 7.89 (t, J= 1.5 Hz, 1H), 7.83 (d, J= 7.8 Hz, 1H), 7.71 (d, J= 7.8 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.93 – 4.71 (m, 2H), 4.54 (d, J= 14.9 Hz, 1H), 4.30 – 4.14 (m, 2H), 3.99 – 3.88 (m, 2H), 2.36 (s, 6H), 1.44 (s, 9H).
13.11	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxamide Prepared via:  *tert*-Butyl 3-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate	LC-MS (Method 8B): Rt 3.57 mins; MS m/z 445.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 7.88 (t,J= 1.8 Hz, 1H), 7.81 (dt,J= 7.7, 1.5 Hz, 1H), 7.71 (dt,J= 8.0, 1.5 Hz, 1H), 7.56 (t,J= 7.8 Hz, 1H), 6.91 (s, 2H), 3.84 (d,J= 12.1 Hz, 2H), 3.41 (s, 2H), 2.95 (d,J= 12.1 Hz, 2H), 2.36 (s, 6H), 1.67 – 1.61 (m, 2H), 1.57 (q,J= 7.9, 6.7 Hz, 2H). 2 x NH protons not observed. Intermediate Data: LC-MS (Method 3B): Rt 1.98 mins; MS m/z 543.4 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.21 (s, 1H), 7.89 (t, J= 1.7 Hz, 1H), 7.83 (dt, J= 7.8, 1.4 Hz, 1H), 7.71 (dt, J= 8.0, 1.5 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.16 (s, 2H), 3.95 (d, J= 12.5 Hz, 2H), 3.04 (d, J= 12.6 Hz, 2H), 2.36 (s, 6H), 1.84 (s, 2H), 1.65 (s, 2H), 1.43 (s, 9H).

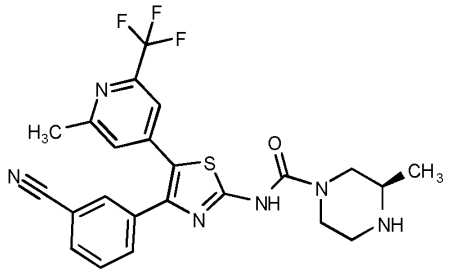
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
13.12	 N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxamide Prepared via:  *tert*-Butyl 2-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-6-oxa-2,9-diazaspiro[4.5]decane-9-carboxylate	LC-MS (Method 8B): Rt 3.81 mins; MS m/z 475.2 = [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.92 (t, J= 1.6 Hz, 1H), 7.74 (dt, J= 7.8, 1.6 Hz, 1H), 7.70 (dt, J= 7.8, 1.6 Hz, 1H), 7.50 (t, J= 7.8 Hz, 1H), 7.02 (s, 2H), 3.84 – 3.70 (m, 3H), 3.70 – 3.57 (m, 2H), 3.43 (d, J= 11.4 Hz, 1H), 2.94 (d, J= 12.6 Hz, 1H), 2.88 (d, J= 12.6 Hz, 1H), 2.84 (t, J= 4.9 Hz, 2H), 2.45 (s, 6H), 2.34 – 2.20 (m, 1H), 2.06 – 1.92 (m, 1H). 2 x NH protons not observed. Intermediate Data: LC-MS (Method 3B): Rt 1.90 mins; MS m/z 573.4 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.10 (s, 1H), 7.89 (t,J= 1.5 Hz, 1H), 7.82 (dt,J= 7.8, 1.5 Hz, 1H), 7.71 (dt,J= 7.8, 1.5 Hz, 1H), 7.56 (t,J= 7.8 Hz, 1H), 6.93 (s, 2H), 3.72 – 3.34 (m, 10H), 2.37 (s, 6H), 2.12 – 2.01 (m, 1H), 1.98 – 1.89 (m, 1H), 1.42 (s, 9H).

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
13.13	 (3R)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(trifluoromethyl)piperazine-1-carboxamide Prepared via:  *tert*-Butyl (2R)-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2-(trifluoromethyl)piperazine-1-carboxylate	LC-MS (Method 8B): Rt 4.07 mins; MS m/z 487.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.41 (s, 1H), 7.89 (t, J= 1.6 Hz, 1H), 7.82 (dt, J= 7.8, 1.6 Hz, 1H), 7.71 (dt, J= 7.8, 1.4 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 6.93 (s, 2H), 4.18 – 4.09 (m, 1H), 3.94 – 3.86 (m, 1H), 3.47 – 3.38 (m, 1H), 3.16 – 3.07 (m, 2H), 3.03 – 2.97 (m, 1H), 2.96 – 2.89 (m, 1H), 2.71 – 2.64 (m, 1H), 2.36 (s, 6H). Intermediate Data: LC-MS (Method 3B): Rt 1.81 mins; MS m/z 585.4 = [M-H]- 1H NMR (500 MHz, DMSO-d6) δ 11.52 (br s, 1H), 7.90 (t, J= 1.5 Hz, 1H), 7.83 (dt, J= 7.8, 1.5 Hz, 1H), 7.71 (dt, J= 7.8, 1.5 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.94 (s, 2H), 4.92 – 4.72 (m, 1H), 4.54 (apr d, J= 14.8 Hz, 1H), 4.31 – 4.13 (m, 1H), 4.00 – 3.88 (m, 1H), 3.45 - 3.51 (m, 1H), 3.17 – 2.91 (m, 2H), 2.36 (s, 6H), 1.44 (s, 9H).

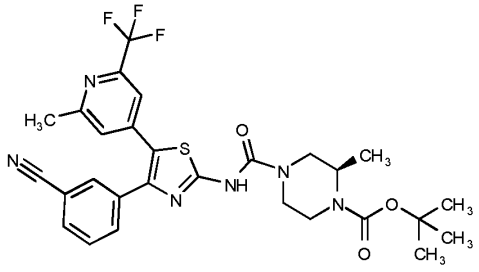
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
13.14	 (3S)-3-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide Prepared via:  *tert*-Butyl (2S)-2-cyano-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]piperazine-1-carboxylate	LC-MS (Method 8B): Rt 2.02 mins; MS m/z 444.4 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.39 (br s, 1H), 7.89 (t, J = 1.6 Hz, 1H), 7.82 (dt, J = 7.8, 1.6 Hz, 1H), 7.71 (dt, J = 7.8, 1.6 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 4.26 – 4.19 (m, 2H), 4.07 – 4.01 (m, 1H), 3.44 (br s, 1H), 3.27 – 3.19 (m, 1H), 3.05 – 2.98 (m, 1H), 2.84 – 2.77 (m, 2H), 2.36 (s, 6H). Intermediate Data: LC-MS (Method 2B): Rt 1.34 mins; MS m/z 544.2 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.60 (s, 1H), 7.90 (t, J= 1.6 Hz, 1H), 7.83 (dt, J= 7.9, 1.6 Hz, 1H), 7.71 (dt, J= 7.9, 1.6 Hz, 1H), 7.57 (t, J= 7.9 Hz, 1H), 6.94 (s, 2H), 5.31 (s, 1H), 4.52 (d, J= 14.0 Hz, 1H), 4.27 (d, J= 11.0 Hz, 1H), 3.89 (d, J= 11.0 Hz, 1H), 3.23 (d, J= 14.0 Hz, 1H), 3.05 – 2.91 (m, 2H), 2.36 (s, 6H), 1.45 (s, 9H).
13.15	 (3R)-3-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide Prepared via:  *tert*-Butyl (2R)-2-cyano-4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]piperazine-1-carboxylate	LC-MS (Method 8A): Rt 1.93 mins; MS m/z 444.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.40 (s, 1H), 7.89 (t, J = 1.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 4.26 – 4.19 (m, 2H), 4.04 (apr d, J = 13.0 Hz, 1H), 3.44 (s, 1H), 3.26 – 3.19 (m, 1H), 3.05 – 2.98 (m, 1H), 2.85 – 2.76 (m, 2H), 2.36 (s, 6H). Intermediate Data: LC-MS (Method 2B): Rt 1.19 mins; MS m/z 544.4 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.60 (s, 1H), 7.90 (t, J = 1.6 Hz, 1H), 7.83 (dt, J = 7.9, 1.6 Hz, 1H), 7.71 (dt, J = 7.9, 1.6 Hz, 1H), 7.57 (t, J = 7.9 Hz, 1H), 6.94 (s, 2H), 5.31 (s, 1H), 4.52 (d, J = 14.0 Hz, 1H), 4.27 (d, J = 11.0 Hz, 1H), 3.89 (d, J = 11.0 Hz, 1H), 3.23 (d, J = 14.0 Hz, 1H), 3.05 – 2.91 (m, 2H), 2.36 (s, 6H), 1.45 (s, 9H).

Example 14

(3R)-N-[4-(3-Cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-3-methyl-piperazine-1-carboxamide



Step 1: *tert*-Butyl (2R)-4-[[4-(3-cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]carbamoyl]-2-methyl-piperazine-1-carboxylate



[00315] The title compound was prepared from 3-[2-amino-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate H) and *tert*-butyl (2R)-2-methylpiperazine-1-carboxylate analogously to Example 6.

LC-MS (Method 5B): Rt 3.29 mins; MS m/z 587.5 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.46 (s, 1H), 7.92 (s, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.53 (s, 1H), 7.33 (s, 1H), 4.22 – 4.11 (m, 2H), 4.06 – 4.00 (m, 1H), 3.77 – 3.71 (m, 1H), 3.17 – 3.1 (m, 1H), 3.08 – 3.00 (m, 1H), 2.99 – 2.90 (m, 1H), 1.41 (s, 9H), 1.07 (d, J = 6.7 Hz, 3H). 1 x CH_3 signal not observed.

Step 2: (3R)-N-[4-(3-Cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-3-methyl-piperazine-1-carboxamide

[00316] To a solution of *tert*-butyl (2R)-4-[[4-(3-cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]carbamoyl]-2-methyl-piperazine-1-carboxylate (step 1) (83 mg, 0.14 mmol) in DCM (3.6 mL) was added TFA (0.71 mL, 9.27 mmol) and the reaction mixture was stirred at room temperature for 1 h. EtOAc (20 mL) and 1M NaOH (aq) (20 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4 x 15 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in*

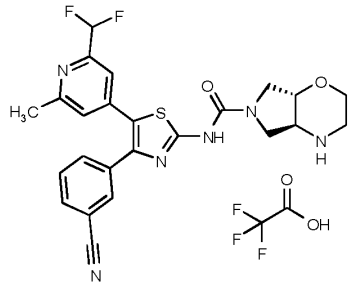
vacuo to afford a yellow oil. The crude product was purified by C18 reverse phase chromatography eluting with a gradient of 10 to 30% MeCN in water (+0.1% ammonium hydroxide modifier) to afford the title compound as a white solid.

LC-MS (Method 8B): Rt 4.37 mins; MS m/z 487.2 = [M+H]+

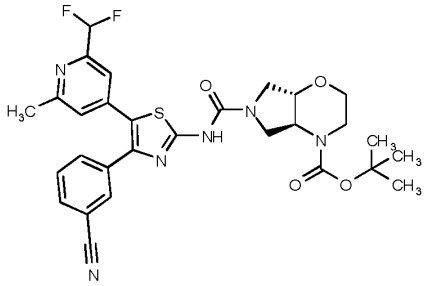
1H NMR (500 MHz, Methanol-d4) δ 7.92 (s, 1H), 7.72 (t, J = 9.1 Hz, 2H), 7.52 (t, J = 7.8 Hz, 1H), 7.44 (s, 1H), 7.36 (s, 1H), 4.14 (d, J = 12.9 Hz, 2H), 3.07 – 2.95 (m, 2H), 2.84 – 2.76 (m, 2H), 2.64 (t, J = 11.9 Hz, 1H), 2.55 (s, 3H), 1.14 (d, J = 6.4 Hz, 3H). 2 x NH protons not observed.

Example 14.1

rac-(4aS,7aS)-N-[4-(3-Cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxamide 2,2,2-trifluoroacetic acid salt



Step 1: *tert*-Butyl rac-(4aS,7aS)-6-[[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]carbamoyl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-4-carboxylate



[00317] The title compound was prepared from 3-[2-amino-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate G) and *tert*-butyl rac-(4aS,7aS)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-4-carboxylate analogously to Example 6.

LC-MS (Method 2B): Rt 1.49 mins; MS m/z 597.2 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.61 (s, 1H), 7.91 (s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.41 (s, 1H), 7.22 (s, 1H), 6.84 (t, J = 54.9 Hz, 1H), 4.21 (p, J = 7.1, 6.6 Hz, 1H), 4.14 (d, J = 12.7 Hz, 1H), 4.08 – 3.97 (m, 1H), 3.78 – 3.60 (m, 2H), 3.55 (ddd, J = 9.3, 7.2, 3.7 Hz, 1H), 3.29 – 3.09 (m, 3H), 3.01 (dt, J = 22.4, 9.8 Hz, 1H), 2.49 (s, 3H), 1.43 (d, J = 9.2 Hz, 9H).

Step 2: rac-(4aS,7aS)-N-[4-(3-Cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxamide 2,2,2-trifluoroacetic acid salt

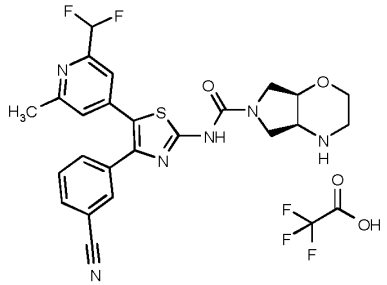
[00318] The title compound was prepared from *tert*-butyl rac-(4aS,7aS)-6-[[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]carbamoyl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-4-carboxylate (step 1) and TFA analogously to Example 14 step 2.

LC-MS (Method 8B): Rt 2.35 mins; MS m/z 497.1 = [M+H]+

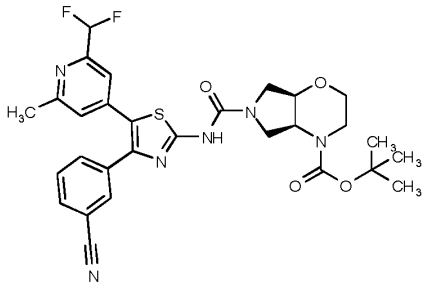
1H NMR (500 MHz, DMSO-d6) δ 11.72 (s, 1H), 9.00 (s, 2H), 7.93 – 7.86 (m, 2H), 7.74 (d, J = 7.9 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.38 (s, 1H), 7.22 (s, 1H), 6.85 (t, J = 54.9 Hz, 1H), 4.23 – 3.97 (m, 3H), 3.80 – 3.59 (m, 2H), 3.46 (dd, J = 10.9, 7.3 Hz, 1H), 3.27 – 3.12 (m, 3H), 2.97 (t, J = 11.0 Hz, 1H). Exchangeable protons not observed.

Example 14.2

rac-(4aS,7aR)-N-[4-(3-Cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxamide 2,2,2-trifluoroacetic acid salt



Step 1: *tert*-Butyl rac-(4aS,7aR)-6-[[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]carbamoyl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-4-carboxylate



[00319] The title compound was prepared from 3-[2-amino-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate G) and *tert*-butyl rac-(4aS,7aR)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-4-carboxylate analogously to Example 6.

LC-MS (Method 2B): Rt 1.48 mins; MS m/z 597.2 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.23 (s, 1H), 7.91 (d, J = 1.7 Hz, 1H), 7.86 (dt, J = 7.7, 1.4 Hz, 1H), 7.74 (dt, J = 7.9, 1.5 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.39 (s, 1H), 7.22 (d, J = 1.6 Hz, 1H), 6.85 (t, J = 54.9 Hz, 1H), 4.44 (s, 1H), 3.99 (s, 1H), 3.86 (s, 2H), 3.75 – 3.41 (m, 5H), 3.05 (d, J = 59.6 Hz, 1H), 2.49 (s, 3H), 1.44 (s, 9H).

Step 2: rac-(4aS,7aR)-N-[4-(3-Cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxamide 2,2,2-trifluoroacetic acid salt

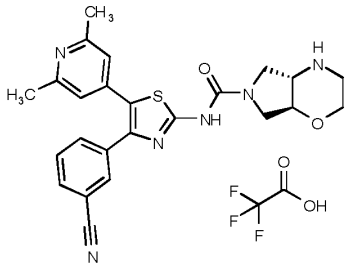
[00320] The title compound was prepared from *tert*-butyl rac-(4aS,7aR)-6-[[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]carbamoyl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-4-carboxylate (step 1) and TFA analogously to Example 14 step 2.

LC-MS (Method 8B): Rt 2.73 mins; MS m/z 467.1 = [M+H]+

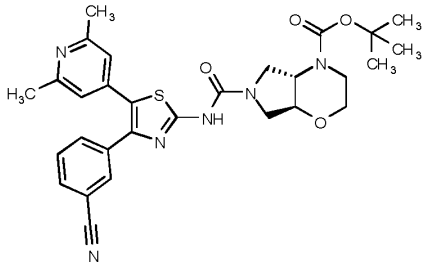
1H NMR (500 MHz, Methanol-d4) δ 7.94 (t, J = 1.7 Hz, 1H), 7.74 (ddt, J = 8.2, 6.9, 1.4 Hz, 2H), 7.53 (t, J = 7.8 Hz, 1H), 7.37 (s, 1H), 7.33 (s, 1H), 6.63 (t, J = 55.2 Hz, 1H), 4.45 (s, 1H), 4.15 – 4.04 (m, 2H), 4.00 (t, J = 9.4 Hz, 1H), 3.95 – 3.80 (m, 2H), 3.78 (s, 2H), 3.51 – 3.42 (m, 1H), 3.24 (dt, J = 12.6, 1.5 Hz, 1H), 2.55 (s, 3H). Exchangeable protons not observed..

Example 14.3

rac-(4aS,7aS)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxamide 2,2,2-trifluoroacetic acid salt



Step 1: *tert*-Butyl rac-(4aS,7aS)-6-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-4-carboxylate



[00321] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl rac-(4aS,7aS)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-4-carboxylate analogously to Example 6.

LC-MS (Method 3B): Rt 1.70 mins; MS m/z 559.4 = [M-H]+

1H NMR (500 MHz, DMSO-d6) δ 11.51 (s, 1H), 7.89 (t, J = 1.6 Hz, 1H), 7.83 (dt, J = 7.8, 1.6 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 4.20 (dd, J = 10.1, 6.5 Hz, 1H), 4.13 (d, J = 12.7 Hz, 1H), 4.07 – 4.02 (m, 1H), 3.72 – 3.60 (m, 2H), 3.56 – 3.51 (m, 1H), 3.28 – 3.20 (m, 1H), 3.20 – 3.07 (m, 2H), 3.06 – 2.95 (m, 1H), 2.36 (s, 6H), 1.46 – 1.37 (m, 9H).

Step 2: rac-(4aS,7aS)-N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxamide 2,2,2-trifluoroacetic acid salt

[00322] The title compound was prepared from *tert*-butyl rac-(4aS,7aS)-6-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-4-carboxylate (step 1) and TFA analogously to Example 14 step 2.

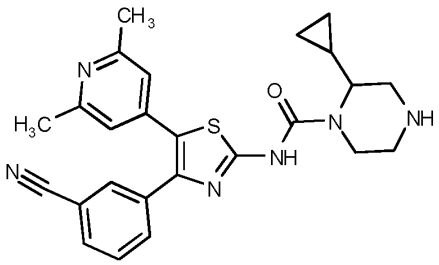
LC-MS (Method 8A): Rt 1.76 mins; MS m/z 461.1 = [M+H]+

1H NMR (500 MHz, Methanol-d4) δ 7.96 (t, J = 1.7 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.59 (t, J = 7.8 Hz, 1H), 7.46 (s, 2H), 4.30 (dd, J = 11.8, 7.1 Hz, 1H), 4.18 (ddd, J = 11.8, 3.7, 1.5 Hz, 1H), 4.06 (br d, J = 12.9 Hz, 1H), 3.87 (td, J = 11.8, 3.2 Hz, 1H), 3.79 (ddd, J = 11.2, 9.6, 7.4 Hz,

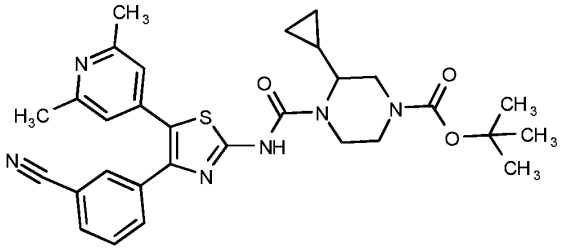
1H), 3.57 (dd, J = 11.2, 7.4 Hz, 1H), 3.46 (t, J = 11.8 Hz, 1H), 3.29 – 3.21 (m, 2H), 3.13 (t, J = 11.2 Hz, 1H), 2.61 (s, 6H). Exchangeable protons not observed.

Example 14.4

N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-cyclopropyl-piperazine-1-carboxamide



Step 1: *tert*-Butyl 4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3-cyclopropyl-piperazine-1-carboxylate



[00323] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl 3-cyclopropylpiperazine-1-carboxylate analogously to Example 4.

LC-MS (Method 2.5A): Rt 0.80 mins; MS m/z 559.3 = [M+H]+

1H NMR (400 MHz, DMSO-d6) δ 11.21 (s, 1H), 7.88 (t, J = 1.8 Hz, 1H), 7.82 (dt, J = 7.7, 1.5 Hz, 1H), 7.70 (dt, J = 8.0, 1.4 Hz, 1H), 7.56 (dd, J = 7.8, 7.8 Hz, 1H), 6.92 (s, 2H), 4.10 – 3.92 (m, 3H), 3.71 – 3.61 (m, 1H), 3.25 – 3.15 (m, 1H), 3.07 – 2.80 (m, 2H), 2.36 (s, 6H), 1.42 (s, 9H), 1.25 – 1.19 (m, 1H), 0.54 – 0.38 (m, 4H).

Step 2: N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-cyclopropyl-piperazine-1-carboxamide

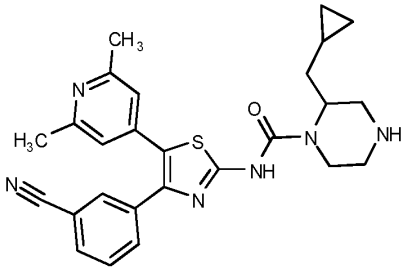
[00324] The title compound was prepared from *tert*-butyl 4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3-cyclopropyl-piperazine-1-carboxylate (step 1) and TFA analogously to Example 14 step 2.

LC-MS (Method 7B): Rt 2.80 mins; MS m/z 459.4 = [M+H]+

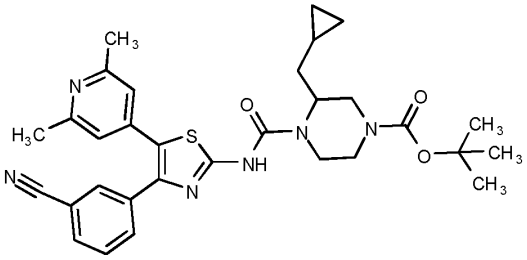
1H NMR (500 MHz, Methanol-d4) δ 7.90 (t, J = 1.7 Hz, 1H), 7.71 (dt, J = 8.0, 1.5 Hz, 1H), 7.69 (dt, J = 7.8, 1.4 Hz, 1H), 7.49 (dd, J = 7.8, 7.8 Hz, 1H), 7.00 (s, 2H), 4.00 – 3.94 (m, 1H), 3.49 (dd, J = 10.3, 3.8 Hz, 1H), 3.38 (td, J = 13.0, 3.2 Hz, 1H), 3.13 – 3.09 (m, 1H), 3.08 – 3.02 (m, 1H), 2.93 – 2.88 (m, 1H), 2.73 (td, J = 12.6, 3.6 Hz, 1H), 2.43 (s, 6H), 1.68 – 1.60 (m, 1H), 0.67 – 0.60 (m, 1H), 0.56 – 0.49 (m, 2H), 0.40 – 0.34 (m, 1H). 2x NH protons not observed.

Example 14.5

N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(cyclopropylmethyl)piperazine-1-carboxamide



Step 1: *tert*-Butyl 4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3-(cyclopropylmethyl)piperazine-1-carboxylate



The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl 3-(cyclopropylmethyl)piperazine-1-carboxylate analogously to Example 4.

LC-MS (Method 2A): Rt 0.87 mins; MS m/z 573.3 = [M+H]+

1H NMR (400 MHz, DMSO-d6) δ 11.28 (s, 1H), 7.88 (t, J = 1.7 Hz, 1H), 7.82 (dt, J = 7.7, 1.4 Hz, 1H), 7.71 (dt, J = 8.0, 1.4 Hz, 1H), 7.56 (dd, J = 7.8, 7.8 Hz, 1H), 6.92 (s, 2H), 4.44 – 4.36 (m, 1H), 4.03 – 3.82 (m, 3H), 3.08 – 2.95 (m, 2H), 2.35 (s, 6H), 1.42 (s, 9H), 0.84 (dd, J = 6.6, 2.4 Hz, 2H), 0.70 – 0.62 (m, 1H), 0.44 – 0.33 (m, 2H), 0.13 – 0.03 (m, 2H). 1 x CH proton not observed.

Step 2: N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(cyclopropylmethyl)piperazine-1-carboxamide

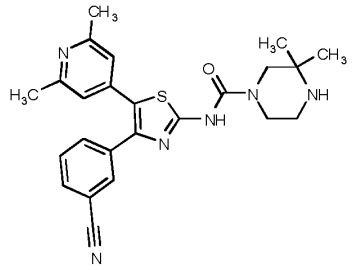
[00325] The title compound was prepared from *tert*-butyl 4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-3-(cyclopropylmethyl)piperazine-1-carboxylate (step 1) and TFA analogously to Example 14 step 2.

LC-MS (Method 7B): Rt 3.14 mins; MS m/z 473.4 = [M+H]+

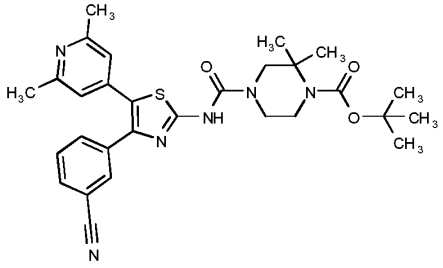
1H NMR (400 MHz, Methanol-d4) δ 7.90 (t, J = 1.4 Hz, 1H), 7.73 – 7.70 (m, 1H), 7.70 – 7.66 (m, 1H), 7.49 (dd, J = 7.8, 7.8 Hz, 1H), 7.00 (s, 2H), 4.36 – 4.29 (m, 1H), 3.96 – 3.89 (m, 1H), 3.14 – 3.04 (m, 2H), 3.03 – 2.97 (m, 1H), 2.92 (dd, J = 13.0, 4.2 Hz, 1H), 2.71 (td, J = 12.6, 3.7 Hz, 1H), 2.43 (s, 6H), 1.79 – 1.62 (m, 2H), 0.74 – 0.65 (m, 1H), 0.48 – 0.42 (m, 2H), 0.17 – 0.10 (m, 2H). - 2x NH protons not observed.

Example 14.6

N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,3-dimethyl-piperazine-1-carboxamide



Step 1: *tert*-Butyl 4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,2-dimethyl-piperazine-1-carboxylate



[00326] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and *tert*-butyl 2,2-dimethylpiperazine-1-carboxylate analogously to Example 6.

LC-MS (Method 2B): Rt 1.62 mins; MS m/z 547.2 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 10.97 (v br s, 1H), 7.89 (t, J = 1.8 Hz, 1H), 7.82 (dt, J = 7.7, 1.5 Hz, 1H), 7.71 (dt, J = 7.9, 1.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 3.71 –

3.65 (m, 2H), 3.65 – 3.57 (m, 2H), 3.57 – 3.51 (m, 2H), 2.36 (s, 6H), 1.42 (d, J = 2.9 Hz, 9H), 1.34 (s, 6H).

Step 2: N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,3-dimethyl-piperazine-1-carboxamide

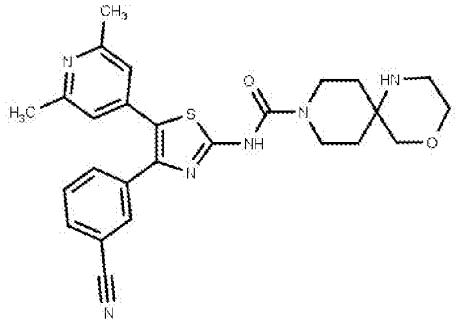
[00327] The title compound was prepared from *tert*-butyl 4-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-2,2-dimethyl-piperazine-1-carboxylate (step 1) and TFA analogously to Example 14 step 2.

LC-MS (Method 8B): Rt 2.82 mins; MS m/z 447.1 = [M+H]+

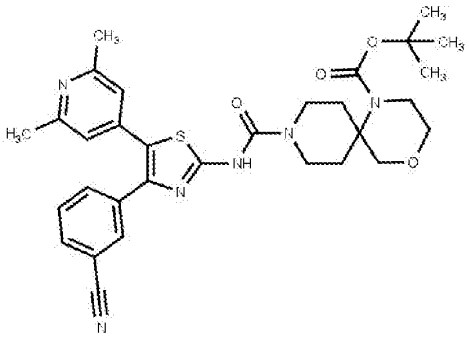
1H NMR (500 MHz, Methanol-d4) δ 7.92 (t, J = 1.7 Hz, 1H), 7.73 (dt, J = 8.0, 1.5 Hz, 1H), 7.70 (dt, J = 7.7, 1.4 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.02 (s, 2H), 3.63 – 3.55 (m, 2H), 3.40 (s, 2H), 3.02 – 2.85 (m, 2H), 2.45 (s, 6H), 1.19 (s, 6H).2 x NH protons not observed.

Example 14.7

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-oxa-1,9-diazaspiro[5.5]undecane-9-carboxamide



Step 1: tert-butyl 9-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-4-oxa-1,9-diazaspiro[5.5]undecane-1-carboxylate



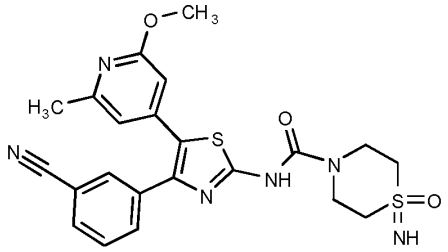
[00328] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and tert-butyl 4-oxa-1,9-

diazaspiro[5.5]undecane-1-carboxylate analogously to Example 4.
LC-MS (Method 2A): Rt 0.74 mins; MS m/z 589.2 = [M+H]+
1H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.76 (t, J = 1.6 Hz, 1H), 7.69 (dt, J = 7.6, 1.4 Hz, 1H), 7.55 (dt, J = 7.9, 1.5 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 6.90 (s, 2H), 3.91 (dt, J = 11.6, 5.1 Hz, 2H), 3.77 (t, J = 5.3 Hz, 2H), 3.60 (s, 2H), 3.54 (t, J = 5.3 Hz, 2H), 3.49 – 3.41 (m, 2H), 2.60 (ddd, J = 14.0, 9.6, 4.5 Hz, 2H), 2.54 (s, 6H), 1.84 – 1.74 (m, 2H), 1.45 (s, 9H).

Step 2: N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-oxa-1,9-diazaspiro[5.5]undecane-9-carboxamide

[00329] The title compound was prepared from tert-butyl 9-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]-4-oxa-1,9-diazaspiro[5.5]undecane-1-carboxylate (step 1) and TFA analogously to Example 14 step 2.
LC-MS (Method 7A): Rt 1.16 mins; MS m/z 489.3 = [M+H]+
1H NMR (400 MHz, MeOD) δ 7.90 (t, J = 1.7 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.48 (dd, J = 7.8, 7.8 Hz, 1H), 7.00 (s, 2H), 3.70 – 3.62 (m, 4H), 3.63 – 3.56 (m, 2H), 3.54 (s, 2H), 2.92 – 2.87 (m, 2H), 2.43 (s, 6H), 1.73 (t, J = 5.9 Hz, 4H). 2 x NH protons not observed.

Example 16
N-[4-(3-Cyanophenyl)-5-(2-methoxy-6-methyl-4-pyridyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide

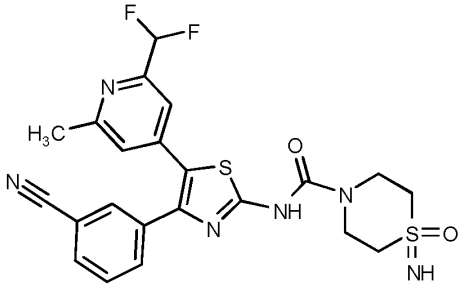
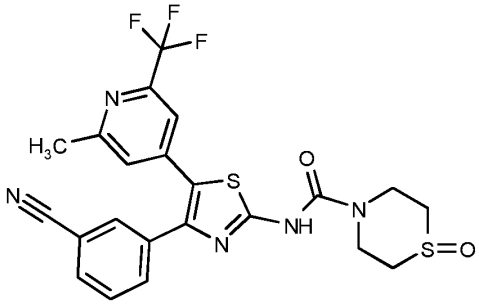
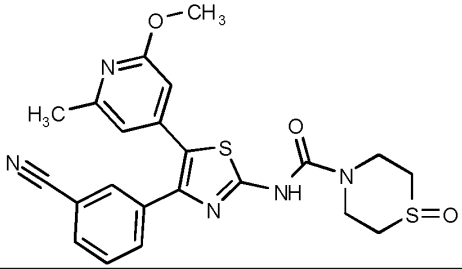


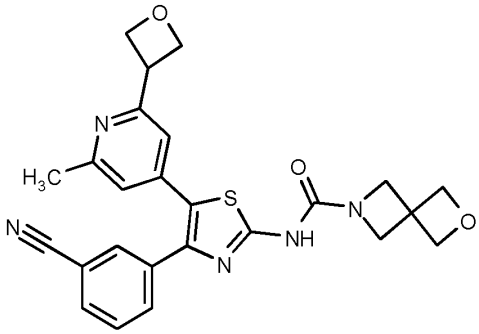
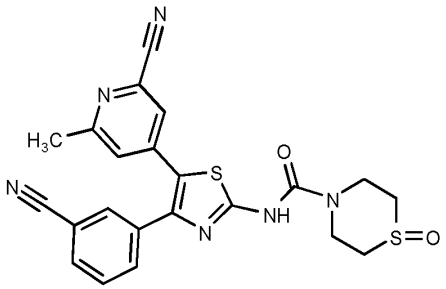
[00330] To a solution of 3-[2-amino-5-(2-methoxy-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate K) (75 mg, 0.23 mmol) and CDI (75 mg, 0.47 mmol) in DMA (1.2 mL) was added DIPEA (0.12 mL, 0.70 mmol) and the reaction mixture was stirred at 50 °C overnight. 1-Imino-1,4-thiazinane 1-oxide (47 mg, 0.35 mmol) was added and stirring continued at 50 °C for a further 1 h. The resulting mixture was purified by C18 reverse phase chromatography eluting with a gradient of 5 to 20% MeCN in water (+0.1% ammonium hydroxide) to afford the title compound as a white solid.
LC-MS (Method 8B): Rt 3.55 mins; MS m/z 483.3 = [M+H]+

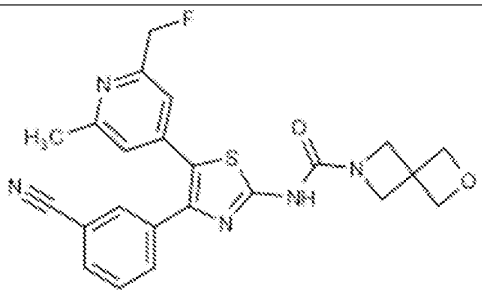
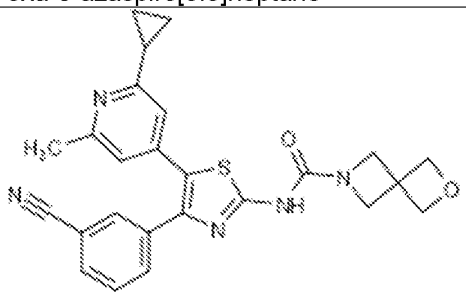
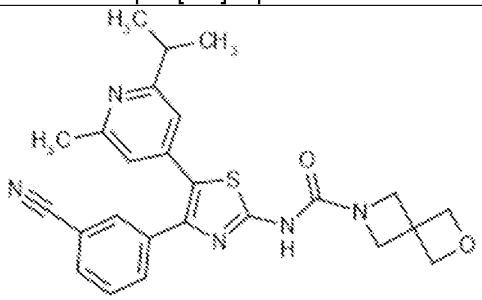
1H NMR (500 MHz, DMSO-d6) δ 11.53 (s, 1H), 7.91 (s, 1H), 7.84 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 6.74 (s, 1H), 6.42 (s, 1H), 4.11 (d, J = 14.4 Hz, 2H), 3.84 (s, 1H), 3.81 (s, 3H), 3.78 – 3.68 (m, 2H), 3.08 (d, J = 5.4 Hz, 4H), 2.34 (s, 3H).

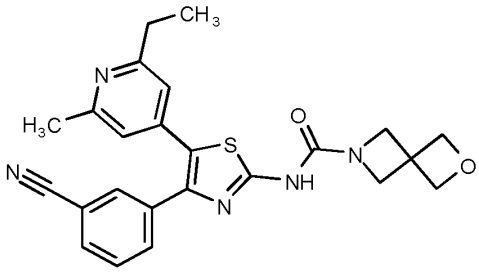
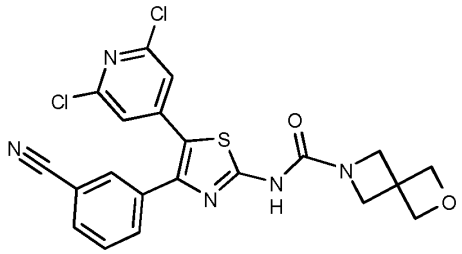
[00331] The compounds of the following tabulated Examples (Table Ex16) were prepared analogously to Example 16 from the appropriate starting compound and amine as indicated in the table.

Table Ex16

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
16.1	 N-[4-(3-Cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide Prepared from Intermediate G and 1-imino-1,4-thiazinane 1-oxide	LC-MS (Method 8B): Rt 3.06 mins; MS m/z 503.1 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.64 (s, 1H), 7.90 (d, J= 1.8 Hz, 1H), 7.87 (d, J= 7.5 Hz, 1H), 7.74 (dt, J= 7.9, 1.5 Hz, 1H), 7.60 (t, J= 7.8 Hz, 1H), 7.38 (s, 1H), 7.21 (s, 1H), 6.84 (t, J= 54.9 Hz, 1H), 4.12 (d, J= 14.3 Hz, 2H), 3.83 (s, 1H), 3.73 (d, J= 14.6 Hz, 2H), 3.09 (d, J= 9.3 Hz, 4H), 2.49 (s, 3H).
16.2	 N-[4-(3-Cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide Prepared from Intermediate H and 1,4-thiazinane 1-oxide hydrochloride	LC-MS (Method 8B): Rt 3.12 mins; MS m/z 506.0= [M+H]+ 1H NMR (500 MHz, Methanol-d4) δ 7.91 (s, 1H), 7.73 (t, J= 9.4 Hz, 2H), 7.53 (t, J= 7.8 Hz, 1H), 7.43 (s, 1H), 7.34 (s, 1H), 4.22 (d, J= 14.7 Hz, 2H), 3.99 (t, J= 13.1 Hz, 2H), 3.02 (td, J= 12.4, 10.7, 3.4 Hz, 2H), 2.89 (d, J= 13.7 Hz, 2H), 2.55 (s, 3H).
16.3		LC-MS (Method 8B): Rt 3.22 mins; MS m/z 468.1= [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.45 (s, 1H), 7.90 (s, 1H), 7.83 (d, J= 7.7 Hz, 1H), 7.71 (d, J= 7.9 Hz, 1H), 7.57 (t, J= 7.8 Hz, 1H), 6.74 (s, 1H), 6.41 (s, 1H), 4.11 (d, J= 14.7 Hz, 2H), 3.80 (s, 3H), 3.77 (d, J= 13.2 Hz, 2H), 2.92 (t, J= 12.8 Hz,

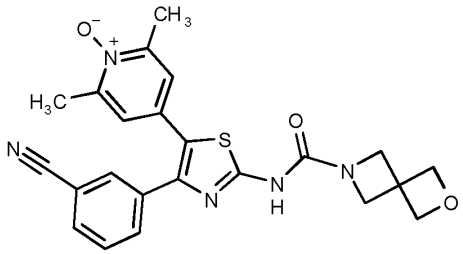
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
	N-[4-(3-Cyanophenyl)-5-(2-methoxy-6-methyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide Prepared from Intermediate K and 1,4-thiazinane 1-oxide hydrochloride	2H), 2.74 (d, J= 13.7 Hz, 2H), 2.34 (s, 3H).
16.4	 N-[4-(3-Cyanophenyl)-5-[2-methyl-6-(oxetan-3-yl)-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide Prepared from Intermediate L and 2-oxa-6-azaspiro[3.3]heptane	LC-MS (Method 8B): Rt 2.59 mins; MS m/z 474.1 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.37 (s, 1H), 7.88 (t, J = 1.6 Hz, 1H), 7.82 (dt, J = 7.8, 1.6 Hz, 1H), 7.72 (dt, J = 8.0, 1.6 Hz, 1H), 7.56 (apr t, J = 7.8 Hz, 1H), 7.05 (s, 1H), 6.98 (s, 1H), 4.80 (dd, J = 8.5, 5.7 Hz, 2H), 4.67 (s, 4H), 4.65 (dd, J = 7.1, 5.7 Hz, 2H), 4.27 (tt, J = 8.5, 7.1 Hz, 1H), 4.20 (s, 4H), 2.44 (s, 3H)
16.5	 N-[5-(2-Cyano-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide Prepared from Intermediate KA and 1,4-thiazinane 1-oxide hydrochloride	LC-MS (Method 8B): Rt 2.94 mins; MS m/z 463.1 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.58 (s, 1H), 7.92 (s, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.49 (s, 1H), 4.12 (d, J = 14.2 Hz, 2H), 3.79 (t, J = 13.1 Hz, 2H), 2.92 (t, J = 12.4 Hz, 2H), 2.74 (d, J = 13.7 Hz, 2H), 2.47 (s, 3H).

Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
16.6	 N-[4-(3-Cyanophenyl)-5-[2-(fluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide Prepared from Intermediate KB and 2-oxa-6-azaspiro[3.3]heptane	LC-MS (Method 8B): Rt 2.95 mins; MS m/z 450.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.40 (s, 1H), 7.88 (t, J = 1.7 Hz, 1H), 7.83 (dt, J = 7.7, 1.4 Hz, 1H), 7.71 (dt, J = 8.0, 1.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.14 (s, 1H), 7.08 (s, 1H), 5.36 (d, J = 46.8 Hz, 2H), 4.67 (s, 4H), 4.20 (s, 4H), 2.42 (s, 3H).
16.7	 N-[4-(3-Cyanophenyl)-5-(2-cyclopropyl-6-methyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide Prepared from Intermediate KC and 2-oxa-6-azaspiro[3.3]heptane	LC-MS (Method 8B): Rt 2.33 mins; MS m/z 458.1 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.34 (s, 1H), 7.87 (t, J = 1.5 Hz, 1H), 7.82 (dt, J = 7.7, 1.5 Hz, 1H), 7.70 (dt, J = 8.0, 1.5 Hz, 1H), 7.57 (apr t, J = 7.8 Hz, 1H), 6.88 (d, J = 1.6 Hz, 1H), 6.87 (d, J = 1.6 Hz, 1H), 4.67 (s, 4H), 4.20 (s, 4H), 2.32 (s, 3H), 1.97 (tt, J = 8.2, 4.8 Hz, 1H), 0.90 – 0.85 (m, 2H), 0.83 – 0.78 (m, 2H)
16.8	 N-[4-(3-Cyanophenyl)-5-(2-isopropyl-6-methyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide Prepared from Intermediate KD and 2-oxa-6-azaspiro[3.3]heptane	LC-MS (Method 8B): Rt 3.56 mins; MS m/z 460.3 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.31 (s, 1H), 7.93 – 7.79 (m, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.02 (s, 1H), 6.79 (s, 1H), 4.67 (s, 4H), 4.20 (s, 4H), 2.89 – 2.81 (m, 1H), 2.41 (s, 3H), 1.08 (d, J = 6.9 Hz, 6H).

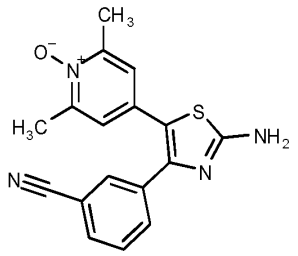
Ex.	Structure and Name	Retention Time, [M+H]+, ^{1}H NMR
16.9	 N-[4-(3-Cyanophenyl)-5-(2-ethyl-6-methyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide Prepared from Intermediate KE and 2-oxa-6-azaspiro[3.3]heptane	LC-MS (Method 8B): Rt 3.97 mins; MS m/z 446.2 = [M+H]+ 1H NMR (500 MHz, CDCl3) δ 7.87 (t, J = 1.5 Hz, 1H), 7.76 (br s, 1H), 7.63 (dt, J = 7.9, 1.5 Hz, 1H), 7.60 (dt, J = 7.8, 1.5 Hz, 1H), 7.39 (apr t, J = 7.8 Hz, 1H), 6.89 (br d, J = 1.2 Hz, 1H), 6.84 (br d, J = 1.2 Hz, 1H), 4.83 (s, 4H), 4.30 (s, 4H), 2.72 (q, J = 7.6 Hz, 2H), 2.48 (s, 3H), 1.19 (t, J = 7.6 Hz, 3H)
16.10	 N-[4-(3-Cyanophenyl)-5-(2,6-dichloro-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide Prepared from Intermediate KF and 2-oxa-6-azaspiro[3.3]heptane	LC-MS (Method 8B): Rt 2.98 mins; MS m/z 470.1 / 472.1 = [M+H]+ 1H NMR (500 MHz, DMSO-d6) δ 11.53 (s, 1H), 7.95 (t,J= 1.6 Hz, 1H), 7.88 (dt,J= 7.8, 1.6 Hz, 1H), 7.76 (dt,J= 7.6, 1.6 Hz, 1H), 7.61 (t,J= 7.8 Hz, 1H), 7.35 (s, 2H), 4.67 (s, 4H), 4.21 (s, 4H).

Example 17

N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-1-oxido-pyridin-1-ium-4-yl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



Step 1: 3-[2-Amino-5-(2,6-dimethyl-1-oxido-pyridin-1-ium-4-yl)thiazol-4-yl]benzonitrile



[00332] mCPBA (110 mg, 0.49 mmol) was added to a suspension of 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) (100 mg, 0.33 mmol) in DCM (2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Further mCPBA (73 mg, 0.33 mmol) was added and stirring continued for 1 h. The resulting solution was diluted in DCM (10 mL) and washed with sat. $NaHCO_3$ solution (2 x 20 mL). The organics were dried over Na_2SO_4 and concentrated *in vacuo* to afford a red oil. The oil was dry loaded onto silica and purified by chromatography on silica eluting with a gradient of 0 to 5% MeOH in DCM to afford a solid that was triturated with Et_2O, filtered and washed with Et_2O (3 x 2 mL) to afford the title compound as a yellow solid.

LC-MS (Method 5A): Rt 1.86 mins; MS m/z 323.1 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.86 (d, J = 1.9 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.55 – 7.49 (m, 1H), 7.46 – 7.39 (m, 2H), 7.14 (s, 2H), 2.27 (s, 6H).

Step 2: N-[4-(3-Cyanophenyl)-5-(2,6-dimethyl-1-oxido-pyridin-1-ium-4-yl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

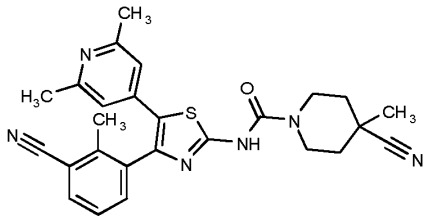
[00333] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-1-oxido-pyridin-1-ium-4-yl)thiazol-4-yl]benzonitrile (step 1) and 2-oxa-6-azaspiro[3.3]heptane analogously to Example 6.

LC-MS (Method 8A): Rt 2.53 mins; MS m/z 448.2 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.92 (s, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.20 (s, 2H), 4.67 (s, 4H), 4.13 (s, 4H), 2.29 (s, 6H). 1 x NH proton not observed.

Example 18

4-Cyano-N-[4-(3-cyano-2-methyl-phenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide



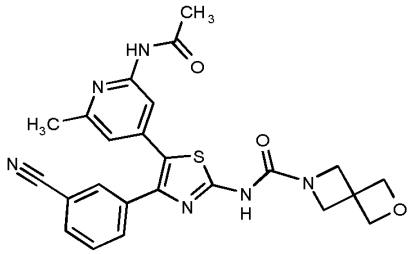
[00334] The title compound was prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]-2-methyl-benzonitrile (Intermediate O) and 4-methylpiperidine-4-carbonitrile hydrochloride analogously to Example 6.

LC-MS (Method 8B): Rt 4.25 mins; MS m/z 471.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.36 (s, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.44 (t, J = 7.7 Hz, 1H), 6.67 (s, 2H), 4.23 (d, J = 14.0 Hz, 2H), 3.03 (t, J = 13.1 Hz, 2H), 2.29 – 2.25 (m, 9H), 1.92 (d, J = 13.5 Hz, 2H), 1.53 (td, J = 13.2, 3.9 Hz, 2H), 1.38 (s, 3H).

Example 19

N-[5-(2-Acetamido-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



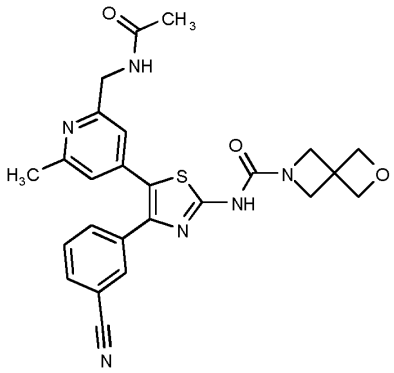
[00335] The title compound was prepared from N-[4-[2-amino-4-(3-cyanophenyl)thiazol-5-yl]-6-methyl-2-pyridyl]acetamide (Intermediate KG) and 2-oxa-6-azaspiro[3.3]heptane analogously to Example 6.

LC-MS (Method 8B): Rt 2.89 mins; MS m/z 475.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.35 (s, 1H), 10.49 (s, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.85 (s, 1H), 7.81 (dt, J = 7.8, 1.5 Hz, 1H), 7.73 (dt, J = 7.8, 1.5 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 1.5 Hz, 1H), 4.67 (s, 4H), 4.20 (s, 4H), 2.33 (s, 3H), 2.02 (s, 3H).

Example 20

N-[5-[2-(Acetamidomethyl)-6-methyl-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



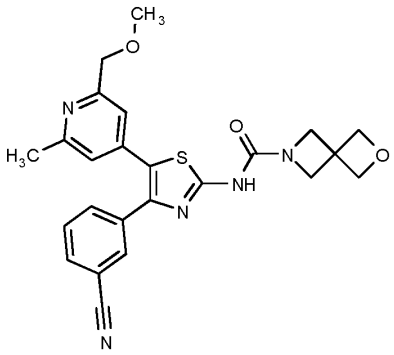
[00336] The title compound was prepared from N-[[4-[2-amino-4-(3-cyanophenyl)thiazol-5-yl]-6-methyl-2-pyridyl]methyl]acetamide (Intermediate KH) and 2-oxa-6-azaspiro[3.3]heptane analogously to Example 6.

LC-MS (Method 8B: Rt 2.59 mins; MS m/z 489.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.37 (s, 1H), 8.30 (t, J = 6.0 Hz, 1H), 7.88 – 7.81 (m, 2H), 7.68 (dt, J = 8.0, 1.5 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.04 (s, 1H), 6.87 (s, 1H), 4.68 (s, 4H), 4.23 – 4.19 (m, 6H), 2.40 (s, 3H), 1.76 (s, 3H). Contains 1% Et2O

Example 21

N-[4-(3-Cyanophenyl)-5-[2-(methoxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



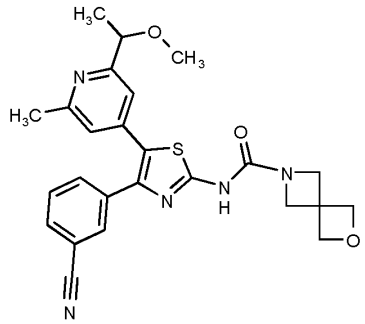
[00337] The title compound was prepared from 3-[2-amino-5-[2-(methoxymethyl)-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate KI) and 2-oxa-6-azaspiro[3.3]heptane analogously to Example 6.

LC-MS (Method 8B): Rt 3.30 mins; MS m/z 462.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.38 (s, 1H), 7.87 (s, 1H), 7.83 (dt, J = 7.7, 1.5 Hz, 1H), 7.73 (dt, J = 8.0, 1.5 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.08 (s, 1H), 6.99 (s, 1H), 4.68 (s, 4H), 4.39 (s, 2H), 4.21 (s, 4H), 3.23 (s, 3H), 2.41 (s, 3H).

Example 22

N-[4-(3-Cyanophenyl)-5-[2-(1-methoxyethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



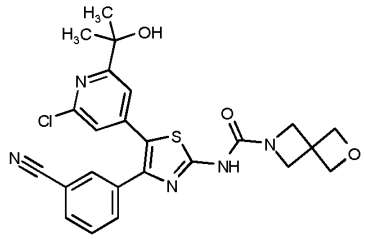
[00338] The title compound was prepared from 3-[2-amino-5-[2-(methoxymethyl)-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate P) and 2-oxa-6-azaspiro[3.3]heptane analogously to Example 6.

LC-MS (Method 8B): Rt 3.92 mins; MS m/z 476.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.45 (s, 1H), 7.91 – 7.87 (m, 2H), 7.83 (dt, J = 7.9, 1.5 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.21 (d, J = 1.6 Hz, 1H), 6.95 (d, J = 1.6 Hz, 1H), 4.74 (s, 4H), 4.33 – 4.20 (m, 5H), 3.10 (s, 3H), 2.51 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H).

Example 23

N-[5-[2-Chloro-6-(1-hydroxy-1-methyl-ethyl)-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



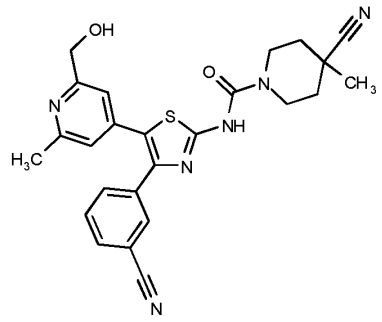
[00339] The title compound was prepared from 3-[2-amino-5-[2-chloro-6-(1-hydroxy-1-methyl-ethyl)-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate Q) and 2-oxa-6-azaspiro[3.3]heptane analogously to Example 6.

LC-MS (Method 8B): Rt 3.40 mins; MS m/z 496.1 = [M+H]+

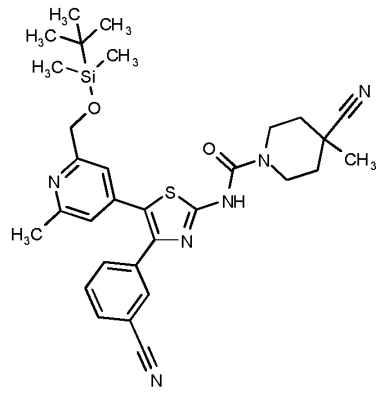
1H NMR (500 MHz, DMSO-d6) δ 11.47 (s, 1H), 7.88 (t, J = 1.6 Hz, 1H), 7.86 (dt, J = 7.8, 1.6 Hz, 1H), 7.76 (dt, J = 7.9, 1.6 Hz, 1H), 7.61 (apr t, J = 7.8 Hz, 1H), 7.46 (d, J = 1.5 Hz, 1H), 7.15 (d, J = 1.5 Hz, 1H), 5.26 (s, 1H), 4.67 (s, 4H), 4.21 (s, 4H), 1.36 (s, 6H).

Example 24

4-Cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide



Step 1: N-[5-[2-[[*tert*-Butyl(dimethyl)silyl]oxymethyl]-6-methyl-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-4-cyano-4-methyl-piperidine-1-carboxamide



[00340] The title compound was prepared from 3-[2-amino-5-[2-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate I) and 4-methylpiperidine-4-carbonitrile hydrochloride analogously to Example 6.

LC-MS (Method 3B): Rt 2.34 mins; MS m/z 587.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.35 (s, 1H), 7.85 (s, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.12 (s, 1H), 7.01 (s, 1H), 4.62 (s, 2H), 4.22 (d, J = 14.0 Hz, 2H), 3.03 (t, J = 12.9 Hz, 2H), 2.42 (s, 3H), 1.92 (d, J = 13.6 Hz, 2H), 1.58 – 1.49 (m, 2H), 1.37 (s, 3H), 0.77 (s, 9H), -0.02 (s, 6H).

Step 2: 4-Cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide

[00341] To a solution of N-[5-[2-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6-methyl-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-4-cyano-4-methyl-piperidine-1-carboxamide (step 1)(188 mg, 0.32 mmol) in THF (6.4 mL) was added TBAF (0.64 mL, 0.64 mmol) and the

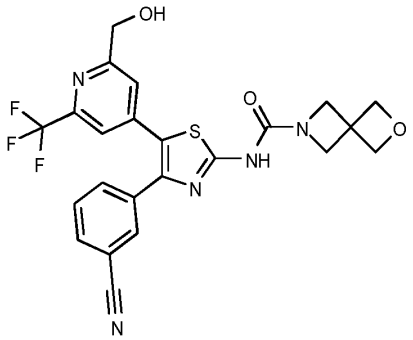
reaction mixture was stirred at room temperature for 90 mins. Additional TBAF (0.64 mL, 0.64 mmol) was added and stirring continued for a further 2.5 h. The resulting mixture was diluted with EtOAc (50 mL) and water (50 mL). The layers were separated and the aqueous phase was extracted further with EtOAc (40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica eluting in 0 to 30% MeOH in EtOAc afforded a yellow solid. The solid was further purified by C18 reverse phase chromatography eluting with a gradient of 10 to 35% MeCN in water (+ 0.1% ammonium hydroxide) to afford a solid which was triturated in Et_2O and filtered to afford the title compound as a white solid.

LC-MS (Method 8B): Rt 3.75 mins; MS m/z 473.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.32 (s, 1H), 7.89 (s, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.14 (s, 1H), 6.98 (s, 1H), 5.33 (t, J = 5.9 Hz, 1H), 4.46 (d, J = 5.9 Hz, 2H), 4.23 (d, J = 14.0 Hz, 2H), 3.02 (t, J = 13.1 Hz, 2H), 2.37 (s, 3H), 1.92 (d, J = 13.6 Hz, 2H), 1.52 (dt, J = 13.4, 7.1 Hz, 2H), 1.37 (s, 3H).

Example 26

N-[4-(3-Cyanophenyl)-5-[2-(hydroxymethyl)-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide



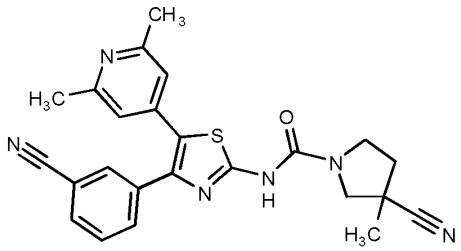
[00342] The title compound was prepared from 3-[2-amino-5-[2-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6-(trifluoromethyl)-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate IA) and 2-oxa-6-azaspiro[3.3]heptane analogously to Example 9.

LC-MS (Method 8B): Rt 3.49 mins; MS m/z 502.2 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.52 (s, 1H), 7.92 (t, J = 1.8 Hz, 1H), 7.88 (dt, J = 7.8, 1.4 Hz, 1H), 7.76 (dt, J = 8.0, 1.4 Hz, 1H), 7.65 (d, J = 1.5 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 1.6 Hz, 1H), 5.63 (t, J = 5.9 Hz, 1H), 4.68 (s, 4H), 4.60 (d, J = 5.9 Hz, 2H), 4.23 (s, 4H).

Example 27

3-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide



[00343] CDI (1.16 g, 7.18 mmol) and DIPEA (1.88 mL, 10.77 mmol) were added to a stirred solution of 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) (1.1 g, 3.59 mmol) in DMA (11 mL) and the solution was heated at 50 °C overnight. 3-Methylpyrrolidine-3-carbonitrile hydrochloride (1.00 g, 6.82 mmol) and additional DIPEA (1.88 mL, 10.77 mmol) were added and the solution was stirred at 50 °C for 30 mins. The resulting mixture was allowed to cool to room temperature and diluted with EtOAc (150 mL). The mixture was washed with 90% aqueous brine (100 mL) and 50% aqueous brine (3 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica eluting with a gradient of 1 to 2% MeOH in DCM afforded a yellow solid. Addition of MeOH (10 mL) afforded a white solid which was collected by filtration, washed with MeOH (2 mL) and Et_2O (20 mL) and dried to afford the title compound as a white solid.
LC-MS (Method 8B): Rt 3.03 mins; MS m/z 443.1 = [M+H]+
1H NMR (500 MHz, DMSO-d6) δ 11.24 (s, 1H), 7.89 (t, J = 1.8 Hz, 1H), 7.82 (dt, J = 7.7, 1.4 Hz, 1H), 7.71 (dt, J = 8.0, 1.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 3.96 – 3.86 (m, 1H), 3.64 (d, J = 34.3 Hz, 2H), 3.42 (d, J = 11.1 Hz, 1H), 2.43 – 2.38 (m, 1H), 2.36 (s, 6H), 2.14 – 2.02 (m, 1H), 1.47 (s, 3H).

Example 27a and Example 27b

[00344] Racemic 3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide (Example 27) was dissolved to 50 mg/mL in EtOH/DCM (4:1) and purified by SFC. The combined fractions of each enantiomer were evaporated to near dryness before being transferred into final vessels with DCM, which was removed under a stream of compressed air at 35 °C, before being stored in a vacuum oven at 35 °C and 5 mbar until constant weight was reached.

Purification Conditions;

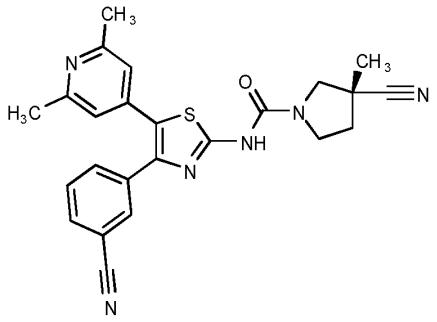
Column Details	Lux iA3 (21.2mm x 250mm, 5um)
Column Temp	40 °C
Flow Rate	50 mL/min
BPR	100 BarG
Detector Wavelength	216 nm
Injection Volume	250 uL (12.5 mg)
Isocratic Conditions	35:65 EtOH:CO_2 (0.2% v/v NH_3)

Chiral Purity Analysis Conditions;

Column Details	Chiralpak IG (4.6mm x 250mm, 5um)
Column Temp	40 °C
Flow Rate	4 mL/min
Detector Wavelength	210-400 nm
Injection Volume	1.0 uL
BPR	125 BarG
Isocratic Conditions	25:75 EtOH:CO_2 (0.2% v/v NH_3)

Example 27a

(3R)-3-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide



(*R*)-Isomer

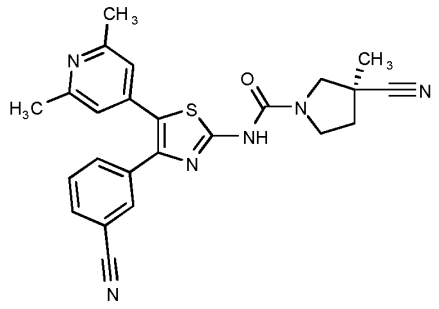
First Eluted Peak: Chiral LCMS retention time: = 7.05 mins

LC-MS (Method 8B): Rt 3.04 mins; MS m/z 443.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.24 (s, 1H), 7.89 (t, J = 1.6 Hz, 1H), 7.82 (dt, J = 7.7, 1.6 Hz, 1H), 7.71 (dt, J = 8.0, 1.6 Hz, 1H), 7.56 (apr t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 3.98 – 3.86 (m, 1H), 3.72 – 3.63 (m, 1H), 3.64 – 3.55 (m, 1H), 3.46 – 3.38 (m, 1H), 2.43 – 2.36 (m, 1H), 2.36 (s, 6H), 2.12 – 2.03 (m, 1H), 1.47 (s, 3H).

Example 27b

(3S)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide



(*S*)-Isomer

Second Eluted Peak: Chiral LCMS retention time: = 8.59 mins

LC-MS (Method 8B): Rt 2.92 mins; MS m/z 443.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.24 (s, 1H), 7.89 (t, J = 1.6 Hz, 1H), 7.82 (dt, J = 7.7, 1.6 Hz, 1H), 7.71 (dt, J = 8.0, 1.6 Hz, 1H), 7.56 (apr t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 3.98 – 3.87 (m, 1H), 3.71 – 3.63 (m, 1H), 3.64 – 3.55 (m, 1H), 3.46 – 3.37 (m, 1H), 2.43 – 2.38 (m, 1H), 2.36 (s, 6H), 2.13 – 2.02 (m, 1H), 1.47 (s, 3H).

[00345] A further sample of Example 27b was obtained under the following conditions:

[00346] Racemic 3-Cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide (Example 27) was dissolved to 25 mg/mL in EtOH/DCM (4:1) and purified by SFC. The combined fractions of each enantiomer were evaporated to near dryness. The resultant solids were transferred into final vessels with DCM, which was removed under a stream of compressed air at 35 °C, before being stored in a vacuum oven at 35 °C and 5 mbar until constant weight was reached. The material was triturated in Et_2O/MeOH under sonication and the resulting thick suspension filtered. The solids were washed with Et_2O/MeOH and vacuum dried on the sinter followed by further drying in a vacuum oven at 50 ºC overnight to afford the title compound as a cream solid.

Purification Conditions:

Column Details	Lux iA3 (21.2mm x 250mm, 5um)
Column Temp	40 °C
Flow Rate	50 mL/min
BPR	100 BarG
Detector Wavelength	217 nm
Injection Volume	500 uL (12.5 mg)
Isocratic Conditions	25:75 EtOH:CO_2 (0.2% v/v NH_3)

Chiral Purity Analysis Conditions;

Column Details	Chiralpak IG (4.6mm x 250mm, 5um)
Column Temp	40 °C
Flow Rate	4 mL/min
Detector Wavelength	210-400 nm
Injection Volume	1.0 uL
BPR	125 BarG
Isocratic Conditions	25:75 EtOH:CO_2 (0.2% v/v NH_3)

Second Eluted Peak: Chiral LCMS retention time: = 9.73 mins

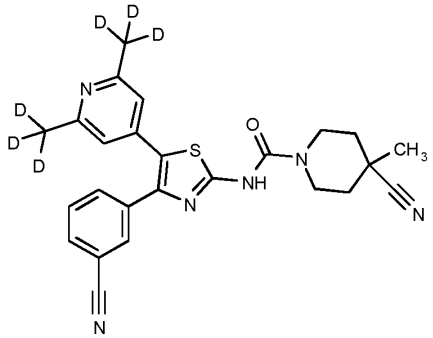
LC-MS (Method 8A): Rt 2.37 mins; MS m/z 443.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.23 (br s, 1H), 7.89 (br t, J = 1.5 Hz, 1H), 7.82 (br dt, J = 7.7, 1.5 Hz, 1H), 7.71 (br dt, J = 8.0, 1.5 Hz, 1H), 7.56 (apr t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 3.92 (br s, 1H), 3.67 (br s, 1H), 3.60 (br s, 1H), 3.41 (br d, J = 11.2 Hz, 1H), 2.39 (s, 1H), 2.36 (s, 6H), 2.12 – 2.03 (m, 1H), 1.47 (s, 3H).

Examples 27a and 27b were alternatively prepared from 3-[2-amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile (Intermediate C) and either (3R)-3-methylpyrrolidine-3-carbonitrile hydroiodide (Intermediate U) or (3S)-3-methylpyrrolidine-3-carbonitrile hydroiodide (Intermediate UA) analogously to Example 6.

Example 28

N-[5-[2,6-Bis(trideuteriomethyl)-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-4-cyano-4-methyl-piperidine-1-carboxamide



[00347] 3-[2-Amino-5-[2,6-bis(trideuteriomethyl)-4-pyridyl]thiazol-4-yl]benzonitrile (Intermediate N) (465 mg, 1.49 mmol) and CDI (483 mg, 2.98 mmol) were dissolved in

anhydrous DMA (7.5 mL) in a sealed tube under nitrogen. DIPEA (778 µL, 4.47 mmol) was added and the resulting solution stirred at 50 ºC for 17 h. 4-Methylpiperidine-4-carbonitrile hydrochloride (478 mg, 2.98 mmol) and additional DIPEA (778 µL, 4.47mmol) were added and the mixture stirred at 50 ºC for 1 h. The mixture was allowed to cool to room temperature before being diluted with EtOAc (80 mL) and washed successively with 80% brine (80 mL), 20% brine (2 x 80 mL) and 50% brine (80 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude material as a pale yellow foam. Purification by chromatography on silica eluting with a gradient of 1 to 2% MeOH in DCM afforded a clear straw coloured glass which was triturated and azeotroped with Et_2O to afford the title compound as a cream solid.

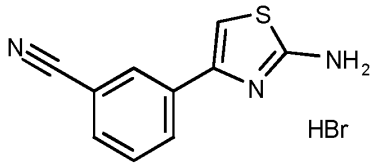
LC-MS (Method 8B): Rt 3.08 mins; MS m/z 463.1 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 11.31 (s, 1H), 7.89 (t, J = 1.6 Hz, 1H), 7.82 (dt, J = 7.8, 1.6 Hz, 1H), 7.70 (dt, J = 8.0, 1.6 Hz, 1H), 7.56 (apr t, J = 7.8 Hz, 1H), 6.93 (s, 2H), 4.22 (d, J = 13.9 Hz, 2H), 3.03 (t, J = 13.3 Hz, 2H), 1.92 (d, J = 13.9 Hz, 2H), 1.53 (td, J = 13.3, 4.0 Hz, 2H), 1.37 (s, 3H).

Preparation of Intermediates

Intermediate A

3-(2-Aminothiazol-4-yl)benzonitrile hydrobromide



[00348] The following was prepared according to the procedure of Wang, Y. and Yang, T. in patent WO2012/100734, page 24, Example 15 step 2.

[00349] To a flask containing 3-(2-bromoacetyl)benzonitrile (5 g, 22.32 mmol) in EtOH (50 mL) was added thiourea (1.87 g, 24.55 mmol) and the mixture was stirred at room temperature for 30 mins. The volume of solvent was reduced by ~50% *in vacuo* resulting in the formation of a suspension. The suspension was sonicated, filtered and dried to afford the title compound as a colourless solid.

LC-MS (Method 3B): Rt 1.62 mins; MS m/z 202.3 = [M+H]+

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (t, J = 1.8 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.37 (s, 1H). NH_2 protons not observed.

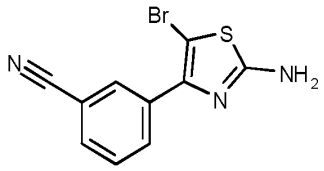
[00350] 3-(2-Aminothiazol-4-yl)benzonitrile may also be prepared as follows:

[00351] To a flask containing thiourea (2.04 g, 26.78 mmol) in pyridine (50 mL) under nitrogen was added 3-(2-bromoacetyl)benzonitrile (3.0 g, 13.39 mmol) and the mixture was stirred at room temperature for 1 h. The resulting mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by chromatography on silica eluting with 0-100% EtOAc in DCM. The resulting solid was recrystallised from EtOAc to afford 3-(2-aminothiazol-4-yl)benzonitrile as a pale yellow solid
LC-MS (Method 7A): Rt 1.75 mins; MS m/z 202.1 = [M+H]+

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (t, *J* = 1.5 Hz, 1H), 8.11 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.70 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.26 (s, 1H), 7.14 (s, 2H).

Intermediate B

3-(2-Amino-5-bromo-thiazol-4-yl)benzonitrile



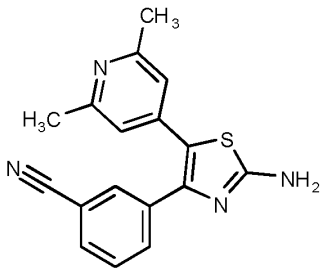
[00352] The following was prepared according to the procedure Wang, Y. and Yang, T. in patent WO2012/100734, page 24-25, Example 15 step 3.

[00353] To a solution of 3-(2-aminothiazol-4-yl)benzonitrile hydrobromide (Intermediate A)(2.6 g, 9.21 mmol) in THF (40 mL) was added NBS (1.97 g, 11.06 mmol) and the reaction mixture was stirred at room temperature for 1 h. The resulting mixture was diluted with EtOAc (60 mL) and washed with water (100 mL). The organic layer was separated and the aqueous further extracted with EtOAc (2 x 50 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to yield an orange solid. The solid was suspended in DCM (20 mL), filtered, washed with DCM and dried to afford the title compound as an off-white solid.
LC-MS (Method 3B): Rt 1.64 mins; MS m/z 279.9/281.9 = [M+H]+

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.16 (t, *J* = 1.7 Hz, 1H), 8.15 (dt, *J* = 7.9, 1.7 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.66 (t, *J* = 7.9 Hz, 1H), 7.42 (s, 2H).

Intermediate C

3-[2-Amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile



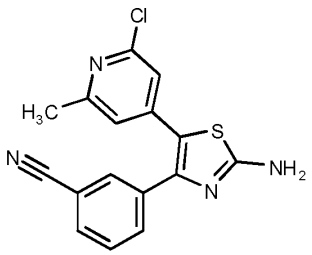
[00354] A solution of potassium carbonate (43.1 g, 312.34 mmol) in water (210 mL) was added to a solution of 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) (35.0 g, 124.94 mmol) and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (34.95 g, 149.93 mmol) in 1,4-dioxane (840 mL) and the mixture de-oxygenated via nitrogen sparging for 20 mins. Bis(tri-*tert*-butylphosphine)palladium(0) (6.38 g, 12.49 mmol) was added, the flask sealed and the contents evacuated and backfilled with nitrogen (3 x cycles). The reaction mixture was stirred at 80 ºC for 1 h and then allowed to cool to room temperature. The mixture was diluted with EtOAc (500 mL) and water (200 mL) and the layers were separated. The organic layer was washed with 20% brine (500 mL), neat brine (200 mL), dried over Na_2SO_4 and filtered through a plug of Celite® (filter material), eluting with EtOAc (4 x 200 mL). The filtrate was concentrated *in vacuo* and the resulting material was triturated in DCM (150 mL) via sonication. The solids were collected by filtration, washed with DCM (3 x 50 mL) and vacuum dried to afford the title compound as a pale tan solid.

LC-MS (Method 2B): Rt 1.26 mins; MS m/z 307.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.81 (br t, J = 1.5 Hz, 1H), 7.79 (br dt, J = 7.6, 1.5 Hz, 1H), 7.66 (br dt, J = 7.9, 1.5 Hz, 1H), 7.52 (apr t, J = 7.8 Hz, 1H), 7.50 – 7.36 (m, 2H), 6.80 (s, 2H), 2.32 (s, 6H).

Intermediate D

3-[2-Amino-5-(2-chloro-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile



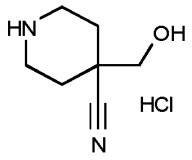
[00355] A solution of 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) (710 mg, 2.53 mmol), 2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (649 mg, 2.56 mmol) and cesium carbonate (1652 mg, 5.07 mmol) in monoglyme (28.4 mL) and water (3.5 mL) was degassed with nitrogen for 5 mins. $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (517 mg, 0.63 mmol) was added and the reaction mixture was heated at 80 °C under nitrogen for 1 h. After cooling to room temperature, the resulting mixture was filtered and the precipitate was washed with EtOAc (50 mL). The filtrate was partitioned between water (20 mL) and brine (20 mL) and the organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by chromatography on silica eluting with 0-50% EtOAc in DCM to afford the title compound as a brown solid.

LC-MS (Method 2A): Rt 1.12 mins; MS m/z 327.0/329.0 = [M+H]+

^{1}H NMR (400 MHz, DMSO-d6) δ 7.86 – 7.80 (m, 2H), 7.69 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.60 (s, 2H), 7.59 – 7.54 (m, 1H), 7.03 – 6.99 (m, 1H), 6.92 – 6.89 (m, 1H), 2.35 (s, 3H).

Intermediate E

4-(Hydroxymethyl)piperidine-4-carbonitrile hydrochloride

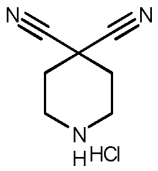


[00356] To a solution of *tert*-butyl 4-cyano-4-(hydroxymethyl)piperidine-1-carboxylate (100 mg, 0.42 mmol) in DCM (1 mL) was added 4M HCl in 1,4-dioxane (2.08 mL, 8.32 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting mixture was concentrated *in vacuo* to afford the title compound as a colourless solid.

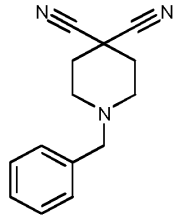
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 2H), 5.66 (t, *J* = 5.8 Hz, 1H), 3.52 (d, *J* = 5.8 Hz, 2H), 3.41 – 3.34 (m, 2H), 2.90 (td, *J* = 13.1, 3.0 Hz, 2H), 2.04 (d, *J* = 14.2 Hz, 2H), 1.85 – 1.73 (m, 2H).

Intermediate F

Piperidine-4,4-dicarbonitrile hydrochloride



Step 1: 1-Benzylpiperidine-4,4-dicarbonitrile



[00357] The following was prepared according to the procedure of Zahler, R. and Vath, J. in patent WO2017027684 (A1), pages 56 and 57.

[00358] K_2CO_3 (1132 mg, 8.19 mmol) was added to a solution of propanedinitrile (0.23 mL, 3.72 mmol) in DMF (5 mL) and the reaction mixture was stirred at 65 °C for 2 h. To this mixture was added N-benzyl-2-chloro-N-(2-chloroethyl)ethanamine hydrochloride (1.0 g, 3.72 mmol) in DMF (5 mL) and stirring continued at 65 °C for 16 h. After cooling to room temperature, the reaction was quenched with ice cold water. The resulting mixture was extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 10-40% EtOAc in petroleum ether afforded the title compound as a colourless oil.

LC-MS (Method 8B): Rt 4.31 mins; MS m/z 226.2 = [M+H]+

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 5H), 3.56 (s, 2H), 2.64 (s, 4H), 2.25 (s, 4H).

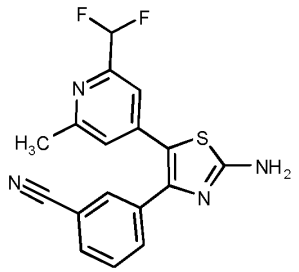
Step 2: Piperidine-4,4-dicarbonitrile hydrochloride

[00359] 1-Chloroethyl carbonochloridate (0.36 mL, 3.31 mmol) was added dropwise to a stirred solution of 1-benzylpiperidine-4,4-dicarbonitrile (step 1) (622 mg, 2.76 mmol) in DCE (5 mL) at 0 °C. The reaction mixture was heated at reflux for 24 h and then concentrated *in vacuo* to give a colourless oil. Methanol (5 mL) was then added and the solution was heated at reflux for 3 h. The resulting mixture was concentrated *in vacuo* to afford the title compound as a colourless solid.

^{1}H NMR (500 MHz, DMSO-d6) δ 9.38 (m, 2H), 3.21 (s, 4H), 2.65 – 2.57 (m, 4H).

Intermediate G

3-[2-Amino-5-(2-difluoromethyl-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile



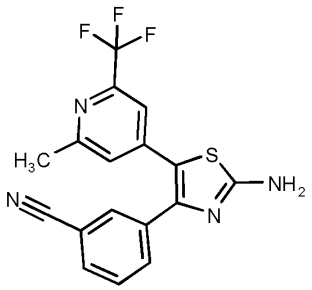
[00360] The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and 2-(difluoromethyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine analogously to Intermediate C.

LC-MS (Method 5B): Rt 2.83 mins; MS m/z 343.1 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.84 (dd, J = 4.8, 3.0 Hz, 2H), 7.70 (d, J = 7.9 Hz, 1H), 7.63 (s, 2H), 7.56 (t, J = 8.1 Hz, 1H), 7.20 (s, 1H), 7.07 (s, 1H), 6.80 (t, J = 55.0 Hz, 1H), 2.44 (s, 3H).

Intermediate H

3-[2-Amino-5-(2-trifluoromethyl-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile



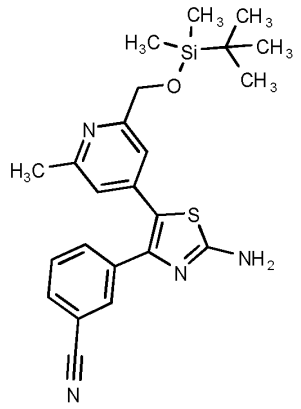
[00361] The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine analogously to Intermediate C.

LC-MS (Method 3B): Rt 1.86 mins; MS m/z 359.3 = [M-H]-

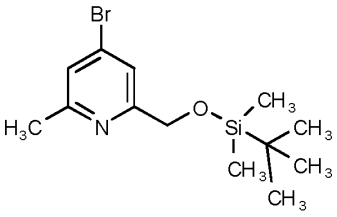
1H NMR (500 MHz, DMSO-d6) δ 7.88 – 7.81 (m, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.68 (s, 2H), 7.57 (dd, J = 9.6, 6.6 Hz, 1H), 7.33 (s, 1H), 7.15 (s, 1H), 2.47 (s, 3H).

Intermediate I

3-[2-Amino-5-[2-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile



Step 1: (4-Bromo-6-methyl-2-pyridyl)methoxy-tert-butyl-dimethyl-silane

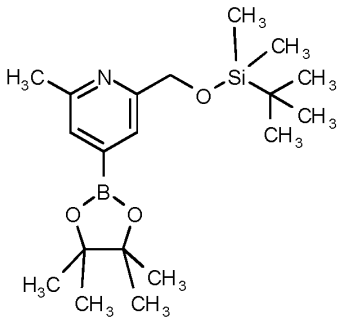


[00362] To a solution of (4-bromo-6-methyl-2-pyridyl)methanol (2.0 g, 9.9 mmol) in DMF (15 mL) at 0 °C was added imidazole (0.03 mL, 12.87 mmol) followed by *tert*-butyldimethylsilyl chloride (1.11 mL, 10.89 mmol) and the reaction mixture was stirred at room temperature for 1 h. The resulting mixture was partitioned between EtOAc (150 mL) and water (150 mL) and the layers separated. The aqueous layer was further extracted with EtOAc (100 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ solution (150 mL), brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a yellow oil which slowly crystallised to give a yellow solid.

1H NMR (500 MHz, DMSO-d6) δ 7.45 (d, J = 0.8 Hz, 1H), 7.38 (s, 1H), 4.70 (s, 2H), 2.43 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H).

Step 2:

2-{[(tert-butyldimethylsilyl)oxy]methyl}-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



[00363] A solution of (4-bromo-6-methyl-2-pyridyl)methoxy-*tert*-butyl-dimethyl-silane (step 1) (2.96 g, 9.35 mmol), bis(pinacolato)diboron (3.56 g, 14.02 mmol), potassium acetate (5.16 g, 37.39 mmol) and $Pd(dppf)Cl_2$ (889 mg, 1.22 mmol) in 1,4-dioxane (45 mL) was heated to 80 °C overnight. The resulting mixture was concentrated *in vacuo* and the residue was dissolved in hexane (adding a small volume of DCM to aid dissolution). The mixture was filtered through Celite® (filter material) and concentrated *in vacuo* to afford the title compound as a brown solid.

1H NMR (500 MHz, DMSO-d6) δ 7.46 (s, 1H), 7.31 (s, 1H), 4.71 (s, 2H), 2.44 (s, 3H), 1.30 (s, 12H), 0.91 (s, 9H), 0.09 (s, 6H).

Step 3: 3-[2-Amino-5-[2-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile

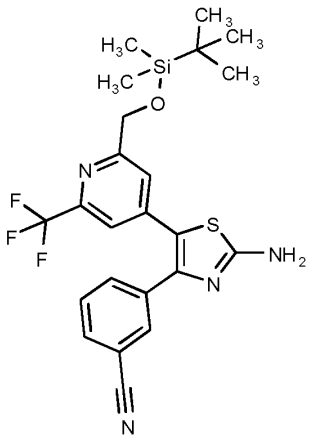
[00364] To a degassed mixture of 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B)(1.0 g, 3.57mmol), 2-{[(tert-butyldimethylsilyl)oxy]methyl}-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (step 2)(2.59 g, 7.14 mmol) and potassium carbonate (1.97 g, 14.28 mmol) in 1,4-dioxane (20 mL) and water (2 mL) was added bis(tri-*tert*-butylphosphine)palladium(0) (182 mg, 0.36 mmol). The reaction mixture was heated at 80 °C for 1 h and then allowed to cool to room temperature. The resulting mixture was diluted in EtOAc (100 mL) and water (100 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica eluting with a gradient of 10 to 40% EtOAc in petroleum ether afforded a solid which was triturated in diethyl ether (8 mL), collected by filtration, washed with diethyl ether (3 x 2 mL) and dried under vacuum overnight to afford the title compound as a yellow solid.

LC-MS (Method 3B): Rt 2.28 mins; MS m/z 435.4 = [M-H]-

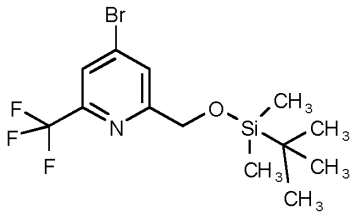
1H NMR (500 MHz, DMSO-d6) δ 7.82 – 7.75 (m, 2H), 7.68 (dt, J = 7.9, 1.5 Hz, 1H), 7.52 (td, J = 7.6, 7.0, 1.3 Hz, 1H), 7.48 (s, 2H), 6.94 (d, J = 2.8 Hz, 2H), 4.59 (s, 2H), 2.37 (s, 3H), 0.78 (s, 9H), -0.02 (s, 6H).

Intermediate IA

3-[2-Amino-5-[2-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6-(trifluoromethyl)-4-pyridyl]thiazol-4-yl]benzonitrile



Step 1: [4-Bromo-6-(trifluoromethyl)-2-pyridyl]methoxy-*tert*-butyl-dimethyl-silane

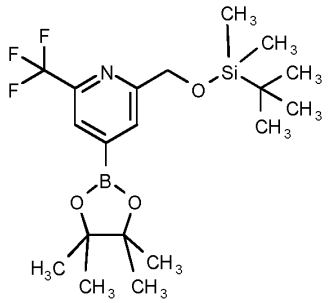


[00365] The title compound was prepared from [4-bromo-6-(trifluoromethyl)-2-pyridyl]methanol and *tert*-butyldimethylsilyl chloride analogously to Intermediate I step 1.

LC-MS (Method 3B): Rt 2.84 mins; MS m/z 370.0 / 372.0 = [M+H]+

1H NMR (500 MHz, Chloroform-d) δ 7.88 (s, 1H), 7.73 – 7.69 (m, 1H), 4.86 (s, 2H), 0.97 (s, 9H), 0.14 (s, 6H).

Step 2: *tert*-Butyl-dimethyl-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)-2-pyridyl]methoxy]silane



[00366] The title compound was prepared from [4-bromo-6-(trifluoromethyl)-2-pyridyl]methoxy-*tert*-butyl-dimethyl-silane (step 1) and bis(pinacolato)diboron analogously to Intermediate I step 2.

1H NMR (500 MHz, Chloroform-d) δ 8.04 (s, 1H), 7.88 (d, J = 0.9 Hz, 1H), 4.89 (s, 2H), 1.36 (s, 12H), 0.96 (s, 9H), 0.13 (s, 6H).

Step 3: 3-[2-Amino-5-[2-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6-(trifluoromethyl)-4-pyridyl]thiazol-4-yl]benzonitrile

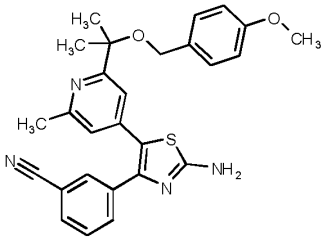
[00367] The title compound was prepared from *tert*-butyl-dimethyl-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)-2-pyridyl]methoxy]silane (step 2) and 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) analogously to Intermediate I step 3.

LC-MS (Method 3B): Rt 2.38 mins; MS m/z 491.2 = [M+H]+

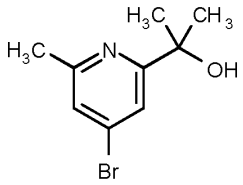
1H NMR (500 MHz, DMSO-d6) δ 7.86 (t, J = 1.8 Hz, 1H), 7.83 (dt, J = 7.7, 1.5 Hz, 1H), 7.75 – 7.68 (m, 3H), 7.54 (t, J = 7.8 Hz, 1H), 7.36 (d, J = 1.6 Hz, 1H), 7.29 (d, J = 1.6 Hz, 1H), 4.70 (s, 2H), 0.79 (s, 9H), 0.00 (s, 6H).

Intermediate J

3-[2-Amino-5-[2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile



Step 1: 2-(4-Bromo-6-methyl-2-pyridyl)propan-2-ol



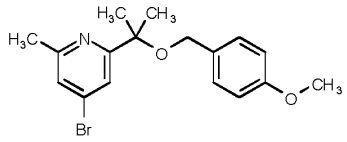
[00368] A solution of ethyl 4-bromo-6-methyl-pyridine-2-carboxylate (1.04 g, 4.25 mmol) in anhydrous THF (20 mL) was added dropwise over 10 mins to a stirred solution of methylmagnesium bromide (3.4M in 2-Me-THF) (2.75 mL, 9.36 mmol) at 0 ºC under nitrogen and stirred for 5 mins. The ice bath was removed and the mixture stirred at room temperature

for 20 mins. The resulting mixture was re-cooled to 5 ºC and the reaction was quenched by addition of 1M HCl (9 mL). The mixture was diluted with water (30 mL) and EtOAc (30 mL) and the pH of the aqueous layer was adjusted to pH 7 by addition of saturated. $NaHCO_3$ solution before the layers were shaken and separated. The aqueous layer was extracted with EtOAc (30 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a pale yellow oil.

LC-MS (Method 3B): Rt 1.59 mins; MS m/z 230.1 / 232.1 = [M+H]+

1H NMR (500 MHz, CDCl3) δ 7.33 (d, J = 1.0 Hz, 1H), 7.24 (d, J = 1.0 Hz, 1H), 5.08 (s, 1H), 2.54 (s, 3H), 1.51 (s, 6H).

Step 2: 4-Bromo-2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-pyridine

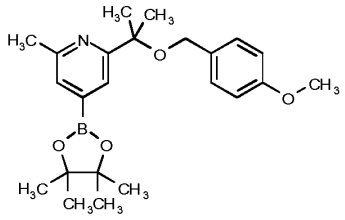


[00369] NaH (60% in oil) (229 mg, 5.74 mmol) was added to a solution of 2-(4-bromo-6-methyl-2-pyridyl)propan-2-ol (step 1)(660 mg, 2.87 mmol) in anhydrous DMF (15 mL) under nitrogen and the mixture stirred at room temperature for 5 mins. 4-Methoxybenzyl bromide (620 µL, 4.3 mmol) was added via syringe and the resulting mixture stirred at room temperature for 1 h. Additional NaH (60% in oil) (229 mg, 5.74 mmol) and 4-methoxybenzyl bromide (413 µL, 2.87 mmol) were added and the mixture stirred at room temperature overnight. The reaction was quenched by the dropwise addition of water (1 mL) before being diluted with EtOAc (75 mL). The mixture was washed with 90% brine (75 mL), 50% brine (3 x 75 mL), brine (75 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica eluting with 5% EtOAc in n-hexane afforded the title compound as a colourless oil.

LC-MS (Method 3B): Rt 2.46 mins; MS m/z 350.1 / 352.1 = [M+H]+

1H NMR (500 MHz, Chloroform-d) δ 7.62 (apr dd, J = 1.7, 0.7 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.20 (d, J = 1.7 Hz, 1H), 6.91 – 6.88 (m, 2H), 4.29 (s, 2H), 3.81 (s, 3H), 2.52 (s, 3H), 1.61 (s, 6H).

Step 3: 2-[1-[(4-Methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



The title compound was prepared from 4-bromo-2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-pyridine (step 2) and bis(pinacolato)diboron analogously to Intermediate I step 2.

LC-MS (Method 3B): Rt 1.19 mins; MS m/z 316.2 = [M+H]+ [NB - mass ion for the parent boronic acid].

1H NMR (500 MHz, DMSO-d6) δ 7.62 (s, 1H), 7.32 (s, 1H), 7.27 – 7.23 (m, 2H), 6.90 – 6.86 (m, 2H), 4.19 (s, 2H), 3.74 (s, 3H), 2.49 (s, 3H), 1.53 (s, 6H), 1.30 (s, 12H).

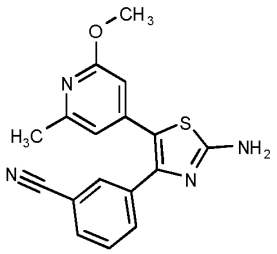
Step 4: 3-[2-Amino-5-[2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile

[00370] A solution of K_2CO_3 (297 mg, 2.15 mmol) in water (1.5 mL) was added to a solution of 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) (215 mg, 0.77 mmol) and 2-[1-[(4-methoxyphenyl)methoxy]-1-methyl-ethyl]-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (step 3) (396 mg, 1.0 mmol) in 1,4-dioxane (6 mL) and the mixture degassed via nitrogen sparging for 10 mins. $Pd(tBu_3P)_2$ (39 mg, 0.08 mmol) was added and the mixture was heated at 50 ºC for 1 h. The resulting mixture was allowed to cool to room temperature and diluted with EtOAc (30 mL). The mixture was washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by chromatography on silica eluting with 1% MeOH in DCM afforded a yellow gummy foam which was dissolved in Et_2O and concentrated to afford the title compound as a yellow solid.
LC-MS (Method 3B): Rt 2.21 mins; MS m/z 471.3 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.78 (t, J = 1.8 Hz, 1H), 7.68 (dd, J = 7.8, 1.8 Hz, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.47 (s, 2H), 7.06 (d, J = 1.7 Hz, 1H), 7.01 (d, J = 1.7 Hz, 1H), 6.99 – 6.94 (m, 2H), 6.85 – 6.81 (m, 2H), 4.09 (s, 2H), 3.75 (s, 3H), 2.44 (s, 3H), 1.43 (s, 6H).

Intermediate K

3-[2-Amino-5-(2-methoxy-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile



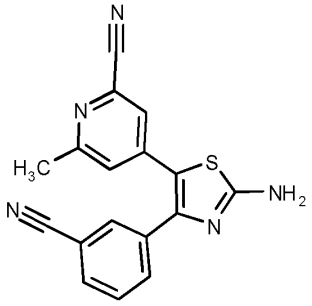
[00371] The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and 2-methoxy-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine analogously to Intermediate C.

LC-MS (Method 3B): Rt 1.81 mins; MS m/z 321.2 = [M-H]-

1H NMR (500 MHz, DMSO-d6) δ 7.82 (s, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.46 (s, 2H), 6.60 (s, 1H), 6.29 (s, 1H), 3.34 (s, 3H), 2.29 (s, 3H).

Intermediate KA

3-[2-Amino-5-(2-cyano-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile



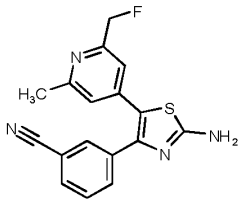
[00372] The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carbonitrile analogously to Intermediate C.

LC-MS (Method 3B): Rt 1.53 mins; MS m/z 318.0 = [M-H]+

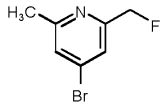
1H NMR (500 MHz, DMSO-d6) δ 7.86 (s, 1H), 7.85 (s, 1H), 7.69 (s, 2H), 7.67 (s, 1H), 7.57 (t,J= 7.8 Hz, 1H), 7.47 (s, 1H), 7.32 (s, 1H), 2.42 (s, 3H).

Intermediate KB

3-[2-Amino-5-[2-(fluoromethyl)-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile



Step 1: 4-Bromo-2-(fluoromethyl)-6-methyl-pyridine

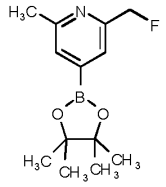


[00373] Diethylaminosulfur trifluoride (0.36 mL, 2.72 mmol) was added dropwise to a solution of (4-bromo-6-methyl-2-pyridyl)methanol (500 mg, 2.47 mmol) in DCM (5 mL) at -40 °C. The mixture was stirred at -40 °C for 30 mins and then allowed to warm to room temperature. The mixture was diluted with DCM (5 mL), water (5 mL) and sat. $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous layer was further extracted with DCM (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification by chromatography on silica eluting with a gradient of 1 to 20% EtOAc in petroleum ether afforded the title compound as a white solid.

LC-MS (Method 3B): Rt 1.66 mins; MS m/z 204.0 / 205.9 = [M+H]+

1H NMR (500 MHz, Chloroform-d) δ 7.50 – 7.42 (m, 1H), 7.31 – 7.29 (m, 1H), 5.42 (d, J = 46.6 Hz, 2H), 2.52 (s, 3H).

Step 2: 2-(Fluoromethyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



[00374] A mixture of 4-bromo-2-(fluoromethyl)-6-methyl-pyridine (step 1)(370 mg, 1.81 mmol), bis(pinacolato)diboron (553 mg, 2.18 mmol) and AcOK (534 mg, 5.44 mmol) in 1,4-dioxane (10 mL) was degassed under nitrogen for 10 mins. $Pd(dppf)C_{l2}$ (133 mg, 0.18 mmol) was added and the flask was purged and back filled with nitrogen (x 3). The reaction mixture was heated to 95 °C for 16 h and then allowed to cool to room temperature. The resulting mixture was diluted with EtOAc (50 mL) and filtered through Celite® (filter material), eluting with EtOAc. The filtrate was concentrated *in vacuo* to afford the title compound as a brown oil.

1H NMR (500 MHz, DMSO-d6) δ 7.93 (s, 1H), 7.45 (d, J = 11.9 Hz, 1H), 5.44 (d, J = 47.1 Hz, 2H), 3.57 (s, 3H), 1.31 (s, 12H).

Step 3: 3-[2-Amino-5-[2-(fluoromethyl)-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile

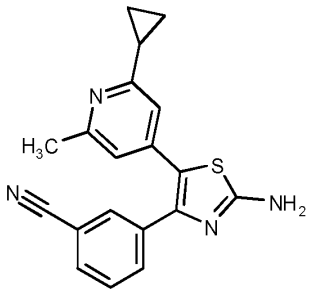
The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and 2-(fluoromethyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (step 2) analogously to Intermediate C.

[00375] LC-MS (Method 3B): Rt 1.56 mins; MS m/z 325.1 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.84 – 7.79 (m, 2H), 7.68 (dt, J = 8.0, 1.4 Hz, 1H), 7.56 – 7.51 (m, 3H), 6.98 (d, J = 15.9 Hz, 2H), 5.32 (d, J = 46.9 Hz, 2H), 2.38 (s, 3H).

Intermediate KC

3-[2-Amino-5-(2-cyclopropyl-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile



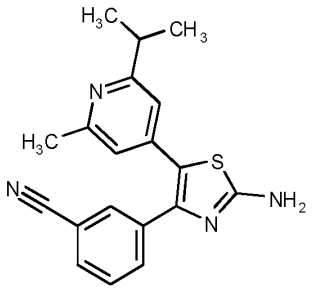
[00376] The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and 2-cyclopropyl-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine analogously to Intermediate C.

LC-MS (Method 3B): Rt 1.33 mins; MS m/z 333.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.81 (t, J = 1.5 Hz, 1H), 7.79 (dt, J = 7.7, 1.5 Hz, 1H), 7.67 (dt, J = 8.0, 1.5 Hz, 1H), 7.54 (apr t, J = 7.8 Hz, 1H), 7.44 (s, 2H), 6.76 (d, J = 1.6 Hz, 1H), 6.75 (d, J = 1.6 Hz, 1H), 2.28 (s, 3H), 1.92 (tt, J = 8.1, 4.8 Hz, 1H), 0.87 – 0.83 (m, 2H), 0.79 – 0.74 (m, 2H).

Intermediate KD

3-[2-Amino-5-(2-isopropyl-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile

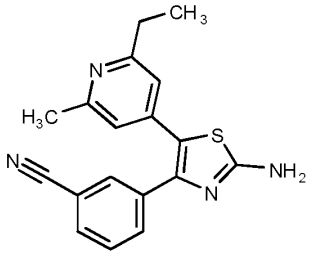


[00377] The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and 2-isopropyl-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine analogously to Intermediate C.
LC-MS (Method 5B): Rt 2.86 mins; MS m/z 335.1 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.80 (dd, J = 7.8, 1.5 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.71 (dt, J = 7.9, 1.5 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.45 (s, 2H), 6.89 (d, J = 1.6 Hz, 1H), 6.68 (d, J = 1.5 Hz, 1H), 3.92 (s, 3H), 2.79 (h, J = 6.8 Hz, 1H), 1.05 (s, 6H).

Intermediate KE

3-[2-Amino-5-(2-ethyl-6-methyl-4-pyridyl)thiazol-4-yl]benzonitrile

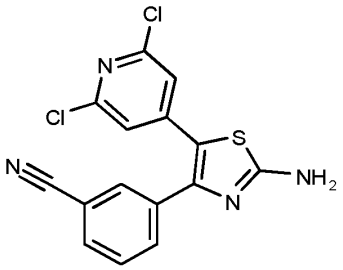


[00378] The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and 2-ethyl-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine analogously to Intermediate C.
LC-MS (Method 5B): Rt 2.64 mins; MS m/z 321.1 = [M+H]+

1H NMR (500 MHz, CDCl3) δ 7.86 (t, J = 1.5 Hz, 1H), 7.66 (dt, J = 7.9, 1.5 Hz, 1H), 7.59 (dt, J = 7.7, 1.5 Hz, 1H), 7.38 (apr t, J = 7.8 Hz, 1H), 6.82 (s, 1H), 6.76 (s, 1H), 5.10 – 4.98 (m, 2H), 2.70 (q, J = 7.6 Hz, 2H), 2.47 (s, 3H), 1.18 (t, J = 7.6 Hz, 3H).

Intermediate KF

3-[2-Amino-5-(2,6-dichloro-4-pyridyl)thiazol-4-yl]benzonitrile



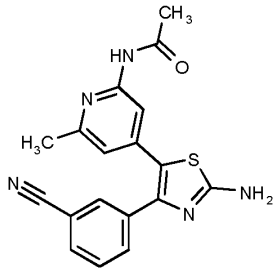
[00379] The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine analogously to Intermediate C.

LC-MS (Method 5B): Rt 3.10 mins; MS m/z 346.9 = [M+H]+

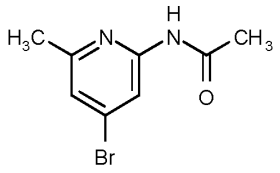
1H NMR (500 MHz, DMSO-d6) δ 7.91 (s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.77 (s, 2H), 7.74 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.15 (s, 2H).

Intermediate KG

N-[4-[2-Amino-4-(3-cyanophenyl)thiazol-5-yl]-6-methyl-2-pyridyl]acetamide



Step 1: N-(4-Bromo-6-methyl-2-pyridyl)acetamide

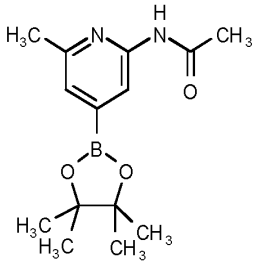


[00380] Triethylamine (0.45 mL, 3.23 mmol) and acetic anhydride (0.75 mL, 7.94 mmol) were added to a stirred solution of 4-bromo-6-methyl-pyridin-2-amine (550 mg, 2.94 mmol) in THF (20 mL) and heated to 50 °C for 22 h followed by heating at reflux for 2 h. The resulting mixture was allowed to cool to room temperature and was partitioned between EtOAc (100 mL) and sat. $NaHCO_3$ solution (100 mL). The layers were separated and the aqueous layer further extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give an off-white solid. The solid was dry loaded onto

silica and purification by chromatography on silica eluting with a gradient of 0 to 8% MeOH afforded the title compound as a white solid.
LC-MS (Method 5A): Rt 2.28 mins; MS m/z 228.9 / 230.9 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 10.66 (s, 1H), 8.13 (d, J = 1.6 Hz, 1H), 7.25 (d, J = 1.6 Hz, 1H), 2.39 (s, 3H), 2.07 (s, 3H).

Step 2: N-[6-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]acetamide



[00381] The title compound was prepared from N-(4-bromo-6-methyl-2-pyridyl)acetamide (step 1) and bis(pinacolato)diboron analogously to Intermediate KB step 2.
1H NMR (500 MHz, Chloroform-d) δ 9.12 (s, 1H), 8.39 (s, 1H), 7.27 (s, 1H), 2.49 (s, 3H), 2.21 (s, 3H), 1.32 (s, 12H).

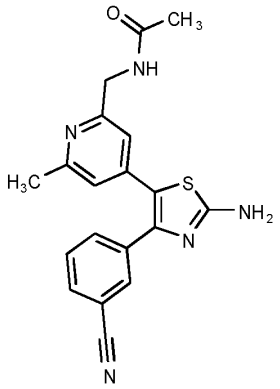
Step 3: N-[4-[2-Amino-4-(3-cyanophenyl)thiazol-5-yl]-6-methyl-2-pyridyl]acetamide

[00382] The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and N-[6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]acetamide (step 2) analogously to Intermediate C.
LC-MS (Method 5B): Rt 2.29 mins; MS m/z 350.1 = [M+H]+

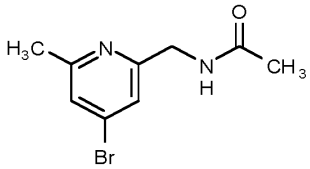
1H NMR (500 MHz, DMSO-d6) δ 10.41 (s, 1H), 7.81 (d, J = 1.7 Hz, 1H), 7.80 – 7.74 (m, 2H), 7.69 (ddd, J = 7.8, 1.7, 1.5 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.45 (s, 2H), 6.69 (d, J = 1.5 Hz, 1H), 2.29 (s, 3H), 2.01 (s, 3H).

Intermediate KH

N-[[4-[2-Amino-4-(3-cyanophenyl)thiazol-5-yl]-6-methyl-2-pyridyl]methyl]acetamide



Step 1: N-[(4-Bromo-6-methyl-2-pyridyl)methyl]acetamide

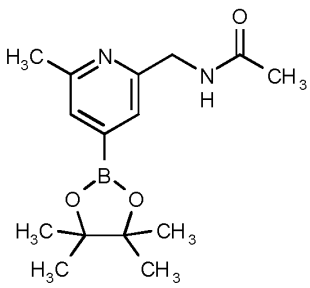


[00383] Triethylamine (0.52 mL, 4.08 mmol) and acetic anhydride (0.46 mL, 4.89 mmol) were added to a stirred solution of (4-bromo-6-methyl-2-pyridyl)methanamine (410 mg, 2.04 mmol) in DCM (15 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred overnight. The resulting mixture was concentrated *in vacuo* to give an orange residue, which was diluted with water (10 mL). The solution was partitioned between sat. $NaHCO_3$ solution (20 mL) and EtOAc (20 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica eluting with a gradient of 0 to 60% EtOAc in DCM afforded the title compound as a white solid.

LC-MS (Method 3B): Rt 1.28 mins; MS m/z 245.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 8.44 (t, J = 6.1 Hz, 1H), 7.44 (d, J = 1.7 Hz, 1H), 7.28 (d, J = 1.7 Hz, 1H), 4.28 (d, J = 6.0 Hz, 2H), 2.44 (s, 3H), 1.91 (s, 3H).

Step 2: N-[[6-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]methyl]acetamide



[00384] The title compound was prepared from N-[(4-bromo-6-methyl-2-pyridyl)methyl]acetamide (step 1) and bis(pinacolato)diboron analogously to Intermediate KB step 2.

1H NMR (500 MHz, DMSO-d6) δ 8.44 (t, J = 6.0 Hz, 1H), 7.32 (s, 1H), 7.27 (s, 1H), 4.30 (d, J = 6.0 Hz, 2H), 2.46 (s, 3H), 1.89 (s, 3H), 1.30 (s, 12H).

Step 3: N-[[4-[2-Amino-4-(3-cyanophenyl)thiazol-5-yl]-6-methyl-2-pyridyl]methyl]acetamide

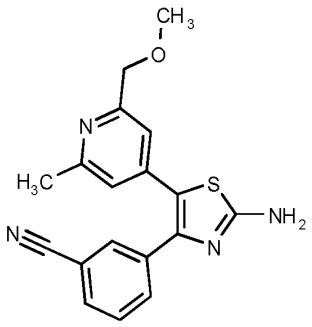
[00385] The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and N-[[6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]methyl]acetamide (step 2) analogously to Intermediate C.

LC-MS (Method 2B): Rt 1.07 mins; MS m/z 364.0 = [M+H]+

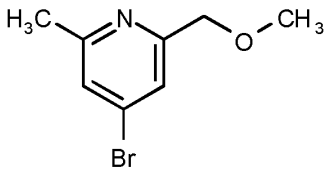
1H NMR (500 MHz, DMSO-d6) δ 8.26 (t, J = 6.0 Hz, 1H), 7.84 – 7.77 (m, 2H), 7.65 (dt, J = 8.0, 1.5 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.48 (s, 2H), 6.90 (d, J = 1.5 Hz, 1H), 6.75 (d, J = 1.6 Hz, 1H), 4.17 (d, J = 6.0 Hz, 2H), 2.37 (s, 3H), 1.75 (s, 3H).

Intermediate KI

3-[2-Amino-5-[2-(methoxymethyl)-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile



Step 1: 4-Bromo-2-(methoxymethyl)-6-methyl-pyridine

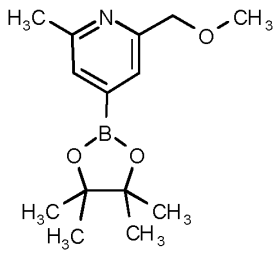


[00386] MeI (0.18 mL, 2.97 mmol) was added dropwise to a stirred solution of (4-bromo-6-methyl-2-pyridyl)methanol (300 mg, 1.48 mmol) and KOH (167 mg, 2.97 mmol) and the mixture was stirred at room temperature for 16 h. Further MeI (0.18 mL, 2.97 mmol) was added dropwise and the mixture was stirred at room temperature for 3 h. The resulting mixture was diluted in EtOAc (20 mL), washed with brine (3 x 20 mL), dried over Na_2SO_4 and concentrated

in vacuo to afford the title compound as a brown oil.
LC-MS (Method 3B): Rt 1.62 mins; MS m/z 218.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.48 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 1.7 Hz, 1H), 4.45 (s, 2H), 3.36 (s, 3H), 2.45 (s, 3H).

Step 2: 2-(Methoxymethyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



[00387] The title compound was prepared from 4-bromo-2-(methoxymethyl)-6-methyl-pyridine (step 1) and bis(pinacolato)diboron analogously to Intermediate KB step 2.
1H NMR (500 MHz, DMSO-d6) δ 7.41 (s, 1H), 7.34 (s, 1H), 4.45 (d, J = 4.3 Hz, 2H), 3.36 (s, 3H), 2.45 (d, J = 6.7 Hz, 3H), 1.31 (s, 12H).

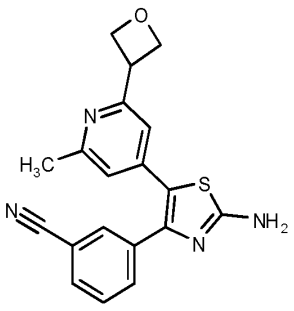
Step 3: 3-[2-Amino-5-[2-(methoxymethyl)-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile

[00388] The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and 2-(methoxymethyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (step 2) analogously to Intermediate C.
LC-MS (Method 3B): Rt 1.50 mins; MS m/z 337.5 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.83 – 7.78 (m, 2H), 7.70 (dt, J = 7.9, 1.5 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.49 (s, 2H), 6.94 (d, J = 1.7 Hz, 1H), 6.88 (d, J = 1.7 Hz, 1H), 4.35 (s, 2H), 3.21 (s, 3H), 2.37 (s, 3H).

Intermediate L

3-[2-Amino-5-[2-methyl-6-(oxetan-3-yl)-4-pyridyl]thiazol-4-yl]benzonitrile



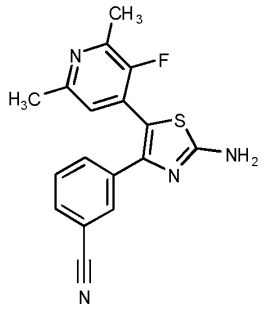
[00389] The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) and 2-methyl-6-(oxetan-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine analogously to Intermediate C.

LC-MS (Method 2B): Rt 1.22 mins; MS m/z 349.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.83 – 7.81 (m, 1H), 7.80 (dt, J = 7.6, 1.4 Hz, 1H), 7.68 (dt, J = 8.0, 1.4 Hz, 1H), 7.54 (apr t, J = 7.8 Hz, 1H), 7.48 (s, 2H), 6.92 (d, J = 1.6 Hz, 1H), 6.84 (d, J = 1.6 Hz, 1H), 4.78 (dd, J = 8.5, 5.6 Hz, 2H), 4.62 (dd, J = 6.8, 5.6 Hz, 2H), 4.22 (tt, J = 8.5, 6.8 Hz, 1H), 2.40 (s, 3H).

Intermediate M

3-[2-Amino-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-4-yl]benzonitrile



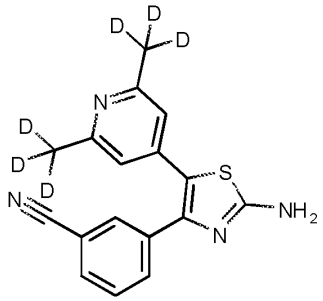
[00390] A mixture of 4-bromo-3-fluoro-2,6-dimethyl-pyridine (100 mg, 0.36 mmol), bis(pinacolato)diboron (181 mg, 0.71 mmol) and AcOK (193 mg, 1.96 mmol) in 1,4-dioxane (6 mL) was degassed under a flow of nitrogen. $Pd(dppf)Cl_2$ (47 mg, 0.06 mmol) was added and the reaction was heated to 100 °C overnight. The resulting mixture was cooled to room temperature, filtered and washed through with DCM (2 x 5 mL). The filtrate was concentrated *in vacuo* and the boronate was taken into 1,4-dioxane (2.5 mL) and water (0.5 mL). 3-(2-Amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) (100 mg, 0.36 mmol) and K_2CO_3 (197 mg, 1.43mmol) were added and the mixture was degassed under flow of nitrogen. Bis(tri-*tert*-butylphosphine)palladium(0) (18 mg, 0.04 mmol) was added and the reaction mixture was heated to 80 °C for 45 mins. After cooling to room temperature, the resulting mixture was concentrated *in vacuo* and purification by chromatography on silica eluting with a gradient of 0 to 3% MeOH in DCM afforded the title compound as a brown solid.

LC-MS (Method 3B): Rt 1.55 mins; MS m/z 325.0 = [M+H]+

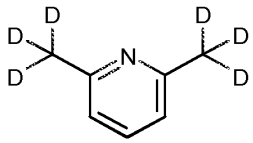
1H NMR (500 MHz, DMSO-d6) δ 7.80 (s, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.56 – 7.47 (m, 3H), 6.99 (d, J = 5.0 Hz, 1H), 2.39 – 2.30 (m, 6H).

Intermediate N (

3-[2-Amino-5-[2,6-bis(trideuteriomethyl)-4-pyridyl]thiazol-4-yl]benzonitrile



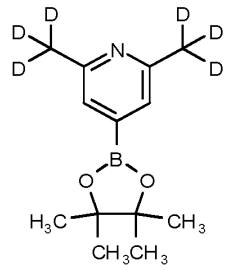
Step 1: 2,6-Bis(trideuteriomethyl)pyridine



[00391] 2,6-Dichloropyridine (5.0 g, 33.79 mmol) and $NiCl_2$(dppp) (916 mg, 1.69 mmol) were placed under nitrogen and anhydrous THF (68 mL) was added via syringe. The mixture was cooled to 0 ºC and treated dropwise with a solution of methyl-d3-magnesium iodide (1M in Et_2O) (100 mL, 100 mmol) over 20 mins. The reaction mixture was heated at reflux for 1.5 h and allowed to cool to room temperature. The reaction was quenched by cautious addition of MeOH (15 mL) followed by 1M aqueous HCl (125 mL). The resulting bi-phasic mixture was stirred vigorously for 5 mins until all of the solids had dissolved and effervescence had fully ceased. The mixture was diluted with Et_2O (125 mL) and the layers separated. The organic layer was extracted with water (125 mL) and the combined aqueous layers adjusted to pH 10 with 10% aqueous NaOH before the mixture was extracted with EtOAc (2 x 300 mL) and the combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, and cautiously concentrated at 35-38 ºC and 170-190 mbar then briefly at 40 ºC and 100 mbar to afford the crude material as a pale orange-brown oil. The oil was purified by vacuum distillation (120-140 ºC under low vacuum) to afford the title compound as a clear, colourless oil.
LC-MS (Method 2B): Rt 1.05 mins; MS m/z 114.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.54 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 7.6 Hz, 2H)

Step 2: 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,6-bis(trideuteriomethyl)pyridine



[00392] Methoxy(cyclooctadiene)iridium(I) dimer (789 mg, 1.19 mmol), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (639 mg, 2.38 mmol) and bis(pinacolato)diboron (10.07 g, 39.67 mmol) were placed in a sealed flask and the contents evacuated and backfilled with nitrogen (3 x cycles). Freshly de-oxygenated anhydrous cyclohexane (50 mL) was added via syringe and the resulting mixture briefly sonicated, causing the bulk of the solids to dissolve and a deep red-brown solution to form. The mixture was stirred vigorously for 1 h at room temperature and treated with a solution of 2,6-bis(trideuteriomethyl)pyridine (step 1) (4.49 g, 39.67 mmol) in de-oxygenated anhydrous cyclohexane (50 mL) added via syringe under nitrogen. The resulting mixture was stirred at room temperature for 19.5 h and then additional bis(pinacolato)diboron (2.01 g, 7.93 mmol) in de-oxygenated anhydrous cyclohexane (10mL) was added via syringe under nitrogen. The mixture was stirred at room temperature for 2 h before additional methoxy(cyclooctadiene)iridium(I) dimer (263 mg, 0.40 mmol) and 4,4′-di-*tert*-butyl-2,2′-dipyridyl (213 mg, 0.79 mmol) were added. Stirring was continued under nitrogen at room temperature for a further 17.5 h after which time the mixture was concentrated *in vacuo* to afford the title compound as a dark brown solid.

LC-MS (Method 2B): Rt 0.92 mins; MS m/z 240.1 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.22 (s, 2H), 1.29 (s, 12H).

Step 3: 3-[2-Amino-5-[2,6-bis(trideuteriomethyl)-4-pyridyl]thiazol-4-yl]benzonitrile

[00393] A solution of K_2CO_3 (10.74 g, 77.68 mmol) in water (60 mL) was added to a solution of 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) (8.7 g, 31.07 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,6-bis(trideuteriomethyl)pyridine (step 2) (8.92 g, 37.29 mmol) in 1,4-dioxane (240 mL) and the reaction mixture was de-oxygenated via nitrogen sparging for 10 mins. $Pd(tBu_3P)_2$ (1.59 g, 3.11 mmol) was added, the flask sealed and the contents evacuated and backfilled with nitrogen (3 x cycles). The reaction mixture was stirred at 50 ºC for 1 h and then allowed to cool to room temperature. The resulting mixture was diluted with EtOAc (500 mL) and washed with water (250 mL), brine (250 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was re-dissolved in ~ 9 : 1 chloroform / MeOH (250 mL) and passed through a short pre-wetted Celite® (filter material) plug, eluting

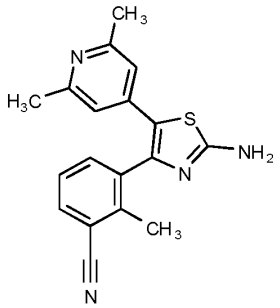
with chloroform. The filtrate was concentrated *in vacuo* to afford a dark brown residue which was triturated in a 5:2 mixture of Et_2O / DCM (70 mL) under sonication. The resulting solids were filtered, washed with DCM (5 x 10 mL) and vacuum dried to afford the title compound as a cream solid.

LC-MS (Method 2B): Rt 1.29 mins; MS m/z 313.1 = [M+H]+

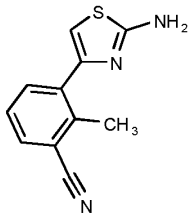
1H NMR (500 MHz, DMSO-d6) δ 7.81 (br t, J = 1.5 Hz, 1H), 7.79 (br dt, J = 7.6, 1.5 Hz, 1H), 7.66 (br dt, J = 7.9, 1.5 Hz, 1H), 7.52 (apr t, J = 7.8 Hz, 1H), 7.48 – 7.39 (m, 2H), 6.80 (s, 2H).

Intermediate O

3-[2-Amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]-2-methyl-benzonitrile



Step 1: 3-(2-Aminothiazol-4-yl)-2-methyl-benzonitrile

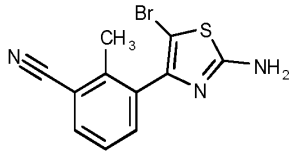


[00394] Bis(tri-*tert*-butylphosphine)palladium(0) (29 mg, 0.06 mmol) was added to a degassed solution of 4-bromothiazol-2-amine (100 mg, 0.56 mmol), (3-cyano-2-methyl-phenyl)boronic acid (180 mg, 1.12 mmol) and potassium carbonate (154 mg, 1.12 mmol) in 1,4-dioxane (4 mL) and water (0.8 mL). The flask was evacuated and backfilled with nitrogen (x 3) and the reaction mixture was stirred at 80 °C overnight. The resulting mixture was allowed to cool to room temperature and was partitioned between EtOAc and 70% brine. The organic layer was separated, washed with 70% brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica eluting with a gradient of 2 to 5% MeOH in DCM afforded a brown solid which was triturated with Et_2O (5 mL) to afford the title compound as a brown solid.

LC-MS (Method 8B): Rt 3.48 mins; MS m/z 216.1 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.81 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 7.11 (s, 2H), 6.76 (s, 1H), 2.60 (s, 3H).

Step 2: 3-(2-Amino-5-bromo-thiazol-4-yl)-2-methyl-benzonitrile



[00395] NBS (52 mg, 0.29 mmol) was added to a stirred solution of 3-(2-aminothiazol-4-yl)-2-methyl-benzonitrile (step 1) (53 mg, 0.24 mmol) in THF (1 mL) and stirred at room temperature for 5 h. The resulting solution was diluted with EtOAc (10 mL) and washed with water (10 mL), sat. $NaHCO_3$ solution (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a brown solid.
LC-MS (Method 8B): Rt 4.00 mins; MS m/z 294.0 / 296.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.90 (dd, J = 7.7, 1.3 Hz, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.44 (s, 2H), 2.45 (s, 3H).

Step 3: 3-[2-Amino-5-(2,6-dimethyl-4-pyridyl)thiazol-4-yl]-2-methyl-benzonitrile

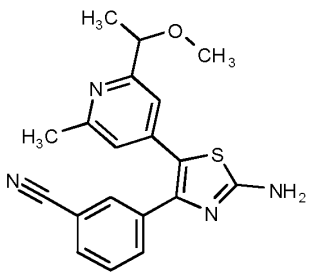
The title compound was prepared from 3-(2-amino-5-bromo-thiazol-4-yl)-2-methyl-benzonitrile (step 2) and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine analogously to Intermediate C.

LC-MS (Method 8B): Rt 3.71 mins; MS m/z 321.1 = [M+H]+

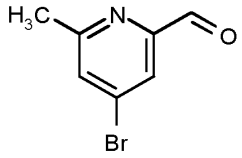
1H NMR (500 MHz, DMSO-d6) δ 7.92 (d, J = 7.5 Hz, 1H), 7.58 (s, 2H), 7.57 – 7.50 (m, 1H), 7.48 (t, J = 7.7 Hz, 1H), 6.55 (s, 2H), 2.34 (s, 3H), 2.29 (s, 6H).

Intermediate P

3-[2-Amino-5-[2-(1-methoxyethyl)-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile



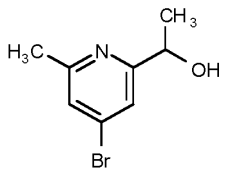
Step 1: 4-Bromo-6-methyl-pyridine-2-carbaldehyde



[00396] Manganese dioxide (1.72 g, 19.8 mmol) was added to a solution of (4-bromo-6-methyl-2-pyridyl)methanol (1.0 g, 4.95 mmol) in chloroform (25 mL) and the mixture stirred at reflux for 16 h. Additional manganese dioxide (215 mg, 2.47 mmol) was added and stirring continued at reflux for 5 h. The resulting mixture was cooled to room temperature and filtered through a plug of Celite® (filter material) eluting with DCM. The filtrate was concentrated *in vacuo* to afford the title compound as a white solid.
LC-MS (Method 3B): Rt 1.45 mins; MS m/z 199.9 / 201.9 = [M+H]+

1H NMR (500 MHz, Chloroform-d) δ 9.99 (s, 1H), 7.93 – 7.91 (m, 1H), 7.56 (dd, J = 1.7, 0.6 Hz, 1H), 2.66 – 2.62 (m, 3H).

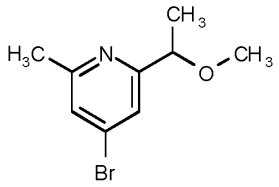
Step 2: 1-(4-Bromo-6-methyl-2-pyridyl)ethanol



[00397] A solution of 4-bromo-6-methyl-pyridine-2-carbaldehyde (step 1) (750 mg, 3.75 mmol) in anhydrous THF (18 mL) was added dropwise over 5 mins to a stirred solution of methylmagnesium bromide (3.4M in 2-Me-THF) (2.21 mL, 7.5 mmol) at 0 ºC under nitrogen and the mixture stirred for 5 mins. The ice bath was removed and the mixture stirred at room temperature for 1 h. The resulting mixture was re-cooled to ~ 5 ºC and the reaction was quenched by addition of 1M HCl (7.5 mL). The mixture was diluted with water (25 mL) and EtOAc (25 mL) and the pH of the aqueous layer was adjusted to pH 8 by addition of sat. $NaHCO_3$ solution before the layers were shaken and separated. The organic layer was washed with additional sat. $NaHCO_3$ solution (20 mL) and brine (20 mL) before being dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a clear yellow oil.
LC-MS (Method 3B): Rt 1.40 mins; MS m/z 216.2 / 218.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.48 (d, J = 1.8 Hz, 1H), 7.41 (d, J = 1.8 Hz, 1H), 5.50 – 5.42 (m, 1H), 4.65 (qd, J = 6.6, 4.8 Hz, 1H), 2.43 (s, 3H), 1.33 (d, J = 6.6 Hz, 3H).

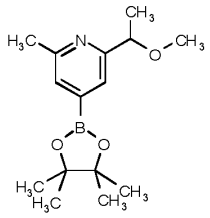
Step 3: 4-Bromo-2-(1-methoxyethyl)-6-methyl-pyridine



[00398] NaH (60% in mineral oil) (74 mg, 1.85 mmol) was added to a stirred solution of 1-(4-bromo-6-methyl-2-pyridyl)ethanol (200 mg, 0.93 mmol) in anhydrous DMF (4 mL) under nitrogen and the resulting solution stirred at room temperature for 10 mins before iodomethane (173 uL, 2.78 mmol) was added. The resulting mixture was stirred at room temperature for 1 h before being carefully quenched by addition of water (1 mL), diluted with EtOAc (20 mL) and washed with 90% brine (25 mL) and 50% brine (3 x 25 mL). The organic layer was dried over Na_2SO4, filtered and concentrated *in vacuo*. Purification by column chromatography on silica eluting with 2% MeOH in DCM afforded the title compound as a yellow oil.LC-MS (Method 3B): Rt 1.75 mins; MS m/z 230.0 / 232.0 = [M+H]+

1H NMR (500 MHz, Chloroform-d) δ 7.41 (s, 1H), 7.23 (d, J = 1.8 Hz, 1H), 4.36 (q, J = 6.6 Hz, 1H), 3.32 (s, 3H), 2.52 (s, 3H), 1.43 (d, J = 6.6 Hz, 3H).

Step 4: 2-(1-Methoxyethyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



[00399] The title compound was prepared from 4-bromo-2-(1-methoxyethyl)-6-methyl-pyridine (step 3) and bis(pinacolato)diboron analogously to Intermediate J step 3.

LC-MS (Method 3B): Rt 0.93 mins; MS m/z 278.1 = [M+H]+ .

Step 5: 3-[2-Amino-5-[2-(1-methoxyethyl)-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile

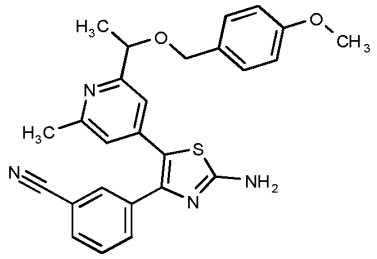
[00400] The title compound was prepared from 2-(1-methoxyethyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (step 4) and 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) analogously to Intermediate J step 4.

LC-MS (Method 3B): Rt 1.57 mins; MS m/z 349.2 = [M-H]-

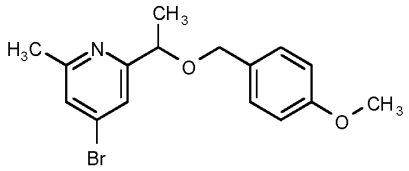
1H NMR (500 MHz, DMSO-d6) δ 7.80 (dt, J = 7.8, 1.5 Hz, 1H), 7.78 (t, J = 1.5Hz, 1H), 7.73 (dt, J = 7.8, 1.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.49 (s, 2H), 7.00 (d, J = 1.6 Hz, 1H), 6.78 (d, J = 1.6 Hz, 1H), 4.18 (q, J = 6.6 Hz, 1H), 3.02 (s, 3H), 2.41 (s, 3H), 1.19 (d, J = 6.6 Hz, 3H).

Intermediate PA

3-[2-Amino-5-[2-[1-[(4-methoxyphenyl)methoxy]ethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile



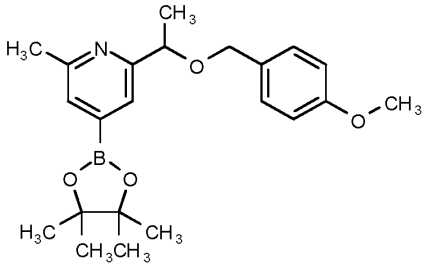
Step 1: 4-Bromo-2-[1-[(4-methoxyphenyl)methoxy]ethyl]-6-methyl-pyridine



[00401] The title compound was prepared from 1-(4-bromo-6-methyl-2-pyridyl)ethanol (Intermediate P step 2) and 4-methoxybenzyl bromide analogously to Intermediate J step 2. LC-MS (Method 3B): Rt 2.23 mins; MS m/z 336.0 / 338.0 = [M+H]+

1H NMR (500 MHz, CDCl3) δ 7.49 (s, 1H), 7.27 – 7.23 (m, 3H), 6.90 – 6.86 (m, 2H), 4.61 – 4.55 (m, 1H), 4.44 (d, J = 11.3 Hz, 1H), 4.38 (d, J = 11.3 Hz, 1H), 3.81 (s, 3H), 2.53 (s, 3H), 1.46 (d, J = 6.6 Hz, 3H).

Step 2: 2-[1-[(4-Methoxyphenyl)methoxy]ethyl]-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



[00402] The title compound was prepared from 4-bromo-2-[1-[(4-methoxyphenyl)methoxy]ethyl]-6-methyl-pyridine (step 1) and bis(pinacolato)diboron analogously to Intermediate J step 3.

LC-MS (Method 3B): Rt 1.00 mins; MS m/z 302.1 = [M+H]+ [NB - mass ion for the parent boronic acid].

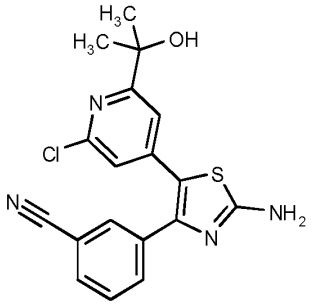
Step 3: 3-[2-Amino-5-[2-[1-[(4-methoxyphenyl)methoxy]ethyl]-6-methyl-4-pyridyl]thiazol-4-yl]benzonitrile

[00403] The title compound was prepared from 2-[1-[(4-methoxyphenyl)methoxy]ethyl]-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (step 2) and 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) analogously to Intermediate J step 4.
LC-MS (Method 3B): Rt 1.91 mins; MS m/z 455.3 = [M-H]-

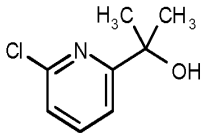
1H NMR (500 MHz, DMSO-d6) δ 7.80 (t, J = 1.7 Hz, 1H), 7.72 – 7.70 (m, 1H), 7.72 – 7.67 (m, 1H), 7.53 – 7.47 (m, 3H), 7.05 – 7.02 (m, 2H), 7.01 (d, J = 1.6 Hz, 1H), 6.89 (d, J = 1.6 Hz, 1H), 6.88 – 6.85 (m, 2H), 4.39 (q, J = 6.5 Hz, 1H), 4.19 (d, J = 11.6 Hz, 1H), 4.15 (d, J = 11.6 Hz, 1H), 3.75 (s, 3H), 2.42 (s, 3H), 1.25 (d, J = 6.5 Hz, 3H).

Intermediate Q

3-[2-Amino-5-[2-chloro-6-(1-hydroxy-1-methyl-ethyl)-4-pyridyl]thiazol-4-yl]benzonitrile



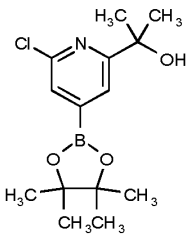
Step 1: 2-(6-Chloro-2-pyridyl)propan-2-ol



[00404] The title compound was prepared from methyl 6-chloropyridine-2-carboxylate and methylmagnesium bromide analogously to Intermediate J step 1.
LC-MS (Method 3B): Rt 1.42 mins; MS m/z 172.0 / 174.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 7.83 (t, J = 7.8 Hz, 1H), 7.64 (dd, J = 7.8, 0.8 Hz, 1H), 7.33 (dd, J = 7.8, 0.8 Hz, 1H), 5.32 (s, 1H), 1.41 (s, 6H).

Step 2: 2-[6-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]propan-2-ol



[00405] The title compound was prepared from 2-(6-chloro-2-pyridyl)propan-2-ol (step 1) and bis(pinacolato)diboron analogously to Intermediate N step 2.
LC-MS (Method 3B): Rt 1.03 mins; MS m/z 298.2 / 300.2= [M+H]+

Step 3: 3-[2-Amino-5-[2-chloro-6-(1-hydroxy-1-methyl-ethyl)-4-pyridyl]thiazol-4-yl]benzonitrile

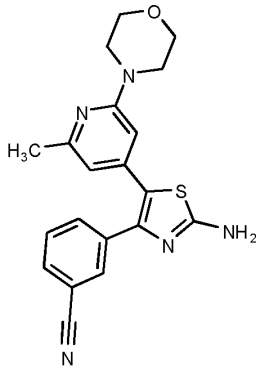
The title compound was prepared from 2-[6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]propan-2-ol (step 2) and 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) analogously to Intermediate J step 4.

LC-MS (Method 3B): Rt 1.67 mins; MS m/z 371.1 / 373.1 = [M+H]+

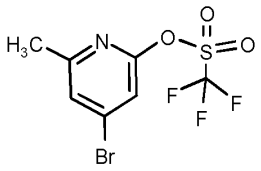
1H NMR (500 MHz, DMSO-d6) δ 7.85 – 7.81 (m, 2H), 7.73 (dt, J = 8.0, 1.5 Hz, 1H), 7.64 – 7.61 (m, 2H), 7.60 – 7.56 (m, 1H), 7.32 (d, J = 1.4 Hz, 1H), 6.99 (d, J = 1.4 Hz, 1H), 5.19 (s, 1H), 1.33 (s, 6H).

Intermediate R

3-[2-Amino-5-(2-methyl-6-morpholino-4-pyridyl)thiazol-4-yl]benzonitrile



Step 1: (4-Bromo-6-methyl-2-pyridyl) trifluoromethanesulfonate N121-87-1 hbarlow

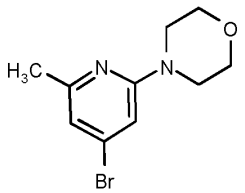


[00406] To a cooled (0 °C) suspension of 4-bromo-6-methyl-pyridin-2-ol (500 mg, 2.66 mmol) in DCM (13.5 mL) was added triethylamine (0.44 mL, 3.19 mmol) followed by dropwise addition of trifluoromethylsulfonyl trifluoromethanesulfonate (0.54 mL, 3.19 mmol) and the mixture was stirred at 0 °C for 10 mins. Additional trifluoromethylsulfonyl trifluoromethanesulfonate (0.26 mL, 1.6 mmol) and triethylamine (0.11 mL, 0.80 mmol) were added and the mixture was stirred for 10 mins at 0 °C. The resulting mixture was added to sat.$NaHCO_3$ solution (50 mL) and extracted with DCM (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica eluting with a gradient of 0 to 15% EtOAc in petroleum ether afforded the title compound as a colourless oil.

LC-MS (Method 3B): Rt 2.08 mins; MS m/z 317.9 / 319.9 = [M-H]-

1H NMR (500 MHz, DMSO-d6) δ 7.84 (s, 1H), 7.83 (s, 1H), 2.48 (s, 3H).

Step 2: 4-(4-Bromo-6-methyl-2-pyridyl)morpholine

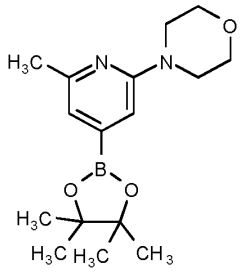


[00407] A mixture of (4-bromo-6-methyl-2-pyridyl) trifluoromethanesulfonate (step 1) (150 mg, 0.47 mmol) and morpholine (82 µL, 0.94 mmol) in DMSO (3 mL) was stirred at 80 °C for 30 mins. The reaction mixture was allowed to cool to room temperature and was diluted with EtOAc (20 mL) and water (20 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica eluting with a gradient of 0 to 15% EtOAc in petroleum ether afforded the title compound as a colourless oil.

LC-MS (Method 3A): Rt 1.47 mins; MS m/z 258.0 = [M+H]+

1H NMR (500 MHz, DMSO-d6) δ 6.83 (s, 1H), 6.76 (d, J = 1.0 Hz, 1H), 3.68 – 3.64 (m, 4H), 3.46 – 3.42 (m, 4H), 2.29 (s, 3H).

Step 3: 4-[6-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]morpholine



[00408] The title compound was prepared from 4-(4-bromo-6-methyl-2-pyridyl)morpholine (step 2) and bis(pinacolato)diboron analogously to Intermediate I step 2. 1H NMR (500 MHz, DMSO-d6) δ 6.75 (s, 1H), 6.74 (s, 1H), 3.69 – 3.65 (m, 4H), 3.42 – 3.38 (m, 4H), 2.31 (s, 3H), 1.28 (s, 12H).

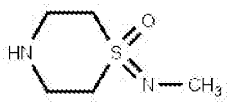
Step 4: 3-[2-Amino-5-(2-methyl-6-morpholino-4-pyridyl)thiazol-4-yl]benzonitrile

[00409] The title compound was prepared from 4-[6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]morpholine (step 3) and 3-(2-amino-5-bromo-thiazol-4-yl)benzonitrile (Intermediate B) analogously to Intermediate I step 3.
LC-MS (Method 5B): Rt 2.84 mins; MS m/z 378.0 = [M+H]+

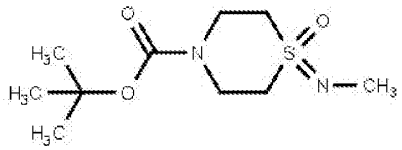
1H NMR (500 MHz, DMSO-d6) δ 7.82 (t, J = 1.5 Hz, 1H), 7.76 (dt, J = 7.8, 1.5 Hz, 1H), 7.70 (dt, J = 7.8, 1.5 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.37 (s, 2H), 6.34 (s, 1H), 6.32 (s, 1H), 3.65 – 3.58 (m, 4H), 3.43 – 3.36 (m, 4H), 2.23 (s, 3H).

Intermediate S

1-Methylimino-1,4-thiazinane 1-oxide



Step 1 – tert-butyl 1-methylimino-1-oxo-1,4-thiazinane-4-carboxylate



[00410] To a mixture of tert-butyl 1-imino-1-oxo-1,4-thiazinane-4-carboxylate (200 mg, 0.85 mmol) in DMF (5 mL) was added sodium hydride (60% in mineral oil) (68 mg, 1.71 mmol) followed by iodomethane (266 µL, 4.27 mmol) and the reaction mixture was stirred at room

temperature for 1.5 h. Additional sodium hydride (60% in mineral oil) (68 mg, 1.71 mmol) followed by iodomethane (266 µL, 4.27 mmol) were added and the reaction mixture was stirred for a further 1.5 h. The mixture was then diluted with 9:1 EtOAc / MeOH (30 mL) and washed with 90% brine (4 x 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound.

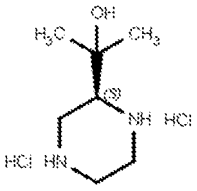
1H NMR (500 MHz, DMSO-d6) δ 3.86 (d, J = 14.7 Hz, 2H), 3.49 – 3.42 (m, 2H), 3.18 – 3.11 (m, 2H), 3.05 – 2.96 (m, 2H), 2.64 (s, 3H), 1.42 (s, 9H).

Step 2 - 1-Methylimino-1,4-thiazinane 1-oxide

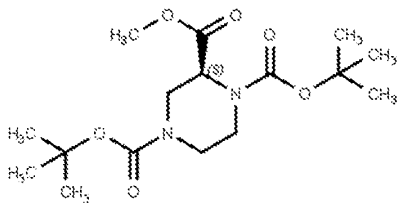
[00411] To a stirred solution of tert-butyl 1-methylimino-1-oxo-1,4-thiazinane-4-carboxylate (step 1) (167 mg, 0.67 mmol) in DCM (5 mL) was added 4 HCl in dioxane (3.36 mL, 13.45 mmol) dropwise. The reaction mixture was stirred at room temperature for 2h. The precipitated solid was collected by filtration, washing with DCM (2 x 2 mL) and concentrated *in vacuo* from MeOH to afford the title compound as a white solid.

Intermediate T

2-[(2S)-Piperazin-2-yl]propan-2-ol dihydrochloride



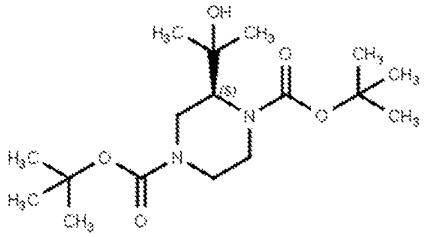
Step 1: 1,4-Di-tert-butyl 2-methyl (2S)-piperazine-1,2,4-tricarboxylate



[00412] A mixture of di-tert-butyl dicarbonate (479 mg, 2.19 mmol), 1-tert-butyl 2-methyl (2S)-piperazine-1,2-dicarboxylate (487 mg, 1.99 mmol) and triethylamine (0.39 mL, 2.79 mmol) in DCM (15 mL) was stirred at room temperature for 18 h. The reaction mixture was diluted with DCM (40 mL) and washed with sat. $NaHCO_3$ solution (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a clear oil which solidified on standing.

1H NMR (500 MHz, DMSO-d6) δ 4.56 (d, J = 37.3 Hz, 1H), 4.28 (dd, J = 31.7, 13.8 Hz, 1H), 3.83 (s, 1H), 3.68 (s, 3H), 3.23 – 2.72 (m, 4H), 1.44 – 1.31 (m, 18H).

Step 2: Di-tert-butyl (2S)-2-(1-hydroxy-1-methyl-ethyl)piperazine-1,4-dicarboxylate



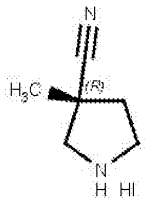
[00413] To a solution of 1,4-di-tert-butyl 2-methyl (2S)-piperazine-1,2,4-tricarboxylate (step 1)(712 mg, 2.07 mmol) in THF (20 mL) at 0°C was added MeMgCl (3 M in THF) (1.72 mL, 5.17 mmol) dropwise. The reaction was allowed to warm to room temperature and was stirred at this temperature for 3 h. The reaction was diluted with DCM (70 mL) and washed with sat. NH_4Cl solution (20 mL). The aq. layer was extracted with DCM (20 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica eluting with a gradient of 1 to 2% MeOH in DCM afforded the title compound as a clear oil.
1H NMR (500 MHz, DMSO-d6) δ 4.39 (s, 1H), 4.03 – 3.43 (m, 4H), 3.17 – 3.04 (m, 2H), 3.01 – 2.82 (m, 1H), 1.39 (s, 18H), 1.17 – 1.01 (m, 6H)

Step 3: 2-[(2S)-Piperazin-2-yl]propan-2-ol dihydrochloride

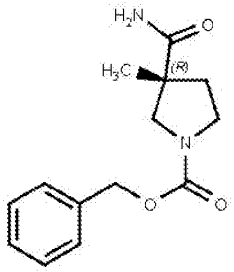
[00414] To a solution of di-tert-butyl (2S)-2-(1-hydroxy-1-methyl-ethyl)piperazine-1,4-dicarboxylate (step 2)(331 mg, 0.96 mmol) in MeOH (8 mL) was added 4N HCl in dioxane (2.4 mL, 9.60 mmol) and the reaction mixture was stirred at room temperature for 6 h before being concentrated *in vacuo* to afford the title compound as a white solid.
1H NMR (500 MHz, DMSO-d6) δ 9.67 (s, 2H), 9.41 (s, 1H), 9.07 (s, 1H), 5.57 (s, 1H), 3.62 – 3.53 (m, 1H), 3.49 – 3.38 (m, 3H), 3.29 – 3.21 (m, 2H), 2.98 (t, J = 12.8 Hz, 1H), 1.26 (s, 3H), 1.19 (s, 3H).

Intermediate U

(3R)-3-Methylpyrrolidine-3-carbonitrile hydroiodide



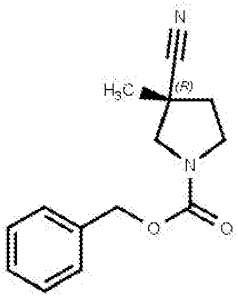
Step 1 - benzyl (3R)-3-carbamoyl-3-methyl-pyrrolidine-1-carboxylate



[00415] Anhydrous THF (19 mL) was added to a mixture of (3R)-1-benzyloxycarbonyl-3-methyl-pyrrolidine-3-carboxylic acid (1.0 g, 3.80 mmol) and CDI (678 mg, 4.18 mmol) under nitrogen and the reaction mixture stirred at room temperature for 1.5 hours. Ammonium hydroxide (35% in water) (8.64 mL, 75.96 mmol) was added and the mixture was stirred at room temperature for 15 mins before the organic solvent was removed *in vacuo*. The crude reaction mixture was diluted with EtOAc (50 mL) and washed with 1M HCl (25 mL), sat. $NaHCO_3$ solution (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated **in vacuo** to afford the title compound as a white solid.

LC-MS (Method 2B): Rt 1.17 mins; MS m/z 263.0 = [M+H]+
1H NMR (500 MHz, DMSO) δ 7.40 – 7.28 (m, 6H), 6.97 (s, 1H), 5.05 (s, 2H), 3.68 (dd, J = 25.8, 10.6 Hz, 1H), 3.42 – 3.33 (m, 1H), 3.31 – 3.25 (m, 1H), 3.11 (dd, J = 13.2, 10.6 Hz, 1H), 2.24 – 2.15 (m, 1H), 1.75 – 1.66 (m, 1H), 1.22 (s, 3H).

Step 2 - benzyl (3R)-3-cyano-3-methyl-pyrrolidine-1-carboxylate



[00416] Benzyl (3R)-3-carbamoyl-3-methyl-pyrrolidine-1-carboxylate (step 1) (996 mg,

3.80 mmol) and Burgess reagent (1.36 g, 5.70 mmol) were dissolved in DCM (9.5 mL) under nitrogen and the resulting mixture stirred at 35 °C for 17 hours. The mixture was cooled to room temperature before being diluted with DCM (40 mL) and washed with 1M HCl (50 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, and concentrated *in vacuo.* Purification by chromatography on silica eluting with a gradient of 10 to 50% EtOAc in petrol afforded the title compound as a colourless syrup.

LC-MS (Method 2B): Rt 1.39 mins; MS m/z 245.0 = [M+H]+

1H NMR (500 MHz, DMSO) δ 7.40 – 7.28 (m, 5H), 5.09 (s, 2H), 3.78 (dd, J = 22.9, 10.9 Hz, 1H), 3.57 – 3.39 (m, 2H), 3.30 – 3.25 (m, 1H), 2.35 – 2.27 (m, 1H), 2.05 – 1.94 (m, 1H), 1.43 (d, J = 3.1 Hz, 3H).

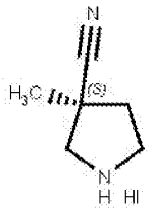
Step 3 - (3R)-3-methylpyrrolidine-3-carbonitrile hydroiodide

[00417] Trimethylsilyl iodide (0.80 mL, 5.65 mmol) was added drop wise to a stirred solution of benzyl (3R)-3-cyano-3-methyl-pyrrolidine-1-carboxylate (step 2) (575 mg, 2.35 mmol) in DCM (24 mL) under nitrogen at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 hour. Methanol (0.95 mL, 23.54 mmol) was added drop wise and the resulting mixture was stirred at room temperature for 30 mins. The formed solid was collected by filtration, washed with DCM (2 x 5 mL) and dried to afford the title compound as a cream solid.

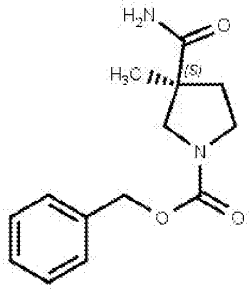
1H NMR (500 MHz, DMSO) δ 9.10 (br s, 2H), 3.66 (d, J = 12.2 Hz, 1H), 3.40 (ddd, J = 11.9, 8.0, 5.4 Hz, 1H), 3.35 – 3.29 (m, 1H), 3.19 (d, J = 12.2 Hz, 1H), 2.43 (ddd, J = 13.2, 7.6, 5.4 Hz, 1H), 2.06 (dt, J = 13.2, 8.1 Hz, 1H), 1.50 (s, 3H).

Intermediate UA

(3S)-3-Methylpyrrolidine-3-carbonitrile hydroiodide



Step 1 - benzyl (3S)-3-carbamoyl-3-methyl-pyrrolidine-1-carboxylate

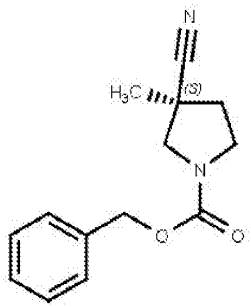


[00418] The title compound was prepared from (3S)-1-benzyloxycarbonyl-3-methyl-pyrrolidine-3-carboxylic acid, CDI and ammonium hydroxide (35% in water) analogously to Intermediate U, step 1.

LC-MS (Method 2B): Rt 1.17 mins; MS m/z 263.0 = [M+H]+ (90% @ 210nm).

1H NMR (500 MHz, DMSO) δ 7.44 – 7.26 (m, 6H), 6.97 (s, 1H), 5.06 (s, 2H), 3.69 (dd, J = 25.8, 10.6 Hz, 1H), 3.46 – 3.34 (m, 1H), 3.31 – 3.28 (m, 1H), 3.11 (dd, J = 13.3, 10.6 Hz, 1H), 2.31 – 2.12 (m, 1H), 1.78 – 1.61 (m, 1H), 1.23 (s, 3H).

Step 2 - benzyl (3S)-3-cyano-3-methyl-pyrrolidine-1-carboxylate



[00419] The title compound was prepared from benzyl (3S)-3-carbamoyl-3-methyl-pyrrolidine-1-carboxylate (step 1) and Burgess reagent analogously to Intermediate U, step 2.

LC-MS (Method 2B): Rt 1.39 mins; MS m/z 245.0 = [M+H]+ (100% @ 254nm).

1H NMR (500 MHz, DMSO) δ 7.38 (d, J = 4.4 Hz, 4H), 7.36 – 7.30 (m, 1H), 5.10 (s, 2H), 3.79 (dd, J = 22.7, 10.9 Hz, 1H), 3.59 – 3.37 (m, 2H), 3.31 – 3.24 (m, 1H), 2.37 – 2.26 (m, 1H), 2.07 – 1.93 (m, 1H), 1.44 (d, J = 3.1 Hz, 3H).

Step 3 - (3S)-3-methylpyrrolidine-3-carbonitrile hydroiodide

[00420] The title compound was prepared from benzyl (3S)-3-cyano-3-methyl-pyrrolidine-1-carboxylate (step 2) and trimethylsilyl iodide analogously to Intermediate U, step 3.

BIOLOGICAL EXAMPLES

Biological Example 1 - Adenosine receptor time-resolved fluorescence resonance energy transfer (TRFRET) binding assay

[00421] All FRET binding experiments were conducted at room temperature in white 384-well plates, in assay binding buffer containing 1x LabMed (Cisbio, France), 100µg/mL saponin, 1% DMSO and 0.02% pluronic acid. Binding of the fluorescently labelled Adenosine receptor antagonist XAC (CA200645, FRET acceptor) to terbium-labelled A1, A2a, A2b and A3 adenosine receptors (FRET donors) was detected by time-resolved FRET due to the close proximity of the donor and acceptor in a binding event. To investigate the ability of unlabelled test compounds to bind to Adenosine A1, A2a, A2b and A3 receptors, dose response curves were constructed that determined the ability of a range of concentrations to inhibit the binding of 30nM CA200645 to the A2b receptor and 100nM CA200645 to the A1, A2a, and A3 receptor.

[00422] Serial dilution (1:3 dilutions) of test compounds in neat DMSO and transfer of a 400nL sample of test compound into the assay plate was carried out using the Mosquito (TTP Labtech, UK). The compound samples were incubated for 2 hours at room temperature with a fixed concentration of CA200645 defined for each receptor (see above) and CHO cell membranes containing the human Adenosine A1 (0.5µg/well), A2a (0.3µg/well), A2b (1µg/well) or A3 (1 µg/well) receptor in 40 µL of assay buffer. Total and non-specific binding of CA200645 was determined in the absence and presence of 10µM XAC, respectively. Following 2 hours incubation, the level of CA200645 binding was detected on a Pherastar FSX (BMG Labtech, Germany) using standard TR-FRET settings. The terbium donor was excited with three laser flashes at a wavelength of 337 nm, and donor and acceptor emission was detected at 620 nm and 665 nm wavelengths, respectively. FRET ratios were obtained by multiplying the acceptor/donor ratio value by 10,000. Specific binding was determined by subtracting the non-specific binding FRET ratio from the total binding FRET ratio. Compound IC50 curves were analysed using GraphPad Prism 7.0 (GraphPad, USA) and Ki affinity values were determined from the obtained IC50 values using the method of Cheng and Prusoff. The results are presented in Table 1.

Table 1

Example Number	A2a Ki (nM)	A2b Ki (nM)	A1 Ki (nM)	A3 Ki (nM)
1	0.42	1.1	9	305
2	0.40	1.0	234	849
3	58.24	50.6	1000	1976
3.1	3.11	6.6	94	267
3.2	0.40	0.7	12	1039
3.3	2.15	3.9	136	
3.4	14.34	14.3		2046
3.5	11.55	11.4	434	928
3.6	0.64	1.5	88	481
3.7	0.20	1.1	14	382
3.8	0.09	0.9	116	538
3.9	0.49	2.2	81	338
3.10	8.17	12.2	135	144
3.11	0.52	1.2	102	1300
3.12	0.25	1.0	18	531
4	1.01	0.7	60	1000
4.1	0.11	0.6	11	145
4.2	0.27	4.4	28	881
4.3	0.70	3.8	187	603
4.4	0.86	4.5	263	568
4.5	1.54	1.4	16	94
4.6	0.18	1.2	41	170

4.7	0.05	1.3	6	125
4.8	0.37	1.5	17	180
4.9	0.14	1.5	9	133
4.10	0.38	2.5	50	157
4.11	1.30	4.7	225	482
4.12	0.26	1.1	31	389
4.13	1.50	1.7	50	195
4.14	2.00	2.4	67	200
4.15	2.30	1.4	91	339
4.16	0.90	2.2	41	265
4.17	1.90	2.8	77	293
4.18	0.60	2.3	94	414
4.19	0.60	1.3	46	232
4.20	1.50	2.6	161	967
4.21	0.30	1.0	10	265
4.22	0.10	0.9	35	165
4.23	0.20	0.7	54	267
4.24	0.18	2.4	15	383
4.25	0.12	1.8	14	120
4.26	0.05	0.4	4	130
4.27	0.10	0.8	6	423
4.28	0.48	2.4	135	77
4.29	0.13	1.3	24	112
4.30	0.41	0.6	7	106
4.31	3.75	4.7	210	425
4.32	0.15	1.1	26	457
4.33	1.91	5.9	62	410

4.34	12.2	13	268	
4.36	2.48	13.8	316	
4.37	4.29	27.1	545	
4.38	1.8	8.1	180	
4.38	0.4	3.5	75	
5	5.75	5.5	601	696
5.1	0.62	1.6	45	229
5.2	0.84	0.9	40	70
5.3	2.31	2.1	90	98
5.4	1.03	5.8	111	33
5.5	0.94	2.4	114	70
5.6	2.13	4.2	22	31
5.7	2.90	1.8	48	247
5.8	0.68	1.8	34	474
5.9	2.32	4.3	82	125
6	0.12	1.1	37	283
6.1	1.05	2.1	40	228
6.2	1.28	0.9	24	166
6.3	0.87	1.5	32	125
6.4	0.67	3.1	103	360
6.5	4.63	23.1	93	
6.6	1.44	1.3	81	233
6.7	0.11	0.7	14	281
6.8	0.72	1.1	23	312
6.9	0.88	0.7	44	412
6.10	0.30	1.2	14	316
6.11	0.39	2.6	42	319

6.12	0.23	2.4	137	298
6.13	0.40	3.4	23	
6.14	0.60	2.6	167	772
6.15	2.02	5.9	263	259
6.16	3.99	17.6	422	565
6.17	0.46	6.5	35	405
6.18	0.33	6.1	70	332
6.19	0.61	1.1	20	130
6.20	0.14	1.9	53	287
6.21	0.86	1.3	6	96
6.22	0.38	1.8	4	107
6.23	2.99	6.5	92	394
6.24	0.99	2.5	129	224
6.25	1.73	1.1	2	94
6.26	0.79	3.8	86	302
6.27	1.01	1.4	45	151
6.28	4.84	3.2	32	226
6.29	0.95	3.4	228	635
6.30	0.82	2.0	97	187
6.31	1.50	2.1	19	186
6.32	0.83	5.4	109	719
6.33	3.65	3.6	51	268
6.34	0.64	2.1	26	166
6.35	9.58	20.9	243	303
6.36	0.87	4.2	133	377
6.37	1.82	10.1	91	356
6.38	0.83	3.6	170	278

6.39	10.1	39.6	383	389
6.40	0.41	4.6	110	330
6.41	0.18	1.3	111	235
6.42	0.39	9.0	44	438
6.43	1.12	8.2	51	175
6.44	0.40	2.4	151	299
6.45	0.44	2.0	104	183
6.46	2.06	1.9	113	235
6.47	0.37	2.5	38	465
6.48	1.11	1.7	96	245
6.49	1.27	2.2	51	324
6.50	1.63	3.4	136	472
6.51	1.26	1.2	120	318
6.52	4.30	8.6	120	238
6.53	0.27	1.6	110	662
6.54	0.38	1.9	53	268
6.55	0.60	2.4	86	273
6.56	0.59	1.2	75	368
6.57	0.88	1.3	32	212
6.58	2.27	7.8	559	848
6.59	1.47	2.2	128	184
6.60	3.09	6.2	185	455
6.61	1.52	3.2	112	57
6.62	35.7	23.3	219	358
6.63	34.3	29.2	343	200
6.64	0.14	1.4	27	235
6.65	45.6	17.3	185	295

6.66	0.43	0.6	37	1215
6.67	2.06	1.0	22	201
6.68	0.36	0.6	30	217
6.69	0.94	1.4	124	156
6.70	9.59	13.1	163	192
6.71	3.45	4.2	110	62
6.72	1.12	1.2	3	94
6.73	2.51	3.7	92	165
6.74	0.63	1.9	23	219
6.75	0.81	4.8	99	361
6.76	12.9	21.7	39	321
6.77	1.44	5.4	133	193
6.78	0.67	0.9	24	37
6.79	1.50	6.0	177	537
6.80	0.80	2.4	130	450
6.81	0.47	2.3	49	292
6.82	3.67	5.1	116	246
6.83	67.6	102.1	129	294
6.84	4.46	8.4	216	568
6.85	12.1	16.0	44	216
6.86	0.68	1.9	2	181
6.87	1.75	6.7	57	37
6.88	1.90	8.0	65	385
6.89	1.01	3.5	326	300
6.90	3.16	10.7	63	106
6.91	1.66	5.3	20	162
6.92	0.39	2.6	66	98

6.93	0.31	1.5	44	161
6.94	5.63	11.3	407	719
6.95	1.05	4.6	29	560
6.96	0.53	1.8	10	502
6.97	0.23	1.1	17	250
6.98	0.91	7.0	309	819
6.99	0.13	0.7	14	77
6.100	0.16	0.6	25	549
6.101	1.10	3.0	30	853
6.102	7.42	10.5	64	195
6.103	0.68	1.7	61	475
6.104	0.20	1.0	31	564
6.105	1.27	1.3	71	368
6.106	1.07	4.5	139	195
6.107	1.37	2.3	69	156
6.108	0.59	0.9	34	145
6.109	10.8	45.5	471	298
6.110	0.26	3.6	13	956
6.111	0.20	6.4	18	
6.112	4.30	23.6	339	
6.113	10.75	8.3	361	
6.114	9.95	23	240	
6.115	8.00	29	177	
6.116	7.39	10	281	
6.120	11.11	63.9	123	
6.121	1.94	6.8	123	
7	2.81	11.1	42	304

7.1	0.99	7.6	47	418
7.2	0.20	1.0	8	337
7.3	1.02	5.7	208	
7.4	2.73	13.5	58	
7.5	1.26	11.9	9	
7.6	4.09	22.6	162	
7.7	5.27	18.2	49	
7.8	6.73	60.2	194	
7.9	10.33	44.2	61	
7.10	29.38	90.0	122	
7.11	12.75	78.7	110	
8	1.83	1.8	59	776
9	0.61	5.3	47	2023
9.1	0.78	7.0	95	1003
9.2	0.79	5.3	102	772
9.3	1.11	8.1	29	1507
9.4	4.19	20.1	410	1545
9.5	2.28	7.5	174	699
9.6	0.51	2.9	12	369
9.7	0.42	3.2	68	742
9.8	0.37	2.4	24	615
9.9	0.31	3.1	48	491
10	1.19	1.4	43	283
11	0.62	1.3	51	515
12	0.16	3.1	6	930
12.1	0.20	3.1	7	1236
12.2	0.28	8.4	6	1525

12.3	0.44	5.0	27	1812
12.3a	0.18	2.6	23	1091
12.3b	0.42	1.2	19	
13	24.34	195.6	373	
13.1	0.64	1.9	164	
13.2	1.90	4.4	27	
13.3	11.37	77.0	322	
13.4	5.13	19.6	54	54
13.5	9.87	18.8	84	226
13.6	16.78	79.7	220	133
13.7	7.46	13.7	174	256
13.8	2.38	12.3	47	41
13.9	2.01	14.9	225	646
13.10	4.56	14.5	61	573
13.11	12.90	58.4	132	226
13.12	0.84	4.6	41	426
13.13	0.48	8.0	19	871
13.14	0.18	4.2	13	
13.15	0.33	5.1	41	
14	2.71	7.4	45	47
14.1	2.67	8.6	41	112
14.2	2.09	8.3	183	132
14.3	3.49	7.6	57	520
14.4	5.79	37.1	58	
14.5	0.43	2.5	61	
14.6	15.6	33	185	
16	2.71	2.4	55	334

16.1	0.29	2.2	22	257
16.2	0.38	1.4	16	135
16.3	5.71	6.2	82	383
16.4	0.13	3.3	12	1712
16.5	11.87	19.9	87	325
16.6	0.16	1.6	42	985
16.7	0.13	1.6	13	478
16.8	0.13	1.1	6	537
16.9	0.10	0.8	9	350
16.10	0.57	1.7	43	254
17	1.29	10.0	12	
18	0.39	3.4	248	852
19	1.86	7.9	137	
20	6.85	39.1	133	2543
21	0.21	3.9	29	1558
22	0.20	3.2	7	2060
23	0.16	5.7	9	1838
24	0.24	2.7	71	683
26	0.24	1.2	38	456
27	0.41	0.8	21	225
27a	0.54	1.2	37	313
27b	0.14	1.0	33	271
28	0.09	1.0	30	381

Biological Example – CD3/CD28 stimulated IL-2 release NECA reversal assay in human PBMCs

[00423] Blood is drawn from healthy volunteers using sodium citrate as the anticoagulant (0.3% final concentration). After centrifugation of the blood over Histopaque-

1077, PBMCs are collected from the Histopaque/plasma interface and washed twice in PBS (300g for 10 mins at room temp). Cells are plated at 50,000 cells/well in 150µl RPMI/10% FCS in 96-well cell culture plates that have been precoated with 1ug/ml CD3 antibody. 50µl diluted compound mix is added to the cells, to obtain final concentrations of 1ug/ml CD28 antibody, 1uM NECA and 0.003-10µM adenosine receptor antagonist. Assay plates are incubated for 24 hours at 37ºC in a humidified incubator. Culture supernatant is tested for IL-2 levels using the human IL-2 Tissue Culture Kit (Meso Scale Discovery). Data for dose-response curves is calculated as % inhibition with 100% inhibition defined from no agonist control wells (+CD3/28 –NECA)

Table 2

Example	IL-2 IC50 (µM)
2	0.0020
3.1	0.0130
3.6	0.0075
3.7	0.0033
3.8	0.0010
3.9	0.0179
3.11	0.0104
3.12	0.008
4	0.0038
4.1	0.0003
4.2	0.0079
4.3	0.0182
4.4	0.0062

4.5	0.0085
4.7	0.0008
4.8	0.0011
4.9	0.0032
4.10	0.0029
4.11	0.0038
4.12	0.002
4.13	0.0141
4.15	0.0103
4.17	0.0085
4.18	0.0061
4.19	0.0054
4.20	0.0013
4.22	0.0011
4.23	0.0006
4.24	0.0028
4.25	0.0011
4.26	0.0004
4.28	0.0047
4.29	0.0021
4.30	0.0013
4.32	0.0007

5.2	0.0202
5.4	0.0718
5.5	0.0306
5.6	0.0305
5.8	0.0184
5.9	0.0183
6	0.0006
6.1	0.0036
6.4	0.0014
6.6	0.0082
6.7	0.0008
6.9	0.0043
6.10	0.0029
6.11	0.0052
6.12	0.0027
6.13	0.0037
6.14	0.0053
6.17	0.0053
6.18	0.005
6.20	0.0018
6.24	0.0047
6.26	0.0032

6.29	0.0053
6.30	0.0069
6.32	0.0086
6.36	0.0042
6.38	0.006
6.40	0.0022
6.41	0.0027
6.42	0.005
6.44	0.0031
6.45	0.0094
6.46	0.0151
6.47	0.0019
6.48	0.0037
6.50	0.0036
6.51	0.0061
6.53	0.0025
6.54	0.0033
6.55	0.0022
6.56	0.0035
6.57	0.0026
6.58	0.0085
6.59	0.0059

6.61	0.0172
6.64	0.0011
6.66	0.0043
6.67	0.0106
6.68	0.0031
6.69	0.0109
6.73	0.0135
6.74	0.0056
6.75	0.0059
6.79	0.0145
6.81	0.0076
6.88	0.0078
6.92	0.0012
6.93	0.0013
6.94	0.0105
6.99	0.0007
7	0.0160
7.1	0.0205
9.2	0.0027
9.7	0.001
9.8	0.0007
9.9	0.0013

10	0.0247
11	0.0105
12.2	0.0004
16.1	0.0067
16.6	0.0026
16.7	0.0009
18	0.0072
24	0.0016
27	0.0009
27b	0.001
28	0.0004

Biological Example – Measurement of pCREB in CD8+T cells in human whole blood

[00424] Heparinised human whole blood was pre-incubated at 37°C with serial dilutions of A2a antagonists for 20 min. and the phosphodiesterase inhibitor rolipram to amplify the pCREB response. The adenosine receptor agonist NECA is then added at a final concentration of 3μM and following a 60 min incubation the blood is fixed and red blood cells lysed. White blood cells are isolated, permeabilized and stained with directly conjugated fluorescent antibodies to phospho-CREB (Alexa Fluor 488) and CD8 (Alexa Fluor 647) and the level of phospho-CREB in CD8+ T cells is measured by FACS using a BD Accuri C6 Flow Cytometer.

Table 3

Example	pCREB IC50 (μM)

2	0.28
3.1	1.77
3.6	0.99
3.7	0.29
3.8	0.75
3.9	0.47
3.11	0.67
3.12	0.60
4	0.13
4.1	0.01
4.2	0.09
4.3	0.17
4.4	0.17
4.5	0.16
4.7	0.09
4.8	0.04
4.9	0.05
4.10	0.10
4.11	0.22
4.12	0.05
4.13	0.55
4.15	0.65

4.17	0.37
4.18	0.35
4.19	5.52
4.20	0.13
4.22	0.11
4.23	0.03
4.24	0.08
4.25	0.05
4.26	0.02
4.28	0.67
4.29	0.05
4.30	0.06
4.32	0.06
5.2	1.18
5.4	1.95
5.5	2.69
5.6	0.72
5.8	0.98
5.9	1.00
6	0.07
6.1	0.15
6.4	0.19

6.6	0.60
6.7	0.02
6.9	0.16
6.10	0.04
6.11	0.05
6.12	0.11
6.13	0.14
6.14	0.05
6.17	0.07
6.18	0.04
6.20	0.02
6.24	0.09
6.26	0.08
6.29	0.51
6.30	0.53
6.32	0.23
6.36	0.09
6.38	0.58
6.40	0.08
6.41	0.12
6.42	0.13
6.44	0.10

6.45	0.31
6.46	0.36
6.47	0.08
6.48	0.14
6.50	0.19
6.51	0.32
6.53	0.13
6.54	0.14
6.55	0.01
6.56	0.07
6.57	0.06
6.58	0.36
6.59	0.10
6.61	0.35
6.64	0.01
6.66	0.30
6.67	0.25
6.68	0.05
6.69	0.43
6.73	0.20
6.74	0.24
6.75	0.18

6.79	0.35
6.81	0.23
6.88	0.48
6.92	0.03
6.93	0.05
6.94	0.19
6.96	0.03
6.97	0.05
6.98	0.05
6.99	0.04
7	0.58
7.1	0.65
9.2	0.02
9.7	0.01
9.8	0.01
9.9	0.02
10	1.06
11	1.13
12.2	0.01
12.3	0.02
12.3a	0.01
12.3b	0.01

13.12	**0.07**
13.13	**0.11**
16.1	**0.12**
16.6	**0.10**
16.7	**0.06**
18	**0.41**
19	**0.29**
21	**0.02**
23	**0.02**
24	**0.02**
26	**0.05**
27	**0.08**
27a	**0.08**
27b	**0.04**
28	**0.06**

MoDC pCREB Assay

[00425] Monocytes are isolated from human whole blood using CD14 microbeads (Miltenyi Biotec 130-050-201) and differentiated to immature monocyte-derived dendritic cells (MoDC) by culture for 5 days in Mo-DC Differentiation Medium (Miltenyi Biotec 130-094-812). MoDCs are seeded into fresh medium into U bottomed 96 well culture plates and pre-incubated at 37°C with serial dilutions of $A_{2A/B}$ antagonists for 15 min. At the same time the cells are co-incubated with the phosphodiesterase inhibitor rolipram (final concentration of 20 μM) to amplify the subsequent pCREB response. Adenosine receptor agonist NECA is then added at 1μM final concentration, leading to an increase in CREB phosphorylation. Following a 45 min incubation at 37°C, the cells are fixed, permeabilized and stained with directly

conjugated fluorescent antibodies to phospho-CREB (Alexa Fluor 488), CD209 (PerCP-Cy5.5) and CD86 (APC). Samples are analysed by FACS to measure fluorescence in corresponding channels, and also forward and Side scatter. The population of CD209+/ CD86-low cells corresponding to immature dendritic cells is gated for analysis of pCREB levels. The adenosine receptor response in this cell population is largely specific to A_{2B}, based on specific response to the highly selective antagonist PSB-603.

[00426] Approximately 5% of the analysed cells are positive for detection of pCREB in the absence of agonist stimulation, representing the background signalling of all pathways upstream of CREB. Following NECA stimulation this is increased to ~80% pCREB +ve, and this increase is essentially fully reversible by A_{2B} or dual $A_{2A/B}$ antagonists.

[00427] IC50 is represented as the point of inflection of a sigmoidal curve

Table 4

Example	MoDC IC50 (μM)
3.6	0.051
3.8	0.011
4.1	0.015
4.4	0.095
4.8	0.012
4.9	0.026
4.12	0.018
4.22	0.011
4.23	0.02
4.24	0.079
4.28	0.01
4.32	0.014
6	0.009

6.6	0.024
6.7	0.007
6.2	0.028
6.36	0.016
6.46	0.038
6.53	0.04
6.56	0.007
6.68	0.003
6.69	0.003
6.74	0.001
6.79	0.083
6.81	0.019
6.92	0.011
6.93	0.009
6.97	0.013
6.98	0.072
6.99	0.008
6.100	0.01
6.104	0.012
6.105	0.004
6.108	0.062
9.8	0.008

12	0.073
12.2	0.055
12.3	0.031
12.3a	0.016
13.12	0.073
16.4	0.036
16.6	0.013
16.7	0.014
16.9	0.018
21	0.019
23	0.182
24	0.021
26	0.017
27a	0.01
27b	0.004
28	0.009

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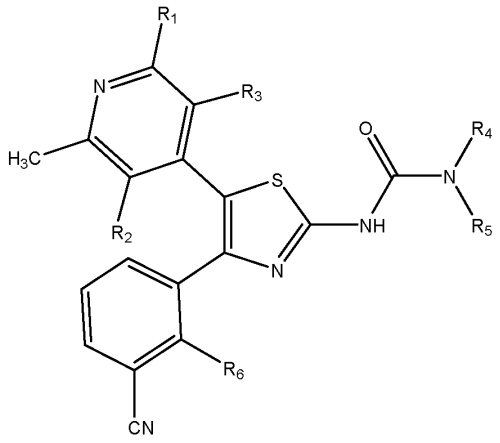
NUMBERED PARAGRAPHS

The following paragraphs define certain aspects and embodiments of the invention.

1. A compound, or pharmaceutically acceptable salt thereof, having the structural formula I' shown below:



I'

wherein:

R_1 is selected from (1-2C)alkyl, halo, (1-2C)haloalkyl, (1-2C)haloalkoxy, cyano, $-(CH_2)_{q1}-OR_{1A}$, $-(CH_2)_{q1}-C(O)R_{1A}$, $-(CH_2)_{q1}-C(O)OR_{1A}$, $-(CH_2)_{q1}-OC(O)R_{1A}$, $-(CH_2)_{q1}-C(O)N(R_{1B})R_{1A}$, $-(CH_2)_{q1}-N(R_{1B})C(O)R_{1A}$, $-(CH_2)_{q1}-S(O)_pR_{1A}$ (where p is 0, 1 or 2), $-(CH_2)_{q1}-SO_2N(R_{1B})R_{1A}$, or $-(CH_2)_{q1}-N(R_{1B})SO_2R_{1A}$,

wherein q1 is 0, 1, or 2; and

wherein R_{1A} and R_{1B} are each independently selected from hydrogen, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkyl(1-2C)alkyl;

R_2 and R_3 are both hydrogen or one of R_2 and R_3 is hydrogen and the other is selected from fluoro, methyl or methoxy;

R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups,

wherein R_{10C} is selected from oxo, thioxo, halo, or cyano substituents, or a group of the formula:

$$-[CR_{7a}R_{7b}]_n-L-Z$$

wherein

n is 0 to 6;

R_{7a} and R_{7b} are each independently selected from hydrogen, fluoro or (1-2C)alkyl;

L is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_a)-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_a)-$, $-N(R_a)C(O)-$, $-N(R_a)C(O)N(R_b)-$, $-C(S)N(R_a)-$, $-N(R_a)C(S)-$,

-$N(R_a)C(S)N(R_b)$-, -$S(O)_2N(R_a)$-, or -$N(R_a)SO_2$-, wherein R_a and R_b are each independently selected from hydrogen or (1-2C)alkyl; and

Z is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, aryl, aryl(1-2C)alkyl, heterocyclyl, heterocyclyl(1-2C)alkyl, heteroaryl or heteroaryl(1-2C)alkyl; and wherein Z is optionally substituted by one or more substituents selected from (1-6C)alkyl, halo, (1-6C)haloalkyl, (1-6C)haloalkoxy, cyano, nitro, -NR_cR_d, -OR_c, -$C(O)R_c$, -$C(O)OR_c$, -$OC(O)R_c$, -$C(O)N(R_c)R_d$, -$N(R_c)C(O)R_d$, -$S(O)_yR_c$ (where y is 0, 1 or 2), -$SO_2N(R_c)R_d$, -$N(R_c)SO_2R_d$, -$(CH_2)_zNR_cR_d$ (where z is 1, 2 or 3) or oxo,

wherein any alkyl moiety in a substituent group on Z is optionally further substituted by cyano, halo, hydroxy, amino, oxo, (1-2C)alkyl or (1-2C)alkoxy and R_c and R_d are each independently selected from hydrogen, (1-6C)alkyl, (1-6C)haloalkyl or (3-6C)cycloalkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N},

wherein R_{10N} is -$S(O)_2NH_2$ or selected from:

(iv) –Z_1;

(v) –L_{1a}–Z_1; or

(vi) –$[CR_{8a}R_{8b}]_{1-6}$–L_{1b}–Z_1;

wherein

R_{2a} and R_{2b} are each independently selected from hydrogen, fluoro or (1-2C)alkyl;

L_{1a} is selected from -C(O)-, -$S(O)_2$-, -C(O)O-, -$C(O)N(R_{a1})$-, -$S(O)_2N(R_{a1})$- or -$N(R_{a1})$-, wherein R_{a1} is selected from hydrogen or (1-2C)alkyl;

L_{1b} is absent or selected from -O-, -S-, -SO-, -SO_2-, -$N(R_{a2})$-, -C(O)-, -C(O)O-, -OC(O)-, -$C(O)N(R_{a2})$-, -$N(R_{a2})C(O)$-, -$N(R_{a2})C(O)N(R_{b2})$-, -$C(S)N(R_{a2})$-, -$N(R_{a2})C(S)$-, -$N(R_{a2})C(S)N(R_{b2})$-, -$S(O)_2N(R_{a2})$-, or -$N(R_{a2})SO_2$, wherein R_{a2} and R_{b2} are each independently selected from hydrogen or (1-2C)alkyl; and

Z_1 is selected from (1-6C)alkyl, (3-6C)cycloalkyl, aryl, heterocyclyl, heteroaryl, (3-6C)cycloalkyl(1-2C)alkyl, aryl(1-2C)alkyl, heterocyclyl(1-2C)alkyl or heteroaryl(1-2C)alkyl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-6C)alkyl, halo, (1-6C)haloalkoxy, cyano, nitro, -NR_eR_f, -OR_e, -$C(O)R_e$, -$C(O)OR_e$, -$OC(O)R_e$, -$C(O)N(R_e)R_f$, -$N(R_e)C(O)R_f$, -$S(O)_yR_e$ (where y is 0, 1 or 2), -$SO_2N(R_e)R_f$, -$N(R_e)SO_2R_f$, -$(CH_2)_zNR_eR_f$ (where z is 1, 2 or 3)

or oxo, and wherein R_e and R_f are each independently selected from hydrogen, (1-6C)alkyl, (1-6C)haloalkyl or (3-6C)cycloalkyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, (1-3C)alkyl or (2-3C)alkanoyl; and

R_6 is selected from hydrogen, halo, methyl, methoxy and trifluoromethyl.

2. A compound according to paragraph 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from methyl, halo or $-CF_3$;

3. A compound according to any one of the preceding paragraphs, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from methyl or chloro;

4. A compound according to any one of the preceding paragraphs, or a pharmaceutically acceptable salt thereof, wherein R_2 and R_3 are both hydrogen or one of R_2 and R_3 is hydrogen and the other is fluoro or methyl.

5. A compound according to any one of the preceding paragraphs, or a pharmaceutically acceptable salt thereof, wherein R_2 and R_3 are both hydrogen.

6. A compound according to any one of the preceding paragraphs, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups,

wherein R_{10C} is selected from oxo, halo, or cyano substituents, or a group of the formula:

$$–[CH_2]_n–L–Z$$

wherein

n is 0 to 2;

L is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_{a2})-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_{a2})-$, $-N(R_{a2})C(O)-$, $-N(R_{a2})C(O)N(R_{b2})-$, $-S(O)_2N(R_{a2})-$, or $-N(R_{a2})SO_2-$, wherein R_{a2} and R_{b2} are each independently selected from hydrogen or methyl; and

Z is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, aryl, heterocyclyl or heteroaryl; and wherein Z is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkyl, (1-2C)haloalkoxy, cyano, $-NR_cR_d$, $-OR_c$, $-C(O)R_c$, $-C(O)OR_c$, $-OC(O)R_c$, $-C(O)N(R_c)R_d$, $-N(R_c)C(O)R_d$, $-S(O)_yR_c$ (where y is 0, 1 or 2), $-SO_2N(R_c)R_d$, $-N(R_c)SO_2R_d$, $-(CH_2)_zNR_cR_d$ (where z is 1 or 2) or oxo;

wherein any alkyl moiety in a substituent group on Z_1 is optionally further substituted by cyano, halo, hydroxy, amino, oxo, (1-2C)alkyl or (1-2C)alkoxy and R_c and R_d are each independently selected from hydrogen, (1-2C)alkyl, (1-2C)haloalkyl or (3-6C)cycloalkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is $-S(O)_2NH_2$ or selected from:

(i) $–Z_1$;

(ii) $–L_{1a}–Z_1$; or

(iii) $–[CR_{8a}R_{8b}]_{1-2}–L_{1b}–Z_1$;

wherein

R_{2a} and R_{2b} are both hydrogen;

L_{1a} is selected from -C(O)-, $-S(O)_2-$ or $-S(O)_2N(R_{a1})-$, wherein R_{a1} is hydrogen or methyl;

L_{1b} is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_{a2})-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_{a2})-$, $-N(R_{a2})C(O)-$, $-N(R_{a2})C(O)N(R_{b2})-$, $-S(O)_2N(R_{a2})-$, or $-N(R_{a2})SO_2$, wherein R_{a2} and R_{b2} are each independently selected from hydrogen or methyl; and

Z_1 is selected from (1-6C)alkyl, (3-6C)cycloalkyl, aryl, heterocyclyl, heteroaryl, (3-6C)cycloalkyl(1-2C)alkyl or aryl(1-2C)alkyl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkoxy, cyano, nitro, $-NR_eR_f$, $-OR_e$, $-C(O)R_e$, $-C(O)OR_e$, $-OC(O)R_e$, $-C(O)N(R_e)R_f$, $-N(R_e)C(O)R_f$, $-S(O)_yR_e$ (where y is 0, 1 or 2), $-SO_2N(R_e)R_f$, $-N(R_e)SO_2R_f$, $-(CH_2)_zNR_eR_f$ (where z is 1, 2 or 3) or oxo, and wherein R_e and R_f are each independently selected from hydrogen or (1-2C)alkyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, (1-2C)alkyl or (2C)alkanoyl.

7. A compound according to any one of the preceding paragraphs, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups,

wherein R_{10C} is selected from oxo, halo, or cyano substituents, or a group of the formula:

$$–[CH_2]_n–L–Z$$

wherein

n is 0 to 2;

L is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_a)-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_a)-$, $-N(R_a)C(O)-$, $-S(O)_2N(R_a)-$, or $-N(R_a)SO_2-$, wherein R_a and R_b are hydrogen; and

Z is selected from hydrogen, (1-4C)alkyl, phenyl, a 4-7 membered heterocyclyl or a 5 or 6-membered heteroaryl; and wherein Z is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkyl, (1-2C)haloalkoxy, cyano, $-NR_cR_d$, $-OR_c$, $-C(O)R_c$, $-C(O)N(R_c)R_d$, $-N(R_c)C(O)R_d$ or $-S(O)_yR_c$ (where y is 0, 1 or 2) or oxo;

wherein R_c and R_d are each independently selected from hydrogen or (1-2C)alkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is $-S(O)_2NH_2$ or selected from:

(i) $–Z_1$;

(ii) $–L_{1a}–Z_1$; or

(iii) $–[CR_{8a}R_{8b}]_{1-2}–L_{1b}–Z_1$;

wherein

R_{2a} and R_{2b} are both hydrogen;

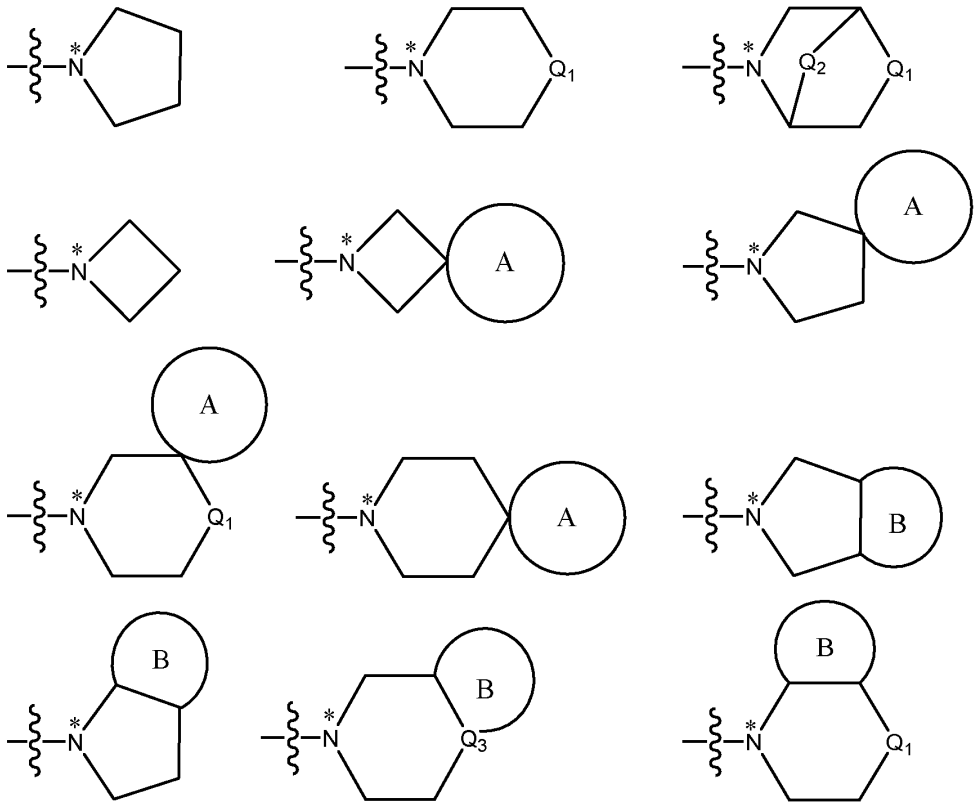
L_{1a} is selected from -C(O)-, $-S(O)_2-$ or $-S(O)_2N(R_{a1})-$, wherein R_{a1} is hydrogen;

L_{1b} is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_{a2})-$, $-C(O)N(R_{a2})-$, $-N(R_{a2})C(O)-$, $-S(O)_2N(R_{a2})-$ or $-N(R_{a2})SO_2$, wherein R_{a2} is hydrogen; and

Z_1 is selected from (1-4C)alkyl, phenyl, a 4-7 membered heterocyclyl or a 5 or 6-membered heteroaryl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkoxy, cyano, $-NR_eR_f$, $-OR_e$, $-C(O)R_e$, $-C(O)N(R_e)R_f$, $-N(R_e)C(O)R_f$, $-S(O)_yR_e$ (where y is 0, 1 or 2); and wherein R_e and R_f are each independently selected from hydrogen or methyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, (1-2C)alkyl or (2C)alkanoyl.

8. A compound according to any one of the preceding paragraphs, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



wherein * denotes the N atom to which R_4 and R_5 are attached;

Q_1 is O, NH, S, S(O), $S(O)_2$, $S(O)(=NR_e)$, $N\text{-}R_{10N}$, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_2 is $-CH_2-$, $-CHR_{10C}-$, $-C(R_{10c})_2-$, $-CHR_{10C}-CH_2-$, $-CH_2-CHR_{10C}-$, $-CHR_{10C}-CHR_{10C}-$, $-C(R_{10c})_2-CH_2-$, or $-CH_2-C(R_{10c})_2-$;

Q_3 is C or N;

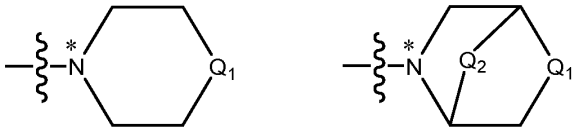
Ring A is a spiro-fused 4, 5 or 6 membered carbocyclic or heterocyclic ring;

Ring B is a fused 4, 5 or 6 membered carbocyclic or heterocyclic ring;

wherein R_e is selected from hydrogen, (1-2C)alkyl or (2C)alkanoyl;

and wherein each of the heterocyclic ring systems is optionally substituted with one or more R_{10c} or R_{10N} substituent groups as defined in any one of paragraphs 1, 6 or 7.

9. A compound according to any one of the preceding paragraphs, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



wherein * denotes the N atom to which R_4 and R_5 are attached;

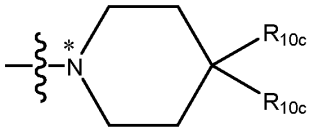
Q_1 is O, NH, S, S(O), $S(O)_2$, $S(O)(=NR_e)$, $N-R_{10N}$, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_2 is $-CH_2-$;

wherein R_e is selected from hydrogen, methyl, or (2C)alkanoyl;

and R_{10c} or R_{10N} are as defined in any one of paragraphs 1, 6 or 7.

10. A compound according to any one of the preceding paragraphs, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring of the structure:



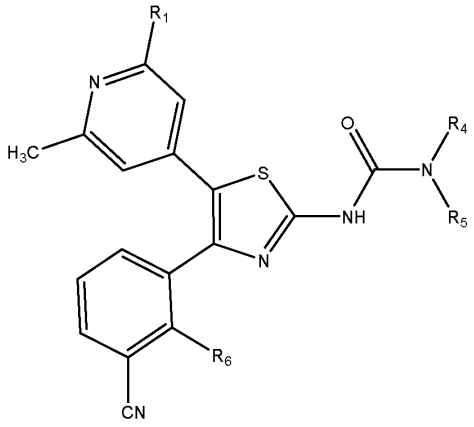
wherein * denotes the N atom to which R_4 and R_5 are attached;

and each R_{10c} is independently selected from the options defined in any one of paragraphs 1, 6 or 7 above.

11. A compound according to any one of the preceding paragraphs, or a pharmaceutically acceptable salt thereof, wherein R_6 is selected from hydrogen, halo or methyl.

12. A compound according to any one of the preceding paragraphs, or a pharmaceutically acceptable salt thereof, wherein R_6 is hydrogen.

13. A compound of the formula:



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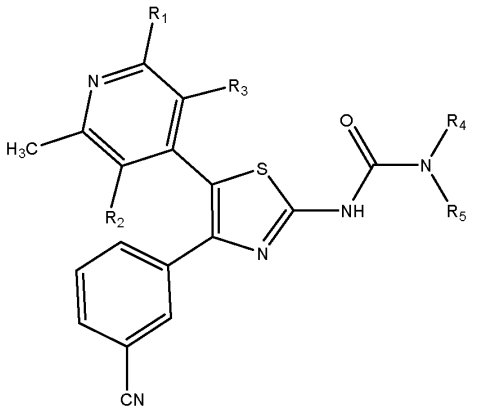

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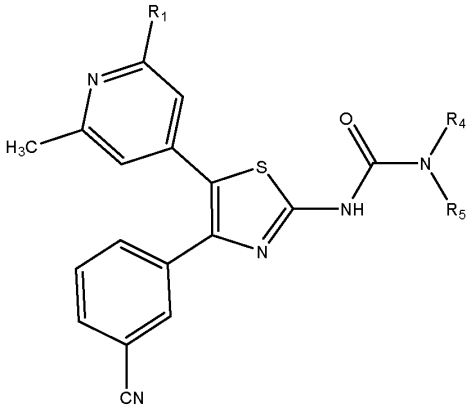


IC'

wherein R_1, R_2, R_3, R_4, R_5 and R_6 are each as defined in any one of paragraphs 1 to 12;

14. A compound, or a pharmaceutically acceptable salt thereof, selected from any one of the following:

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]morpholine-4-carboxamide;

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide;
(2R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]pyrrolidine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-(2-hydroxy-2-methyl-propyl)pyrrolidine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)morpholine-4-carboxamide;
(2S)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-methyl-piperazine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-hydroxy-4-methyl-piperidine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-cyano-4-methyl-piperidine-1-carboxamide;
(3S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide formate;
(3R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide formate
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide;
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperazine-1-carboxamide;
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxyethyl)piperazine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide;

(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-pyrrolidine-1-carboxamide;
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(methoxymethyl)piperidine-1-carboxamide;
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-fluoro-piperidine-1-carboxamide;
(3S)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-3-methyl-azetidine-1-carboxamide;
(3R)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-piperazine-1-carboxamide
N4-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]morpholine-2,4-dicarboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-3-oxo-piperazine-1-carboxamide;
(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)morpholine-4-carboxamide;
4-acetyl-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methylsulfonyl-piperazine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-sulfamoyl-piperazine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide;
(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)morpholine-4-carboxamide;
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methoxy-piperidine-1-carboxamide;
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(hydroxymethyl)piperidine-1-carboxamide;

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)azetidine-1-carboxamide;
3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]azetidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,1-dioxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3-dimethyl-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
N1-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1,4-dicarboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxyethyl)-3-oxo-piperazine-1-carboxamide;
4,4-Dicyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)azetidine-1-carboxamide;
(2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid;
methyl (2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylate;
(3S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(hydroxymethyl)piperazine-1-carboxamide;
(3R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(hydroxymethyl)piperazine-1-carboxamide;
(3S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide;
(3R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide;
(1S,4S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide;
(3R)-N1-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1,3-dicarboxamide;
(3S)-N1-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1,3-dicarboxamide;

4-Amino-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide;
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide;
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide;
(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide;
4-Amino-4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide; and
1-acetylimino-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide.

15. A pharmaceutical composition comprising a compound according to any one of paragraphs 1 to 14, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable diluent or carrier.

16. A compound according to any one of paragraphs 1 to 14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to paragraph 15, for use in therapy.

17. A compound according to any one of paragraphs 1 to 14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to paragraph 15, for use:

(i) in the treatment of a proliferative condition;

(ii) in the treatment of cancer;

(iii) in the treatment of cancer, wherein the compound or pharmaceutical composition is administered in combination with one or more additional anticancer agents;

(iv) in the treatment of cancer, wherein the compound or pharmaceutical composition is administered in combination with one or more additional anticancer agents selected from the group consisting of:

other forms of cancer immunotherapy and anti-cancer chemotherapeutic agents;
A2b antagonists;
anti-PD-1 and PDL-1 antibodies (e.g. pembrolizumab, nivolumab, durvalumab, avelumab and atezolizumab); and
anti-CTLA4 antibodies (e.g ipilimumab).

18. A method of treating a proliferative disorder in a patient in need of such treatment, the method comprising administering a therapeutically effective amount of a compound according

to any one of paragraphs 1 to 14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to paragraph 15.

19. A method of treating cancer in a patient in need of such treatment, the method comprising administering a therapeutically effective amount of a compound according to any one of paragraphs 1 to 14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to paragraph 15.

20. A method of treating a proliferative disorder in a patient in need of such treatment, the method comprising administering a therapeutically effective amount of a compound according to any one of paragraphs 1 to 14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to paragraph 15 in combination with one or more additional anticancer agents.

21. A method according to paragraph 20, wherein the one or more additional anticancer agents is selected from:

other forms of cancer immunotherapy and anti-cancer chemotherapeutic agents;

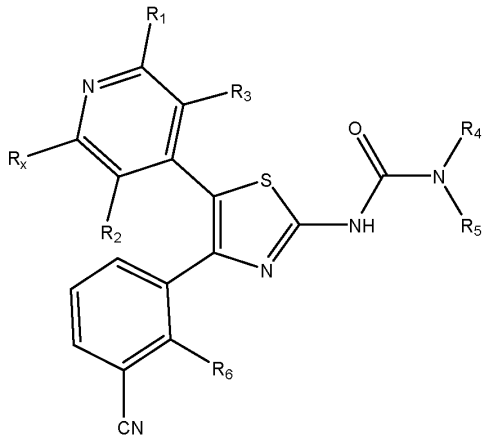
A2b antagonists;

anti-PD-1 and PDL-1 antibodies (e.g. pembrolizumab, nivolumab, durvalumab, avelumab and atezolizumab); and

anti-CTLA4 antibodies (e.g ipilimumab).

CLAIMS

1. A compound, or pharmaceutically acceptable salt thereof, having the structural formula I shown below:



I

wherein:

R_x is selected from methyl, CD_3, chloro and CF_3;

R_1 is selected from (1-3C)alkyl, halo, (1-3C)haloalkyl, (1-3C)haloalkoxy, (1-3C)hydroxyalkyl, cyano, cyclopropyl, oxetan-3-yl, $-(CR_{1C}R_{1D})_{q1}-OR_{1A}$, $-(CR_{1C}R_{1D})_{q1}-C(O)R_{1A}$, $-(CR_{1C}R_{1D})_{q1}-C(O)OR_{1A}$, $-(CR_{1C}R_{1D})_{q1}-OC(O)R_{1A}$, $-(CR_{1C}R_{1D})_{q1}-C(O)N(R_{1B})R_{1A}$, $-(CR_{1C}R_{1D})_{q1}-N(R_{1B})C(O)R_{1A}$, $-(CR_{1C}R_{1D})_{q1}-S(O)_pR_{1A}$ (where p is 0, 1 or 2), $-(CR_{1C}R_{1D})_{q1}-SO_2N(R_{1B})R_{1A}$, or $-(CR_{1C}R_{1D})_{q1}-N(R_{1B})SO_2R_{1A}$,

wherein q1 is 0, 1, or 2; and

wherein R_{1A} and R_{1B} are each independently selected from hydrogen, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkyl(1-2C)alkyl;

wherein R_{1C} and R_{1D} are each independently selected from hydrogen or (1-2C)alkyl;

R_2 and R_3 are both hydrogen or one of R_2 and R_3 is hydrogen and the other is selected from fluoro, methyl or methoxy;

R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups,

wherein R_{10C} is selected from oxo, thioxo, halo, or cyano substituents, or a group of the formula:

$$-[CR_{7a}R_{7b}]_n-L-Z$$

wherein

n is 0 to 6;

R_{7a} and R_{7b} are each independently selected from hydrogen, fluoro or (1-2C)alkyl;

L is absent or selected from -O-, -S-, -SO-, -SO_2-, -N(R_a)-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_a)-, -N(R_a)C(O)-, -N(R_a)C(O)N(R_b)-, -C(S)N(R_a)-, -N(R_a)C(S)-, -N(R_a)C(S)N(R_b)-, -$S(O)_2$N(R_a)-, or -N(R_a)SO_2-, wherein R_a and R_b are each independently selected from hydrogen or (1-2C)alkyl; and

Z is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, aryl, aryl(1-2C)alkyl, heterocyclyl, heterocyclyl(1-2C)alkyl, heteroaryl or heteroaryl(1-2C)alkyl; and wherein Z is optionally substituted by one or more substituents selected from (1-6C)alkyl, halo, (1-6C)haloalkyl, (1-6C)haloalkoxy, cyano, nitro, -NR_cR_d, -OR_c, -C(O)R_c, -C(O)OR_c, -OC(O)R_c, -C(O)N(R_c)R_d, -N(R_c)C(O)R_d, -$S(O)_yR_c$ (where y is 0, 1 or 2), -SO_2N(R_c)R_d, -N(R_c)SO_2R_d, -$(CH_2)_zNR_cR_d$ (where z is 1, 2 or 3) or oxo,

wherein any alkyl moiety in a substituent group on Z is optionally further substituted by cyano, halo, hydroxy, amino, oxo, (1-2C)alkyl or (1-2C)alkoxy and R_c and R_d are each independently selected from hydrogen, (1-6C)alkyl, (1-6C)haloalkyl or (3-6C)cycloalkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N},

wherein R_{10N} is -$S(O)_2NH_2$ or selected from:

(i) –Z_1;

(ii) –L_{1a}–Z_1; or

(iii) –[$CR_{8a}R_{8b}$]$_{1-6}$–L_{1b}–Z_1;

wherein

R_{2a} and R_{2b} are each independently selected from hydrogen, fluoro or (1-2C)alkyl;

L_{1a} is selected from -C(O)-, -$S(O)_2$-, -C(O)O-, -C(O)N(R_{a1})-, -$S(O)_2$N(R_{a1})- or -N(R_{a1})-, wherein R_{a1} is selected from hydrogen or (1-2C)alkyl;

L_{1b} is absent or selected from -O-, -S-, -SO-, -SO_2-, -N(R_{a2})-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{a2})-, -N(R_{a2})C(O)-, -N(R_{a2})C(O)N(R_{b2})-, -C(S)N(R_{a2})-, -N(R_{a2})C(S)-, -N(R_{a2})C(S)N(R_{b2})-, -$S(O)_2$N(R_{a2})-, or -N(R_{a2})SO_2, wherein R_{a2} and R_{b2} are each independently selected from hydrogen or (1-2C)alkyl; and

Z_1 is selected from (1-6C)alkyl, (3-6C)cycloalkyl, aryl, heterocyclyl, heteroaryl, (3-6C)cycloalkyl(1-2C)alkyl, aryl(1-2C)alkyl, heterocyclyl(1-2C)alkyl or heteroaryl(1-2C)alkyl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-6C)alkyl, halo, (1-6C)haloalkoxy, cyano, nitro, -

NR_eR_f, $-OR_e$, $-C(O)R_e$, $-C(O)OR_e$, $-OC(O)R_e$, $-C(O)N(R_e)R_f$, $-N(R_e)C(O)R_f$, $-S(O)_yR_e$ (where y is 0, 1 or 2), $-SO_2N(R_e)R_f$, $-N(R_e)SO_2R_f$, $-(CH_2)_zNR_eR_f$ (where z is 1, 2 or 3) or oxo, and wherein R_e and R_f are each independently selected from hydrogen, (1-6C)alkyl, (1-6C)haloalkyl or (3-6C)cycloalkyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, (1-3C)alkyl or (2-3C)alkanoyl; and

R_6 is selected from hydrogen, halo, methyl, methoxy and trifluoromethyl.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_x is selected from methyl or CD_3.

3. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from (1-3C)alkyl, halo, (1-3C)haloalkyl, (1-3C)haloalkoxy, (1-3C)hydroxyalkyl, cyano, cyclopropyl, oxetan-3-yl, $-(CH_2)_{q1}-OR_{1A}$ and $-(CH_2)_{q1}-C(O)R_{1A}$;

wherein q1 is 0 or 1; and

wherein R_{1A} is selected from hydrogen or (1-2C)alkyl.

4. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from methyl, CD_3, isopropyl, halo, (1-3C)hydroxyalkyl, cyano, cyclopropyl, oxetan-3-yl, -OMe, $-CH_2F$, $-CHF_2$ or $-CF_3$

5. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_2 and R_3 are both hydrogen or one of R_2 and R_3 is hydrogen and the other is fluoro or methyl.

6. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_2 and R_3 are both hydrogen.

7. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups,

wherein R_{10C} is selected from oxo, halo, or cyano substituents, or a group of the formula:

$$–[CH_2]_n–L–Z$$

wherein

n is 0 to 2;

L is absent or selected from -O-, -S-, -SO-, -SO_2-, -N(R_{a2})-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{a2})-, -N(R_{a2})C(O)-, -N(R_{a2})C(O)N(R_{b2})-, -$S(O)_2$N(R_{a2})-, or -N(R_{a2})SO_2-, wherein R_{a2} and R_{b2} are each independently selected from hydrogen or methyl; and

Z is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, aryl, heterocyclyl or heteroaryl; and wherein Z is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkyl, (1-2C)haloalkoxy, cyano, -NR_cR_d, -OR_c, -C(O)R_c, -C(O)OR_c, -OC(O)R_c, -C(O)N(R_c)R_d, -N(R_c)C(O)R_d, -$S(O)_yR_c$ (where y is 0, 1 or 2), -SO_2N(R_c)R_d, -N(R_c)SO_2R_d, -$(CH_2)_z$N$R_c$$R_d$ (where z is 1 or 2) or oxo;

wherein any alkyl moiety in a substituent group on Z_1 is optionally further substituted by cyano, halo, hydroxy, amino, oxo, (1-2C)alkyl or (1-2C)alkoxy and R_c and R_d are each independently selected from hydrogen, (1-2C)alkyl, (1-2C)haloalkyl or (3-6C)cycloalkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is -$S(O)_2NH_2$ or selected from:

(i) –Z_1;

(ii) –L_{1a}–Z_1; or

(iii) –[$CR_{8a}R_{8b}$]$_{1-2}$–L_{1b}–Z_1;

wherein

R_{2a} and R_{2b} are both hydrogen;

L_{1a} is selected from -C(O)-, -$S(O)_2$- or -$S(O)_2$N(R_{a1})-, wherein R_{a1} is hydrogen or methyl;

L_{1b} is absent or selected from -O-, -S-, -SO-, -SO_2-, -N(R_{a2})-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{a2})-, -N(R_{a2})C(O)-, -N(R_{a2})C(O)N(R_{b2})-, -$S(O)_2$N(R_{a2})-, or

$-N(R_{a2})SO_2$, wherein R_{a2} and R_{b2} are each independently selected from hydrogen or methyl; and

Z_1 is selected from (1-6C)alkyl, (3-6C)cycloalkyl, aryl, heterocyclyl, heteroaryl, (3-6C)cycloalkyl(1-2C)alkyl or aryl(1-2C)alkyl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkoxy, cyano, nitro, $-NR_eR_f$, $-OR_e$, $-C(O)R_e$, $-C(O)OR_e$, $-OC(O)R_e$, $-C(O)N(R_e)R_f$, $-N(R_e)C(O)R_f$, $-S(O)_yR_e$ (where y is 0, 1 or 2), $-SO_2N(R_e)R_f$, $-N(R_e)SO_2R_f$, $-(CH_2)_zNR_eR_f$ (where z is 1, 2 or 3) or oxo, and wherein R_e and R_f are each independently selected from hydrogen or (1-2C)alkyl;

and wherein any S atoms present in the heterocyclic ring may optionally be present as S(=O), $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, (1-2C)alkyl or (2C)alkanoyl.

8. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups,

wherein R_{10C} is selected from oxo, halo, or cyano substituents, or a group of the formula:

$$–[CH_2]_n–L–Z$$

wherein

n is 0 to 2;

L is absent or selected from -O-, -S-, -SO-, $-SO_2-$, $-N(R_a)-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_a)-$, $-N(R_a)C(O)-$, $-S(O)_2N(R_a)-$, or $-N(R_a)SO_2-$, wherein R_a and R_b are hydrogen; and

Z is selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, phenyl, a 4-7 membered heterocyclyl or a 5 or 6-membered heteroaryl; and wherein Z is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkyl, (1-2C)haloalkoxy, cyano, $-NR_cR_d$, $-OR_c$, $-C(O)R_c$, $-C(O)N(R_c)R_d$, $-N(R_c)C(O)R_d$ or $-S(O)_yR_c$ (where y is 0, 1 or 2) or oxo;

wherein R_c and R_d are each independently selected from hydrogen or (1-2C)alkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is $-S(O)_2NH_2$ or selected from:

(i) $–Z_1$;

(ii) $–L_{1a}–Z_1$; or

(iii) $–[CR_{8a}R_{8b}]_{1-2}–L_{1b}–Z_1$;

wherein

R_{2a} and R_{2b} are both hydrogen;

L_{1a} is selected from $-C(O)-$, $-S(O)_2-$ or $-S(O)_2N(R_{a1})-$, wherein R_{a1} is hydrogen;

L_{1b} is absent or selected from $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-N(R_{a2})-$, $-C(O)N(R_{a2})-$, $-N(R_{a2})C(O)-$, $-S(O)_2N(R_{a2})-$ or $-N(R_{a2})SO_2$, wherein R_{a2} is hydrogen; and

Z_1 is selected from (1-4C)alkyl, phenyl, a 4-7 membered heterocyclyl or a 5 or 6-membered heteroaryl, with the proviso that when Z_1 is a heterocyclyl group directly linked to a N atom it is a carbon-linked heterocyclyl; and wherein Z_1 is optionally substituted by one or more substituents selected from (1-2C)alkyl, halo, (1-2C)haloalkoxy, cyano, $-NR_eR_f$, $-OR_e$, $-C(O)R_e$, $-C(O)N(R_e)R_f$, $-N(R_e)C(O)R_f$, $-S(O)_yR_e$ (where y is 0, 1 or 2); and wherein R_e and R_f are each independently selected from hydrogen or methyl;

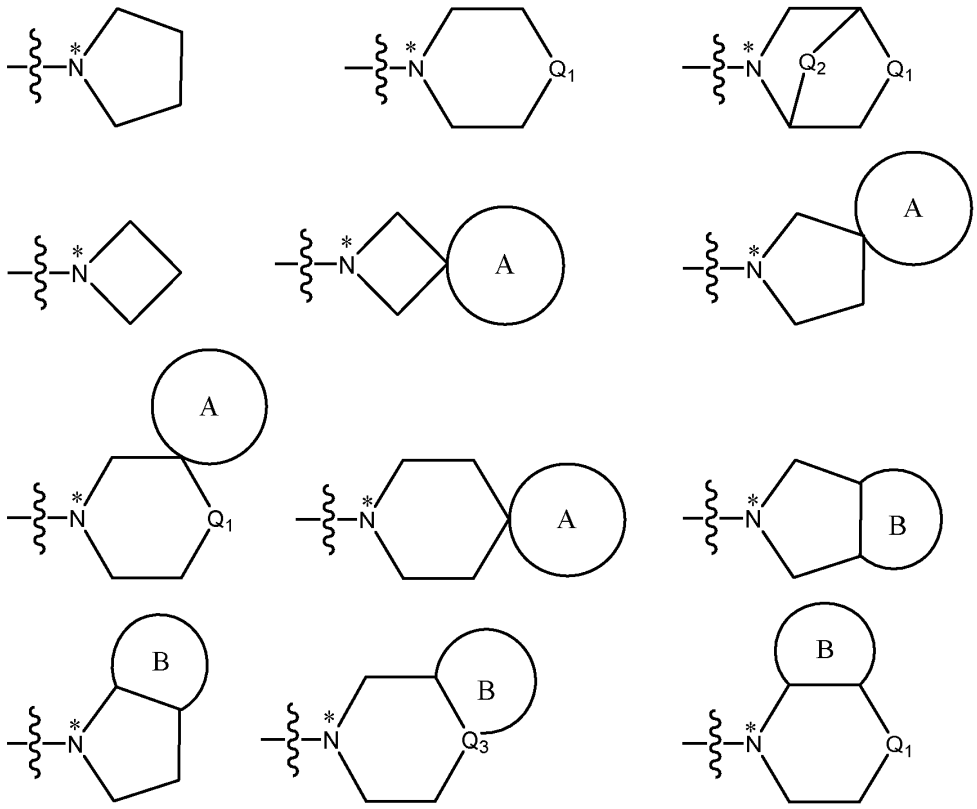
and wherein any S atoms present in the heterocyclic ring may optionally be present as $S(=O)$, $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, (1-2C)alkyl or (2C)alkanoyl.

9. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form heterocyclic ring which is optionally substituted on any available carbon atom by one or more R_{10C} substituent groups, wherein R_{10C} is selected from oxo, halo, cyano, (1-4C)alkyl or (3-6C)cycloalkyl;

and wherein any available N atoms are optionally in the form of a N-oxide or are optionally substituted by one or more R_{10N}, wherein R_{10N} is $-S(O)_2NH_2$ or (1-4C)alkyl,

and wherein any S atoms present in the heterocyclic ring may optionally be present as $S(=O)$, $S(=O)_2$ or $S(=O)(=NR_e)$ wherein R_e is selected from hydrogen, methyl or (2C)alkanoyl.

10. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



wherein * denotes the N atom to which R_4 and R_5 are attached;

Q_1 is O, NH, S, S(O), $S(O)_2$, S(O)(=NR_e), N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_2 is -CH_2-, -CHR_{10C}-, -$C(R_{10c})_2$-, -CHR_{10C}-CH_2-, -CH_2-CHR_{10C}-, -CHR_{10C}-CHR_{10C}-, -$C(R_{10c})_2$-CH_2-, or -CH_2-$C(R_{10c})_2$-;

Q_3 is CH, CR_{10C} or N;

Ring A is a spiro-fused 4, 5 or 6 membered carbocyclic or heterocyclic ring;

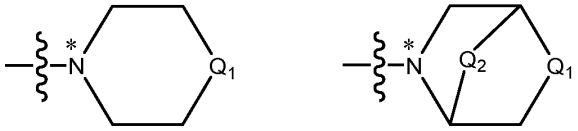
Ring B is a fused 4, 5 or 6 membered carbocyclic or heterocyclic ring;

wherein R_e is selected from hydrogen, (1-2C)alkyl or (2C)alkanoyl;

and wherein each of the heterocyclic ring systems is optionally substituted with one or more R_{10c} or R_{10N} substituent groups as defined in any one of claims 1, 6, 7 or 8.

11. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are linked such that, together with the nitrogen

atom to which they are attached, they form a heterocyclic ring selected from any one of the following options:



wherein * denotes the N atom to which R_4 and R_5 are attached;

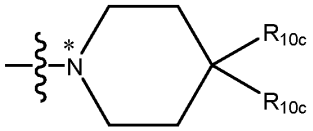
Q_1 is O, NH, S, S(O), $S(O)_2$, $S(O)(=NR_e)$, N-R_{10N}, CH_2, CHR_{10C} or $C(R_{10c})_2$;

Q_2 is -CH_2-;

wherein R_e is selected from hydrogen, methyl, or (2C)alkanoyl;

and R_{10c} or R_{10N} are as defined in any one of claims 1, 6, 7 or 8.

12. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring of the structure:



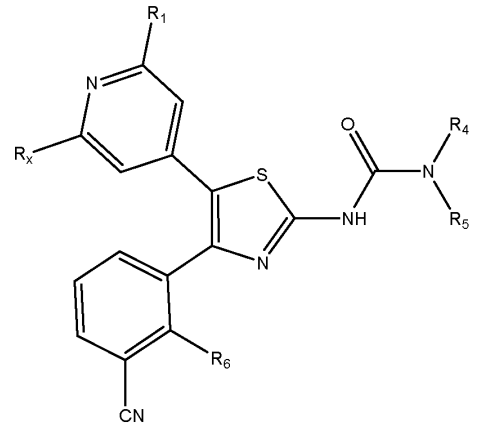
wherein * denotes the N atom to which R_4 and R_5 are attached;

and each R_{10c} is independently selected from the options defined in any one of claims 1, 6 , 7 or 8 above.

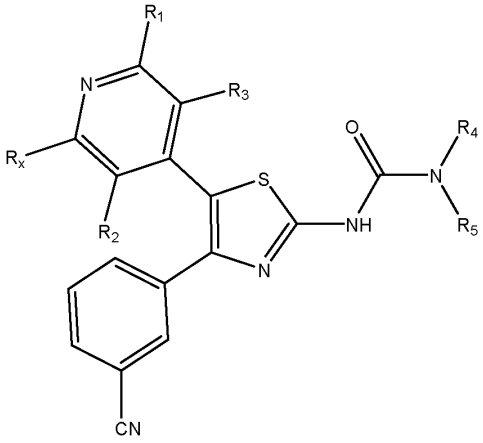
13. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_6 is selected from hydrogen, halo or methyl.

14. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_6 is hydrogen.

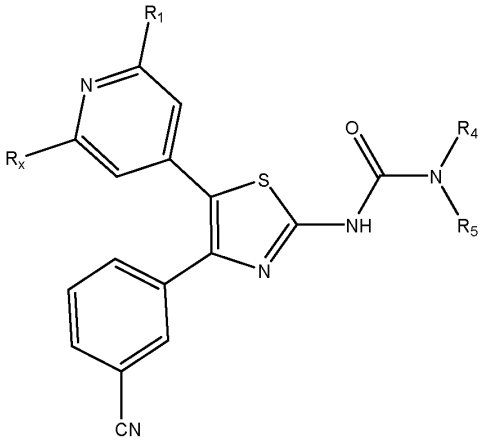
15. A compound of the formula IA, IB or IC:



IA



IB



IC

wherein R_x, R_1, R_2, R_3, R_4, R_5 and R_6 are each as defined in any one of claims 1 to 12;

16. A compound, or a pharmaceutically acceptable salt thereof, selected from any one of the following:

N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]morpholine-4-carboxamide
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide
(2R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1-carboxamide
(3R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]pyrrolidine-1-carboxamide
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-(2-hydroxy-2-methyl-propyl)pyrrolidine-1-carboxamide
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)morpholine-4-carboxamide
(2S)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-methyl-piperazine-1-carboxamide
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-hydroxy-4-methyl-piperidine-1-carboxamide
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-cyano-4-methyl-piperidine-1-carboxamide
(3S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperazine-1-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide

(3R)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-piperazine-1-carboxamide
N4-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]morpholine-2,4-dicarboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-3-oxo-piperazine-1-carboxamide
(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)morpholine-4-carboxamide
4-acetyl-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methylsulfonyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-sulfamoyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)morpholine-4-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methoxy-piperidine-1-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(hydroxymethyl)piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)azetidine-1-carboxamide
3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,1-dioxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3-dimethyl-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide

N1-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1,4-dicarboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxyethyl)piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxyethyl)-3-oxo-piperazine-1-carboxamide
4,4-dicyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxy-2-methyl-propyl)piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-methyl-1,7-diazaspiro[3.4]octane-7-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-hydroxy-1,1-dimethyl-ethyl)piperazine-1-carboxamide
(8aS)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxamide
(8aR)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide
(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-pyrrolidine-1-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(methoxymethyl)piperidine-1-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-fluoro-piperidine-1-carboxamide
(3S)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-3-methyl-azetidine-1-carboxamide
(2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylic acid
methyl (2R)-4-[[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]carbamoyl]piperazine-2-carboxylate

(3S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(hydroxymethyl)piperazine-1-carboxamide
(3R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-(hydroxymethyl)piperazine-1-carboxamide
(3S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide
(3R)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide
(1S,4S)-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide
(3R)-N1-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1,3-dicarboxamide
(3S)-N1-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]piperazine-1,3-dicarboxamide
4-amino-N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide
(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methylsulfonyl-pyrrolidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-7-azaspiro[3.5]nonane-7-carboxamide
N-[5-(2-chloro-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
(1R,4R)-5-acetyl-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide
(1S,4S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
N-[5-[2,6-bis(trideuteriomethyl)-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
(4aS,7aR)-N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxamide

N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-9-methyl-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxamide
(4aS,7aS)-N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
3-cyano-N-[4-(3-cyanophenyl)-5-[2-methyl-6-(oxetan-3-yl)-4-pyridyl]thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-[2-methyl-6-(oxetan-3-yl)-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-morpholino-azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-tetrahydropyran-4-yl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-pyrrolidin-1-yl-azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(dimethylamino)azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(morpholinomethyl)piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-3,6-diazabicyclo[3.2.0]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,4-diazabicyclo[3.2.1]octane-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-5,6,8,8a-tetrahydro-1H-oxazolo[3,4-a]pyrazine-7-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,2-dioxo-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]thiazine-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-oxo-3,6,7,8,9,9a-hexahydro-1H-pyrido[1,2-a]pyrazine-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-9-oxo-3,4,6,7,8,9a-hexahydro-1H-pyrazino[1,2-a]pyrazine-2-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-1,3,4,8,9,9a-hexahydropyrazino[1,2-c][1,3]oxazine-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-1,3,4,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-2-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-sulfamoyl-pyrrolidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-2,7-diazaspiro[3.5]nonane-7-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-pyrazol-1-yl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(1,2,4-oxadiazol-3-yl)piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3-dioxo-5,6,8,8a-tetrahydroimidazo[1,5-a]pyrazine-7-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-2,8-diazaspiro[4.5]decane-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(1H-imidazol-2-yl)piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-10-oxo-3,9-diazaspiro[5.5]undecane-3-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxamide
N1-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-N4-methyl-piperidine-1,4-dicarboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide
(3S)-N1-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1,3-dicarboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(2-oxoimidazolidin-1-yl)piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-methylimino-1-oxo-1,4-thiazinane-4-carboxamide

N1-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-N4-(2-hydroxyethyl)piperidine-1,4-dicarboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-7-oxa-2,5-diazaspiro[3.5]nonane-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6,9-dioxo-1,3,4,7,8,9a-hexahydropyrazino[1,2-a]pyrazine-2-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-oxo-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-3-oxo-2,8-diazaspiro[4.5]decane-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-8-methyl-6,9-dioxo-3,4,7,9a-tetrahydro-1H-pyrazino[1,2-a]pyrazine-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-2,8-diazaspiro[4.5]decane-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-2,9-diazaspiro[5.5]undecane-9-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-(1-hydroxy-1-methyl-ethyl)piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-3,4,7,8,9,9a-hexahydro-1H-pyrazino[1,2-c]pyrimidine-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-3,4,7,8,9,9a-hexahydro-1H-pyrido[1,2-a]pyrazine-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-hydroxy-6-methyl-2-azaspiro[3.3]heptane-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-1,8-diazaspiro[4.5]decane-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,2-dioxo-2λ^{6}-thia-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)morpholine-4-carboxamide
(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide
(3aR,6aS)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrole-5-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-3-oxa-1,9-diazaspiro[5.5]undecane-9-carboxamide
(1S,5S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-methyl-3,6-diazabicyclo[3.2.2]nonane-3-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-methyl-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
(3aS,6aS)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxa-2-azaspiro[3.4]octane-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-7-oxa-2-azaspiro[3.5]nonane-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-2,7-diazaspiro[3.4]octane-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxo-2,5,7-triazaspiro[3.4]octane-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxo-1,9-diazaspiro[5.5]undecane-9-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5-oxo-2,6-diazaspiro[3.4]octane-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-ethyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide
1-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]piperidine-4-carboxylic acid
(3S)-1-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]pyrrolidine-3-carboxylic acid
3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)azetidine-1-carboxamide
(3R)-1-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]pyrrolidine-3-carboxylic acid

4-cyano-N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-hydroxy-3-methyl-azetidine-1-carboxamide
3-cyano-N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-oxo-2,7-diazaspiro[3.5]nonane-7-carboxamide
3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-azetidine-1-carboxamide
1-[[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]carbamoyl]azetidine-3-carboxylic acid
(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)pyrrolidine-1-carboxamide
(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-azetidine-1-carboxamide
(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)azetidine-1-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-morpholine-4-carboxamide
(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxamide
(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)morpholine-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-1-oxo-2,8-diazaspiro[4.5]decane-8-carboxamide
(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-azetidine-1-carboxamide
N-[4-(3-cyano-2-methyl-phenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
(3R)-N1-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]pyrrolidine-1,3-dicarboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-oxa-7-azaspiro[3.4]octane-7-carboxamide

(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)azetidine-1-carboxamide
(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(1-hydroxy-1-methyl-ethyl)azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-morpholino-pyrrolidine-1-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-5-oxo-piperazine-1-carboxamide
(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-morpholine-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxa-1-azaspiro[3.3]heptane-1-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(hydroxymethyl)morpholine-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1,3-dimethyl-2-oxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methylsulfonyl-pyrrolidine-1-carboxamide
(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-5-oxo-piperazine-1-carboxamide
(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)azetidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-methyl-5-oxo-2,6-diazaspiro[3.4]octane-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-methyl-2-oxo-1,8-diazaspiro[4.5]decane-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methylsulfonyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-hydroxy-4-methyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
(4aR,7aS)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxamide

N-[4-(3-cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5,8-diazaspiro[3.5]nonane-5-carboxamide
trans-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-dimethyl-piperazine-1-carboxamide
4-amino-4-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,6-diazabicyclo[3.1.1]heptane-6-carboxamide
(1R,4R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide
cis-(2S,5S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,5-dimethyl-piperazine-1-carboxamide
(2R,6R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,6-dimethyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2,2-dimethyl-piperazine-1-carboxamide
1-acetylimino-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3-oxo-2,7-diazaspiro[3.5]nonane-7-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3-(1-hydroxy-1-methyl-ethyl)pyrrolidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-(oxetan-3-yl)piperazine-1-carboxamide

N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-1,3-dimethyl-2,4-dioxo-1,3,8-triazaspiro[4.5]decane-8-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]piperidine-1-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-(hydroxymethyl)piperidine-1-carboxamide
4,4-dicyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]piperidine-1-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methoxy-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(3-fluoro-2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
1-cyanoimino-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-[2-(1-hydroxy-1-methyl-ethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(1-hydroxy-1-methyl-ethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-6-oxa-2-azaspiro[3.4]octane-2-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(1-hydroxy-1-methyl-ethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(1-hydroxyethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
rac-(3S,5R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,5-dimethyl-piperazine-1-carboxamide
(3S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(trifluoromethyl)piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-(trifluoromethyl)piperazine-1-carboxamide
(3S)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide

(3R)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4,7-diazaspiro[2.5]octane-7-carboxamide
(3S,5S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,5-dimethyl-piperazine-1-carboxamide
(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-piperazine-1-carboxamide
(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)piperazine-1-carboxamide
(2S)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(hydroxymethyl)piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxamide
(2R)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-methyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-9-oxa-2,6-diazaspiro[4.5]decane-2-carboxamide
(3R)-N-[4-(3-cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-3-methyl-piperazine-1-carboxamide
(4aS,7aS)-N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxamide
(4aS,7aR)-N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxamide
rac-(4aS,7aS)-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-cyclopropyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-2-(cyclopropylmethyl)piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3,3-dimethyl-piperazine-1-carboxamide
N-[4-(3-cyanophenyl)-5-(2-methoxy-6-methyl-4-pyridyl)thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(difluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-1-imino-1-oxo-1,4-thiazinane-4-carboxamide

N-[4-(3-cyanophenyl)-5-(2,6-dichloro-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-methyl-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-(2-methoxy-6-methyl-4-pyridyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-[2-methyl-6-(oxetan-3-yl)-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[5-(2-cyano-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-1-oxo-1,4-thiazinane-4-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(fluoromethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2-cyclopropyl-6-methyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2-isopropyl-6-methyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2-ethyl-6-methyl-4-pyridyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-1-oxido-pyridin-1-ium-4-yl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
4-cyano-N-[4-(3-cyano-2-methyl-phenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-4-methyl-piperidine-1-carboxamide
N-[5-(2-acetamido-6-methyl-4-pyridyl)-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[5-[2-(acetamidomethyl)-6-methyl-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(methoxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(1-methoxyethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[5-[2-chloro-6-(1-hydroxy-1-methyl-ethyl)-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
4-cyano-N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]thiazol-2-yl]-4-methyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-[2-(hydroxymethyl)-6-(trifluoromethyl)-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide

3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide
N-[5-[2,6-bis(trideuteriomethyl)-4-pyridyl]-4-(3-cyanophenyl)thiazol-2-yl]-4-cyano-4-methyl-piperidine-1-carboxamide
N-[4-(3-cyanophenyl)-5-[2-[(1R)-1-hydroxyethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
N-[4-(3-cyanophenyl)-5-[2-[(1S)-1-hydroxyethyl]-6-methyl-4-pyridyl]thiazol-2-yl]-2-oxa-6-azaspiro[3.3]heptane-6-carboxamide
(3R)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide
(3S)-3-cyano-N-[4-(3-cyanophenyl)-5-(2,6-dimethyl-4-pyridyl)thiazol-2-yl]-3-methyl-pyrrolidine-1-carboxamide.

17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable diluent or carrier.

18. A compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 17, for use in therapy.

19. A compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 17, for use:
(i) in the treatment of a proliferative condition;
(ii) in the treatment of cancer;
(iii) in the treatment of cancer, wherein the compound or pharmaceutical composition is administered in combination with one or more additional anticancer agents;
(iv) in the treatment of cancer, wherein the compound or pharmaceutical composition is administered in combination with one or more additional anticancer agents selected from the group consisting of:

1) other forms of cancer immunotherapy and anti-cancer chemotherapeutic agents;
2) adenosine pathway modulators, including, but not limited to A2b antagonists, CD73 inhibitors and CD39 inhibitors;
3) anti-PD-1 and PDL-1 antibodies (e.g. cetrelimab, pembrolizumab, nivolumab, durvalumab, avelumab and atezolizumab); and
4) anti-CTLA4 antibodies (e.g ipilimumab).

20. A method of treating a proliferative disorder in a patient in need of such treatment, the method comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 17.

21. A method of treating cancer in a patient in need of such treatment, the method comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 17.

22. A method of treating a proliferative disorder in a patient in need of such treatment, the method comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 17 in combination with one or more additional anticancer agents.

23. A method according to claim 21, wherein the one or more additional anticancer agents is selected from:

1) other forms of cancer immunotherapy and anti-cancer chemotherapeutic agents;
2) adenosine pathway modulators, including, but not limited to A2b antagonists, CD73 inhibitors and CD39 inhibitors;
3) anti-PD-1 and PDL-1 antibodies (e.g. cetrelimab, pembrolizumab, nivolumab, durvalumab, avelumab and atezolizumab); and
4) anti-CTLA4 antibodies (e.g ipilimumab).