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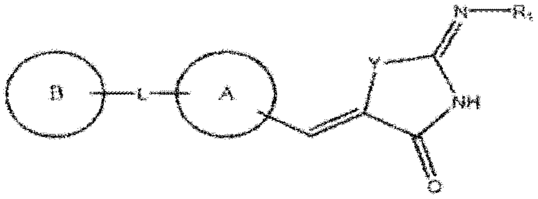
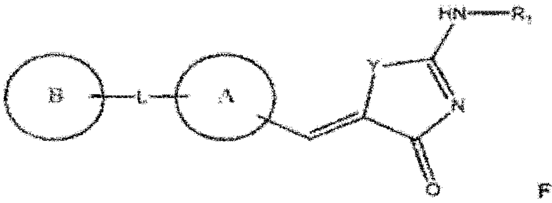
(58) Field of Search:
Other: **CAS ONLINE**

(54) Title of the Invention: **PIM kinase inhibitors**
Abstract Title: **Substituted heterocyclic compounds and their use as PIM kinase inhibitors**

(57) A compound of formula I or II or a salt, hydrate or solvate thereof:



Formula I



Formula II

wherein R_1 is hydrogen or a substituent; Y is sulfur or NR_b where R_b is hydrogen or (1-3C)alkyl; ring A is either (i) an optionally substituted 5-membered heteroaryl ring comprising a nitrogen atom and one or more heteroatoms selected from nitrogen, oxygen and sulfur, or (ii) an optionally substituted 5-membered heteroaryl ring; L is a chain linker or is absent; ring B is optionally substituted and is selected from (4-7C)cycloalkyl, heteroaryl, heterocyclyl and aryl. Preferably, Y is sulfur, ring A is selected from 1,3-thiazolyl, 1,3-oxazolyl and pyridyl, L is either absent or is –N(Me)C(O)- and ring B is selected from optionally substituted phenyl and substituted pyridyl. The compounds of formula I or II inhibit PIM (Proviral Integration site for the Moloney murine leukemia virus) kinase and may be useful in the treatment and/or prevention of proliferative disorders, such as cancer.

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PIM KINASE INHIBITORS

FIELD OF THE INVENTION

[0001] The present invention relates to compounds which inhibit PIM (Proviral Integration site for the Moloney murine leukemia virus) Kinase. The compounds of the present invention are therefore potentially useful therapeutic agents for the treatment and/or prevention of proliferative disorders, such as cancer, in which PIM kinase activity is implicated. The present invention also relates to processes for preparing said compounds, to pharmaceutical compositions comprising them and to the therapeutic uses of these compounds.

BACKGROUND OF THE INVENTION

[0002] Proliferative disorders, such as cancer, are caused by uncontrolled and unregulated cellular proliferation. Precisely what causes a cell to become malignant and proliferate in an uncontrolled and unregulated manner has been the focus of intense research over recent decades. This research has led to the identification of numerous tumour-specific or tumour-associated targets, which can then be targeted by anticancer agents.

[0003] Of particular therapeutic relevance are protein kinases which regulate most, if not all, signalling pathways within the cellular environment. The human protein kinase family contains more than 500 members which perform this regulatory function. Currently, over 200 kinase inhibitors are in clinical trials for a range of therapeutic utilities, and a growing number of inhibitors are now used in clinical practice. Apart from a few exceptions, the pharmaceutical and biotech industries have focused on the development of tyrosine kinase inhibitors, and the majority of approved inhibitors target receptor tyrosine kinases. Serine / threonine kinases comprise the largest kinase family (~400 targets) and represent a significant set of targets for the treatment of cancer. The inventors recognised a need to provide a series of compounds which are designed to target the protein kinases of the PIM (Proviral Integration site for the Moloney murine leukemia virus) family, since they play a pivotal role in the development of haematopoietic malignancies as well as in prostate cancer, and there is growing evidence of their role in a number of other malignancies.

[0004] PIM kinases are early target genes of the transcription factor STAT5. PIM1 and PIM2 are overexpressed in leukaemia and lymphoma, as well as some solid cancers and high PIM1 expression levels in prostate cancer have been linked to poor prognosis. In addition, PIM is a target of aberrant somatic hypermutation in diffuse, large-cell lymphomas and T-cell lymphomas are induced in PIM1 transgenic mice and by viral insertions at the PIM1 locus. PIM3 is less well characterised, but is reported to play a role in liver and pancreatic tumours, amongst others.

[0005] Using PIM inhibitors of the imidazopyridazine class, Knapp *et al.* (Cancer Res 2007; 67: (14). July 15, 2007 p6916-6924) were able to show that chemical inhibition of PIM1 specifically reduces cell survival of human leukaemia cell lines in a PIM1 dependent manner and reduces survival and clonogenic growth of primary cells derived from AML patients. This study demonstrated for the first time that inhibition of signalling through PIM1 represents a promising avenue for leukaemia treatment.

[0006] Protein kinases constitute a large protein family, and developing selective inhibitors targeting a largely conserved active site represents a tremendous challenge. A number of approved drugs that inhibit kinases target an inactive state of the catalytic domain (so-called ‘Type II’ inhibitors), and are relatively non-selective. PIM kinases possess a unique ATP binding site; the presence of a proline residue in the kinase hinge region allows for the formation of only one hydrogen bond to ATP or ATP-mimetics. A number of known PIM inhibitors are thought to bind to PIM1 with a unique and unusual binding mode whereby they interact with the opposite site of the ATP binding pocket, Lys67 providing one of the critical binding interactions. This region of the ATP binding site is much more diverse between kinases and suggests the development of highly selective PIM inhibitors may be achievable.

[0007] It is therefore an object of the present invention to provide a compound which selectively inhibits PIM Kinase to thereby provide a therapeutic treatment of proliferative disorders such as cancer.

SUMMARY OF THE INVENTION

[0008] 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.

[0009] According to a second aspect of the present invention, there is provided a pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in admixture with a pharmaceutically acceptable diluent or carrier.

[0010] According to a third aspect of the present invention, there is provided a method of inhibiting PIM Kinase, *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.

[0011] According to a fourth 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 a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein.

[0012] According to a fifth 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, or a pharmaceutical composition as defined herein.

[0013] According to a sixth 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, or a pharmaceutical composition as defined herein.

[0014] According to a seventh 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.

[0015] According to an eighth 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 a proliferative condition.

[0016] According to a ninth 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.

[0017] According to a tenth 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 production of a PIM kinase inhibitory effect.

[0018] According to an eleventh 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 proliferative condition.

[0019] According to a twelth aspect of the present invention, there is provide 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 cancer. Suitably, the medicament is for use in the treatment of human cancers.

[0020] According to a thirteenth 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 in the production of a PIM kinase inhibitory effect.

[0021] According to a fourteenth aspect of the present invention, there is provided provides a process for preparing a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein.

[0022] According to a fifteenth 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.

[0023] According to a sixteenth 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.

[0024] Suitably, the proliferative disorder is cancer, suitably a human cancer.

[0025] 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

[0026] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0027] 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.

[0028] 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.

[0029] 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.

[0030] The term "(m-nC)" or "(m-nC) group" used alone or as a prefix, refers to any group having m to n carbon atoms.

[0031] 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.

[0032] "(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.

[0033] "(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.

[0034] "(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.

[0035] "(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.

[0036] "(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.

[0037] The term "halo" refers to fluoro, chloro, bromo and iodo.

[0038] The term "heterocyclyl", "heterocyclic" or "heterocycle" means a non-aromatic saturated or partially saturated monocyclic, fused, bridged, or spiro bicyclic heterocyclic ring system(s). The term heterocyclyl includes both monovalent species and divalent species. 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 heterocycles contain from about 7 to about 17 ring atoms, suitably from 7 to 12 ring atoms. 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 dihydro-oxathiolyl, tetrahydro-oxazolyl, tetrahydro-oxadiazolyl, tetrahydrodioxazolyl, tetrahydro-oxathiazolyl, hexahydrotriazinyl, tetrahydro-oxazinyl, 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.

[0039] 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.

[0040] “Heterocyclyl(1-6C)alkyl” means a heterocyclyl group covalently attached to a (1-6C)alkylene group, both of which are defined herein.

[0041] The term “heteroaryl” or “heteroaromatic” means an aromatic mono-, bi-, or polycyclic ring incorporating one or more (for example 1-4, 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.

[0042] 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[2,3-b]furanyl, 2H-furo[3,2-b]-pyranyl, 5H-pyrido[2,3-d]-o-oxazinyl, 1H-pyrazolo[4,3-d]-oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, imidazo[1,2-b][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 non-aromatic, 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 and 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl

[0043] 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.

[0044] Examples of six membered heteroaryl groups include but are not limited to pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl and triazinyl.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] “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.

[0049] 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.

[0050] 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.

[0051] 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.

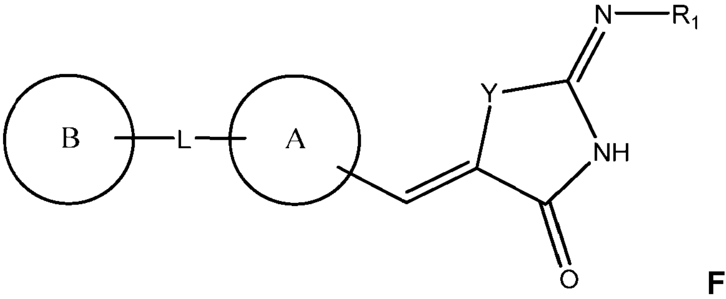
[0052] The term "optionally substituted" refers to either groups, structures, or molecules that are substituted and those that are not substituted.

[0053] 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.

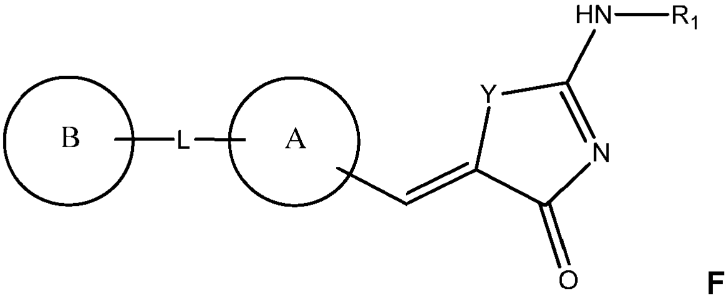
[0054] The phrase “compound of the invention” means those compounds which are disclosed herein, both generically and specifically.

Compounds of the invention

[0055] The present invention provides a compound of Formula I or Formula II:



Formula I



Formula II

wherein:

R_1 is selected from hydrogen or a (1-8C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-4C)alkyl, aryl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, heteroaryl, or heteroaryl(1-3C)alkyl group which is optionally substituted with one or more R_a;

R_a is selected from the group consisting of halogeno, trifluoromethyl, trifluoromethoxy, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, ureido, sulfonylamino, (1-6C)alkyl, (1-6C)hydroxyalkyl, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, (1-6C)haloalkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkoxycarbonyl, (1-6C)alkanoyl, (1-6C)alkanoyloxy, (1-6C)alkyl-$S(O)_n$– wherein n is an integer from 0 to 2, *N'*-((1-6C)alkyl)ureido, *N',N'*-((1-6C)alkyl)$_2$ureido, *N'*-((1-6C)alkyl)-*N*-((1-6C)alkyl)ureido, *N',N'*-((1-6C)alkyl)$_2$-*N*-((1-6C)alkyl)ureido, (1-6C)alkanoylamino, *N*-((1-6C)alkyl)-(1-6C)alkanoylamino, *N*-((1-6C)alkyl)carbamoyl, *N,N*-((1-6C)alkyl)$_2$carbamoyl, (1-6C)alkylsulfonylamino, *N*-((1-6C)alkyl)aminosulfonyl, *N,N*-((1-6C)alkyl)$_2$aminosulfonyl, (1-6C)alkoxycarbonylamino, *N*-((1-6C)alkyl)- (1-6C)alkoxycarbonylamino, (1-6C)alkylsulfonylaminocarbonyl, *N*-((1-6C)alkyl)- (1-6C)alkylsulfonylaminocarbonyl, aryl, aryl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, heteroaryl or heteroaryl(1-3C)alkyl;

Y is S or NR_b, where R_b is selected from hydrogen or (1-3C)alkyl;

Ring A is selected from:

(i) a 5-membered heteroaryl ring comprising a nitrogen atom and one or more other heteroatoms selected from the group consisting of N, O or S; or
(ii) a 6-membered heteroaryl ring;

wherein Ring A is optionally substituted by (1-3C)alkyl, halo, trifluoromethyl, trifluoromethoxy, cyano, -CO-O-R_c (wherein R_c is selected from hydrogen, methyl or ethyl) or -CO-NR_dR_e (wherein R_d and R_e are each independently selected from hydrogen or methyl);

L is absent, -O-, -S-, -CH_2-, -C(O)-, -C(O)NR_f-, -NR_fC(O)-, -NR_f-, -N(R_f)CON(R_g)-, -S(O)-, -SO_2-, -SO_2N(R_f)-, -N(R_f)SO_2-, -P(O)(OR_h)- wherein R_f and R_g are each independently selected from hydrogen or (1-3C)alkyl; and R_h is selected from (1-3C)alkyl, (4-7C)cycloalkyl or aryl;

Ring B is selected from the group consisting of (4-7C)cycloalkyl, heteroaryl, heterocyclyl or aryl,

wherein

(i) Ring B is optionally substituted on the ring atoms adjacent to the ring atom bonded to L (i.e. in the *ortho* position) by halogeno, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, ureido, methyl, methoxy, ethoxy, (1-3C)alkylthio, (1-3C)alkylsulphinyl, (1-3C)alkylsulphonyl, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, *N*-(1-3C)alkylsulphamoyl, *N*,*N*-di-[(1-3C)alkyl]sulphamoyl, (1-3C)alkanesulphonylamino and *N*-(1-3C)alkyl-(1-3C)alkanesulphonylamino; and
(ii) Ring B may be optionally substituted on any other ring atom by halogeno, trifluoromethyl, trifluoromethoxy, SF_5, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, ureido, or a group of the formula:

$$-L^1-Q^1$$

wherein:

L^1 is selected from a direct bond, -CR_iR_j-, -O-, -S-, -SO-, -SO_2-, -N(R_i)-, -C(O)-, -CH(OR_i)-, -C(O)N(R_i)-, -N(R_i)C(O)-, -C(O)O-, -OC(O)-,

-P(O)(R_h)O-, -N(R_i)C(O)N(R_j)-, -S(O)$_2$N(R_i)-, -N(R_i)SO$_2$-, or -N(R_i)-SO$_2$-N(R_j)-, wherein R_i and R_j are each independently selected from hydrogen or (1-4C)alkyl;

Q^1 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-4C)alkyl, aryl, aryl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, heteroaryl or heteroaryl(1-3C)alkyl, each of which is optionally substituted with one or more substituents independently selected from halo, cyano, nitro, hydroxy, amino, trifluoromethyl, trifluoromethoxy, (1-4C)alkyl or (1-4C)alkoxy;

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0056] Suitably the double bond, of Formula I or II between Ring A and the core ring bearing the Y group, is the *Z*-isomer.

[0057] Particular novel compounds of the invention include, for example, compounds of the formula I or formula II, or pharmaceutically acceptable salts thereof, wherein, unless otherwise stated, each of Y, R_1, R_a, R_b, R_c, R_d, R_e, R_f, R_g, R_h, R_i, R_j, L^1, Q^1, Ring A, L, and Ring B has any of the meanings defined hereinbefore or in any of paragraphs (1) to (33) hereinafter:-

(1) Y is S or NH;

(2) Y is S;

(3) Y is NH;

(4) R_1 is selected from hydrogen or a (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, aryl(1-2C)alkyl, heterocyclyl, heterocyclyl(1-2C)alkyl, heteroaryl, or heteroaryl(1-2C)alkyl group which is optionally substituted with one or more R_a, wherein R_a has any one of the definitions set out herein;

(5) R_1 is selected from hydrogen or a (1-8C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-4C)alkyl, aryl(1-3C)alkyl, or heterocyclyl(1-3C)alkyl group which is optionally substituted with one or more R_a, wherein R_a has any one of the definitions set out herein;

(6) R_1 is selected from hydrogen or a (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, aryl(1-2C)alkyl, or heterocyclyl(1-2C)alkyl group which is optionally substituted with one or more R_a, wherein R_a has any one of the definitions set out herein;

(7) R_a is selected from the group consisting of halogeno, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, mercapto, amino, carboxy, carbamoyl, sulfonylamino, (1-3C)alkyl, (1-3C)hydroxyalkyl, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, (1-3C)haloalkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-3C)alkoxy, (1-3C)alkoxycarbonyl, (1-3C)alkanoyl, (1-3C)alkanoyloxy, aryl, aryl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, heteroaryl or heteroaryl(1-3C)alkyl;

(8) R_a is selected from the group consisting of halogeno, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, mercapto, amino, carboxy, carbamoyl, sulfonylamino, (1-3C)alkyl, (1-3C)hydroxyalkyl, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, (1-3C)haloalkyl, (1-3C)alkoxy, (1-3C)alkoxycarbonyl, (1-3C)alkanoyl, (1-3C)alkanoyloxy;

(9) R_a is selected from the group consisting of halogeno, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, mercapto, amino, carboxy, carbamoyl, sulfonylamino, (1-3C)alkyl, (1-3C)hydroxyalkyl, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, (1-3C)alkoxy and (1-3C)alkanoyl;

(10) R_a is selected from the group consisting of hydroxy, (1-6C)alkyl, (1-6C)hydroxyalkyl, (1-3C)alkylamino, and di-[(1-3C)alkyl]amino;

(11) R_a is selected from the group consisting of hydroxy, (1-3C)alkyl, (1-3C)hydroxyalkyl, and di-[methyl]amino;

(12) Ring A is:

(i) a 5-membered heteroaryl ring comprising a nitrogen atom and one other heteroatom selected from the group consisting of O and S; or

(ii) a 6-membered heteroaryl ring;

(13) Ring A is:

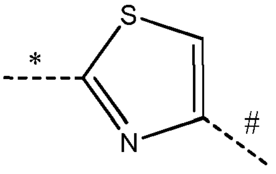
(i) a 5-membered heteroaryl ring comprising a nitrogen atom and one other heteroatom selected from the group consisting of O and S; or

(ii) a pyridyl ring;

(14) Ring A is a 5-membered heteroaryl ring comprising a nitrogen atom and a sulfur atom.

(15) Ring A is a thiazole, oxazole, or pyridyl ring, optionally substituted as described herein;

(16) Ring A is selected from the group including:



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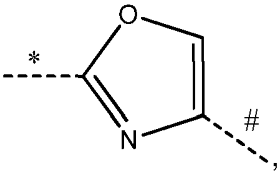
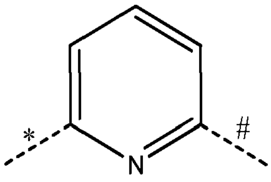
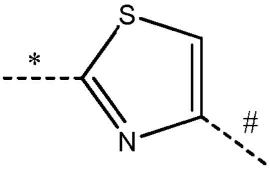


, or



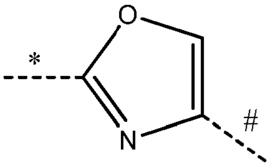
where * indicates the point of attachment to L (or to Ring B if L is absent), and # indicates the point of attachment to the carbon-carbon double bond of formula I or II;

(17) Ring A is:



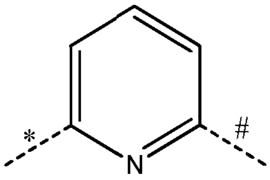
where * indicates the point of attachment to L (or to Ring B if L is absent), and # indicates the point of attachment to the carbon-carbon double bond of formula I or II;

(18) Ring A is:



where * indicates the point of attachment to L (or to Ring B if L is absent), and # indicates the point of attachment to the carbon-carbon double bond of formula I or II;

(19) Ring A is:



where * indicates the point of attachment to L (or to Ring B if L is absent), and # indicates the point of attachment to the carbon-carbon double bond of formula I or II;

(20) L is absent, -O-, -S-, -CH$_2$-, -C(O)-, -C(O)NR$_f$-, -NR$_f$C(O)-, -NR$_f$-, -S(O)-, -SO$_2$-, wherein R$_f$ is independently selected from hydrogen or (1-2C)alkyl;

(21) L is absent, -CH$_2$-, -C(O)NR$_f$- or -NR$_f$C(O)-, wherein R$_f$ is independently selected from hydrogen or methyl;

(22) L is absent;

(23) L is -CH$_2$-;

(24) L is -C(O)NR$_f$- or -NR$_f$C(O)-, wherein R$_f$ is independently selected from hydrogen or methyl;

(25) Ring B is selected from the group consisting of (4-7C)cycloalkyl, 5 or 6-membered heteroaryl and aryl,

wherein

(i) Ring B is optionally substituted on the ring atoms adjacent to the ring atom bonded to L (i.e. in the *ortho* position) by halogeno, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, methyl, methoxy, ethoxy, (1-2C)alkylthio, (1-2C)alkylsulphinyl, (1-2C)alkylsulphonyl, (1-2C)alkylamino, di-[(1-2C)alkyl]amino; and

(ii) Ring B may be optionally substituted on any other ring atom by halogeno, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, mercapto, amino, carboxy, carbamoyl, or a group of the formula:

$$-L^1-Q^1$$

wherein:

L^1 is selected from a direct bond, -O-, -S-, -SO-, $-SO_2-$, $-N(R_i)-$, -C(O)-, $-CH(OR_i)-$, $-C(O)N(R_i)-$, $-N(R_i)C(O)-$, -C(O)O-, -OC(O)-, $-P(O)(R_h)O-$, $-N(R_i)C(O)N(R_j)-$, $-S(O)_2N(R_i)-$, $-N(R_i)SO_2-$, or $-N(R_i)-SO_2-N(R_j)-$, wherein R_i and R_j are each independently selected from hydrogen or (1-4C)alkyl;

Q^1 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-4C)alkyl, aryl, aryl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, heteroaryl or heteroaryl(1-3C)alkyl, each of which is optionally substituted with one or more substituents independently selected from halo, cyano, nitro, hydroxy, amino, trifluoromethyl, trifluoromethoxy, (1-4C)alkyl or (1-4C)alkoxy;

(26) Ring B is selected from the group consisting of (5-6C)cycloalkyl, 5 or 6-membered heteroaryl and phenyl,

wherein

Ring B may be optionally substituted on any ring atom other than those ring atoms in the positions *ortho* to the point of attachment to L by halogeno, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, mercapto, amino, carboxy, carbamoyl, or a group of the formula:

$$-L^1-Q^1$$

wherein:

L^1 is selected from a direct bond, -O-, -S-, -SO-, $-SO_2-$, $-N(R_i)-$, -C(O)-, $-CH(OR_i)-$, $-C(O)N(R_i)-$, $-N(R_i)C(O)-$, -C(O)O-, -OC(O)-, $-P(O)(R_h)O-$, $-N(R_i)C(O)N(R_j)-$, $-S(O)_2N(R_i)-$, $-N(R_i)SO_2-$, or $-N(R_i)-SO_2-N(R_j)-$, wherein R_i and R_j are each independently selected from hydrogen or (1-4C)alkyl;

Q^1 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-4C)alkyl, aryl, aryl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, heteroaryl or heteroaryl(1-3C)alkyl, each of which is optionally substituted with one or more substituents independently selected from halo, cyano, nitro, hydroxy, amino, trifluoromethyl, trifluoromethoxy, (1-4C)alkyl or (1-4C)alkoxy;

(27) Ring B is selected from the group consisting of (5-6C)cycloalkyl, 5 or 6-membered heteroaryl and phenyl,

wherein

Ring B may be optionally substituted on any ring atom other than those ring atoms in the positions *ortho* to the point of attachment to L by halogeno, trifluoromethyl, trifluoromethoxy, hydroxy, or a group of the formula:

$$-L^1-Q^1$$

wherein:

L^1 is selected from a direct bond, $-SO_2-$, $-N(R_i)SO_2-$, or $-N(R_i)-SO_2-N(R_j)-$, wherein R_i and R_j are each independently selected from hydrogen or (1-4C)alkyl;

Q^1 is selected from hydrogen, (1-6C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, each of which is optionally substituted with one or more substituents independently selected from (1-4C)alkyl;

(28) Ring B is aryl which is optionally substituted as described herein;

(29) Ring B is phenyl which is optionally substituted as described herein.

(30) Ring B is (5-6C)cycloalkyl which is optionally substituted as defined herein.

(31) Ring B is cyclohexyl which is optionally substituted as defined herein;

(32) Ring B is a 5 or 6-membered heteroaryl which is optionally substituted as defined herein;

(33) Ring B is pyridyl which is optionally substituted as defined herein.

[0058] In an embodiment of the invention, R_1 has any one of the definitions set out herein, provided that a (1-8C)alkyl or (3-8C)cycloalkyl group is substituted by one or more R_a.

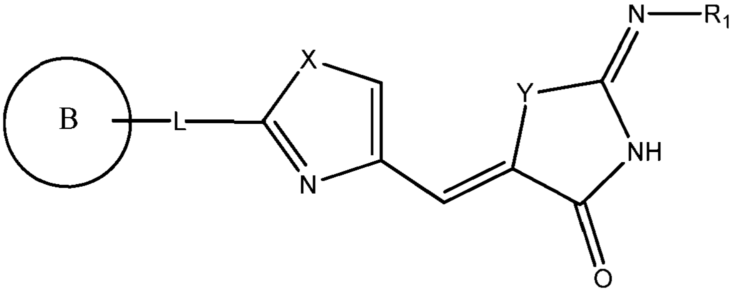
[0059] In another embodiment of the invention, R_1 has any one of the definitions set out herein, provided that a (1-8C)alkyl or (3-8C)cycloalkyl group is substituted by one or more hydroxyl, (1-4C)hydroxyalkyl or di-[(1-3C)alkyl]amino.

[0060] In an embodiment, Ring B has any one of the definitions set out herein and is optionally substituted as described herein with only one or two substituent groups selected form those defined herein.

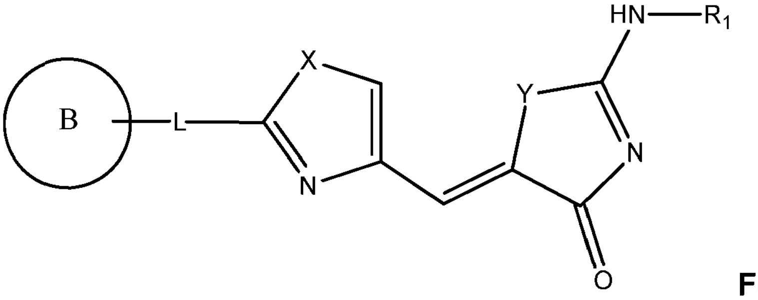
[0061] In another embodiment, Ring B is optionally substituted as described herein with only a single substituent group; wherein the single substiuent occupies the *meta-* or *para-* position of Ring B (relative to the bond connecting Ring B to L or directly to Ring A where L is absent).

[0062] In yet another embodiment, Ring B is optionally substituted as described herein with only a single substituent group; wherein the single substiuent occupies the *para-position of Ring B (relative to the bond connecting Ring B to L or directly to Ring A* where L is absent).

[0063] In a particular group of compounds of the invention, the compounds have the structural formula Ia or IIa (a sub-definition of formula I or II):



Formula Ia

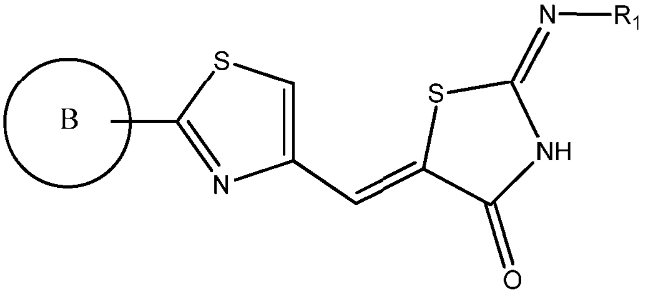


Formula IIa

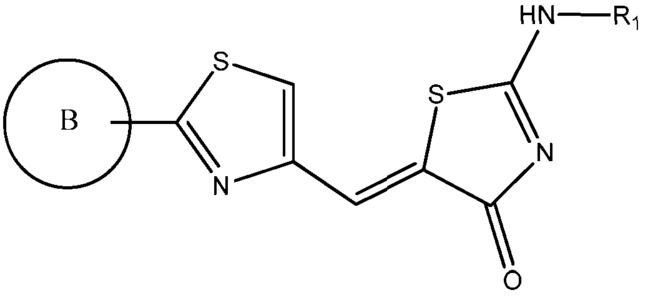
wherein X is selected from O, S, or NR_b, and wherein Y, R_1, R_b, L, and Ring B have any one of the meanings defined herein.

[0064] In an embodiment, X is S or O.

[0065] In a particular embodiment, X is S and L is absent, i.e. the compounds have the structural formula Ib or IIb (a sub-definition of formula I or II):



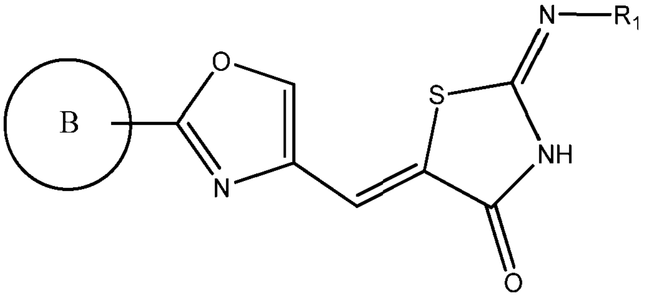
Formula Ib



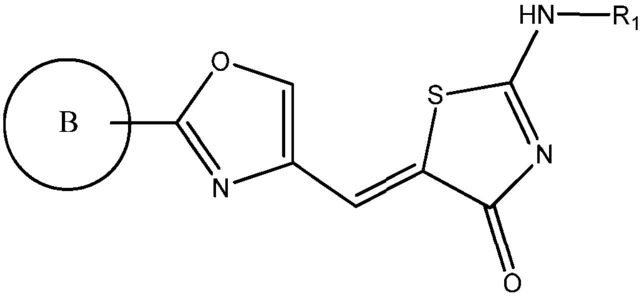
Formula IIb

wherein R_1 and Ring B have any one of the meanings defined herein.

[0066] In another embodiment, X is O and L is absent, i.e. the compounds have the structural formula Ic or IIc (a sub-definition of formula I or II):



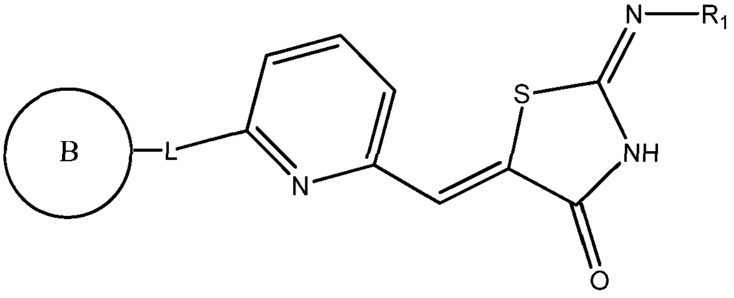
Formula Ic



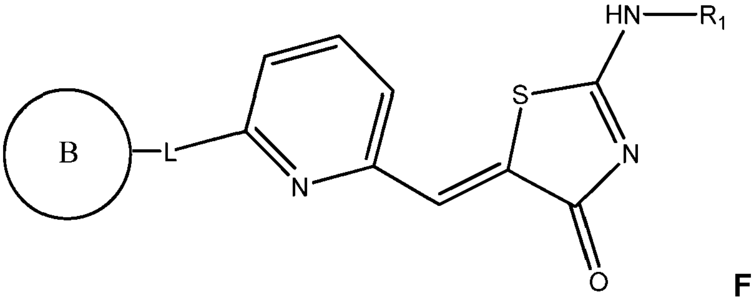
Formula IIc

wherein R_1 and Ring B have any one of the meanings defined herein.

[0067] In another embodiment, the compounds have the structural formula Id or IId (a sub-definition of formula I or II):



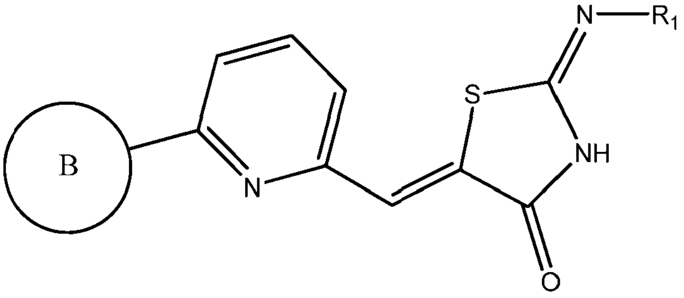
Formula Id



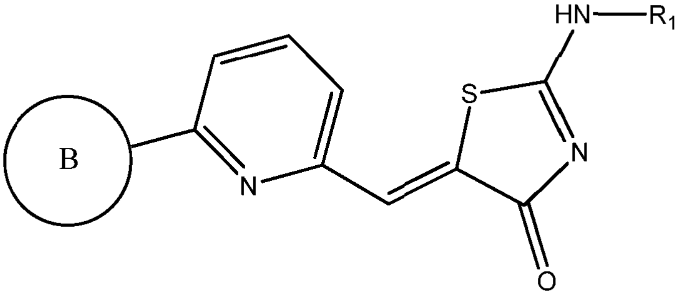
Formula IId

wherein R_1, L and Ring B have any one of the meanings defined herein.

[0068] In a further embodiment L is absent in the compounds of formula Id or IId, i.e. the compounds have the structural formula Ie or IIe (a sub-definition of formula I or II):



Formula Ie



Formula IIe

wherein R_1, L and Ring B have any one of the meanings defined herein.

[0069] Suitably, Ring B in Formulae Ia, IIa, Ib, IIb, Ic, IIc, Id, IId, Ie and IIe above has any one of the definitions set out in any one of paragraphs (25) to (33) above.

[0070] Suitably, if R_1 is hydrogen, the compound is defined by formula I (or any of its subdefinitions, e.g. formula Ia, Ib, Ic), whereas if R_1 is any group, as defined herein, other than hydrogen, the compound is defined by formula II (or any of its subdefinitions, e.g. formula IIa, IIb, IIc).

[0071] Particular compounds of the invention include any one of the following:

(*Z*)-5-((2-(4-Fluorophenyl)thiazol-4-yl)methylene)-2-iminothiazolidin-4-one;

(*Z*)-5-((2-(4-Fluorophenyl)thiazol-4-yl)methylene)-2-((1-methylpiperidin-4-yl)methylamino)thiazol-4(5*H*)-one;

(*Z*)-5-((2-(2-Hydroxyphenyl)thiazol-4-yl)methylene)-2-iminothiazolidin-4-one;

(*Z*)-5-((2-(2-Hydroxyphenyl)thiazol-4-yl)methylene)-2-(((1-methylpiperidin-4-yl)methyl)amino)thiazol-4(5 H)-one;

(Z)-2-(((1-cyclopropylpiperidin-4-yl)methyl)amino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(*Z*)-2-((3-Hydroxy-2,2-dimethylpropyl)amino)-5-((2-(2-hydroxyphenyl)thiazole-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-(((1-(Hydroxymethyl)cyclopropyl)methyl) amino)-5-((2-(2-hydroxy phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-(((1-(Hydroxymethyl)cyclobutyl)methyl)amino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(Z)-2-((4-hydroxy-1-methylpiperidin-4-yl)methylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1R,2R)-2-(hydroxymethyl)cyclopentylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1R,2R)-2-(hydroxymethyl)cyclopentylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1S,2R,5S)-2-(hydroxymethyl)-5-isopropylcyclopentylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1-(2-hydroxyethyl)piperidin-4-yl)methylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(*Z*)-5-((2-(4-Hydroxyphenyl)thiazol-4-yl)methylene)-2-iminothiazolidin-4-one;

(*Z*)-5-((2-(4-Hydroxyphenyl)thiazol-4-yl)methylene)-2-(((1-methylpiperidin-4-yl) methyl)amino)thiazol-4(5 H)-one;

(*Z*)-*N*-(3-(4-((2-Imino-4-oxothiazolidin-5-ylidene)methyl)thiazol-2-yl)phenyl)methanesulfonamide;

(*Z*)-*N*-(4-(4-((2-Imino-4-oxothiazolidin-5-ylidene)methyl)thiazol-2-yl) phenyl)methanesulfonamide;

(*Z*)-*N*-(4-(4-((2-(((1-Methylpiperidin-4-yl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl) methanesulfonamide;

(*Z*)-*N*-(3-(4-((2-Imino-5-oxo-1,3-dithiolan-4-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide;

(*Z*)-*N*-Methyl-*N*-(3-(4-((2-(((1-methylpiperidin-4-yl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)methanesulfonamide;

N-(3-(4-((*Z*)-(2-(((1*R*,2*S*)-2-Hydroxycyclopentyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide;

N-(3-(4-((*Z*)-(2-(((1*R*,2*S*)-2-Hydroxycyclopentyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide;

(*Z*)-*N*-(3-(4-((2-(((1-(Hydroxymethyl)cyclopropyl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide;

(*Z*)-*N*-(3-(4-((2-(((1-(Hydroxymethyl)cyclobutyl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide;

(*Z*)-*N*-(3-(4-((2-(((1-(Hydroxymethyl)cyclopentyl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide;

(Z)-N-(3-(4-((2-((4-hydroxy-1-methylpiperidin-4-yl)methylamino)-4-oxothiazol-5(4H)-ylidene)methyl)thiazol-2-yl)phenyl)-N-methylmethanesulfonamide;

(*Z*)-2-Imino-5-((2-(3-*N*,*N*-dimethylsulfamoylamino)thiazol-4-yl)methylene)thiazolidin-4-one;

N-(3-(4-((Z)-(2-((3-hydroxy-2,2-dimethylpropyl)amino)-4-oxothiazol-5(4H)-ylidene)methyl)thiazol-2-yl)phenyl)-N,N-dimethylsulfonamide;

(*Z*)-2-Imino-5-((2-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)thiazol-4-

yl)methylene)thiazolidin-4-one;

(*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one;

(*Z*)-2-Imino-5-((2-(4-(trifluoromethoxy)phenyl) thiazol-4-yl)methylene)thiazolidin-4-one;

(*Z*)-2-(Cyclopropylmethylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-((1*S*,2*S*)-2-Hydroxycyclopentylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-(3-Hydroxybenzylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-((1*R*,4*R*)-4-Hydroxycyclohexylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-(2-(Dimethylamino)ethylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one

(*Z*)-2-((3-Hydroxy-2,2-dimethylpropyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-(((1-(Hydroxymethyl)cyclopropyl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-(((1-(Hydroxymethyl)cyclobutyl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(Z)-2-((4-Hydroxy-1-methylpiperidin-4-yl)methylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene) thiazol-4(5H)-one;

(Z)-2-(3-Hydroxy-2,2-dimethylpropylamino)-5-((2-(2-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((3-hydroxy-2,2-dimethylpropyl)amino)-5-((2-(3-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((3-hydroxy-2,2-dimethylpropyl)amino)-5-((2-(2-hydroxy-5-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-imino-5-((2-(3-(methylsulfonyl)phenyl)thiazol-4-yl)methylene) thiazolidin-4-one;

(*Z*)-2-Imino-5-((2-(4-(methylsulfonyl)phenyl)thiazol-4-yl)methylene)-1,3-dithiolan-4-one;

(*Z*)-2-Imino-5-((2-(3-(piperidin-1-yl)phenyl)thiazol-4-yl)methylene)-1,3-dithiolan-4-one;

(Z)-2-Imino-5-((2-(4-(piperidin-1-ylmethyl)phenyl)thiazol-4-yl)methylene)thiazolidin-4-one;

(Z)-2-((3-Hydroxy-2,2-dimethylpropyl)amino)-5-((2-(4-(piperidin-1-ylmethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(Z)-2-imino-5-((2-(3-(morpholinomethyl)phenyl)thiazol-4-yl)methylene)thiazolidin -4-one;

(*Z*)-2-Imino-5-((2-(4-(trifluoromethyl)phenyl) thiazol-4-yl)methylene) thiazolidin-4-one;

(Z)-2-(Cyclopropylmethylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1R,2S)-2-Hydroxycyclopentylamino)-5-((2-(4-(trifluoromethyl)phenyl) thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-(2-(dimethylamino)ethylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1r,4r)-4-hydroxycyclohexylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1-methylpiperidin-4-yl)methylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-(3-hydroxybenzylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl) methylene) thiazol-4(5H)-one;

(Z)-5-((2-(4-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-(3-hydroxy-2,2-dimethylpropylamino)thiazol-4(5H)-one;

(Z)-5-((2-(5-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-((1S,2S)-2-(hydroxymethyl)cyclopentylamino)thiazol-4(5H)-one;

(Z)-5-((2-(5-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-(3-hydroxy-2,2-dimethylpropylamino)thiazol-4(5H)-one;

(*Z*)-5-((2-(3-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-((3-hydroxy-2,2-dimethylpropyl)amino)thiazol-4(*5H*)-one;

(*Z*)-5-((2-(3-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-((4-hydroxy-1-

methylpiperidin-4-yl)methyl)amino)thiazol-4(*5H*)-one;

(*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one acetate;

(*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one methane sulfonate;

(*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one Hydrochloride;

(*Z*)-2-Amino-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one methane sulfonate;

(Z)-2-(4-((2-((3-Acetoxy-2,2-dimethylpropyl)amino)-4-oxothiazol-5(4H)-ylidene)methyl)thiazol-2-yl)phenyl acetate;

N-(4-((*Z*)-((*E*)-2-(3-Hydroxy-2,2-dimethylpropylimino)-4-oxothiazolidin-5-ylidene)methyl)thiazol-2-yl)-*N*-methylbenzamide;

(Z)-N-(4-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol-2-yl)cyclohexanecarboxamide;

(*Z*)-2-((1-Methylpiperidin-4-yl)methylamino)-5-((2-phenyloxazol-4-yl)methylene)thiazol-4(5H)-one;

(2E,5Z)-2-(3-Hydroxy-2,2-dimethylpropylimino)-5-((6-phenylpyridin-2-yl)methylene)thiazolidin-4-one;

(2E,5Z)-2-((1-(Hydroxymethyl)cyclopropyl)methylimino)-5-((6-phenylpyridin-2-yl)methylene)thiazolidin-4-one;

((2E,5Z)-2-((4-Hydroxy-1-methylpiperidin-4-yl)methylimino)-5-((6-phenylpyridin-2-yl)methylene)thiazolidin-4-one;

((2E,5Z)-2-((4-Hydroxy-1-methylpiperidin-4-yl)methylimino)-5-((6-phenylpyridin-2-yl)methylene)thiazolidin-4-one;

(*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((6-(4-(trifluoromethoxy) phenyl)pyridin-2-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-*N*-(3-(6-((2-Imino-4-oxothiazolidin-5-ylidene)methyl)pyridin-2-yl) phenyl)methanesulfonamide;

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0072] The various functional groups and substituents making up the compounds of the formula I or II are typically chosen such that the molecular weight of the compound of the formula I or II does not exceed 1000. More usually, the molecular weight of the compound will be less than 750, for example less than 700, or less than 650, or less than 600, or less than 550. More preferably, the molecular weight is less than 525 and, for example, is 500 or less.

[0073] A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition 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-(2-hydroxyethyl)amine.

[0074] 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 non-superimposable 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 S-sequencing 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”.

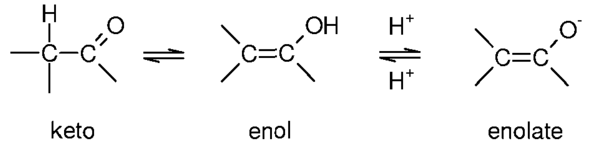
[0075] The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is 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 well-known 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.

[0076] 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 ^{1}H, ^{2}H(D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; and O may be in any isotopic form, including ^{16}0 and^{18}0; and the like.

[0077] It is also to be understood that certain compounds of the formula I or II 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.

[0078] It is also to be understood that certain compounds of the formula I or II may exhibit polymorphism, and that the invention encompasses all such forms that possess antiproliferative activity.

[0079] Compounds of the formula I or II may exist in a number of different tautomeric forms and references to compounds of the formula I or II 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 or II. 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.



[0080] Compounds of the formula I or II containing an amine function may also form N-oxides. A reference herein to a compound of the formula I or II 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 (*m*CPBA), for example, in an inert solvent such as dichloromethane.

[0081] The compounds of formula I or II may be administered in the form of a pro-drug 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 or II 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 or II.

[0082] Accordingly, the present invention includes those compounds of the formula I or II 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 or II 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 or II may be a synthetically-produced compound or a metabolically-produced compound.

[0083] A suitable pharmaceutically acceptable pro-drug of a compound of the formula I or II 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.

[0084] 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.

[0085] A suitable pharmaceutically acceptable pro-drug of a compound of the formula I or II 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

C_{1-6}alkyl esters such as methyl, ethyl and *tert*-butyl, C_{1-6}alkoxymethyl esters such as methoxymethyl esters, C_{1-6}alkanoyloxymethyl esters such as pivaloyloxymethyl esters, 3-phthalidyl esters, C_{3-8}cycloalkylcarbonyloxy- C_{1-6}alkyl 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 C_{1-6}alkoxycarbonyloxy- C_{1-6}alkyl esters such as methoxycarbonyloxymethyl and 1-methoxycarbonyloxyethyl esters.

[0086] A suitable pharmaceutically acceptable pro-drug of a compound of the formula I or II 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 or II 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 C_{1-10}alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C_{1-10}alkoxycarbonyl groups such as ethoxycarbonyl, *N,N*–$(C_{1-6})_2$carbamoyl, 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-(C_{1-4}alkyl)piperazin-1-ylmethyl. Suitable pharmaceutically acceptable ether forming groups for a hydroxy group include α-acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

[0087] A suitable pharmaceutically acceptable pro-drug of a compound of the formula I or II 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 C_{1-4}alkylamine such as methylamine, a (C_{1-4}alkyl)$_2$amine such as dimethylamine, *N*-ethyl-*N*-methylamine or diethylamine, a C_{1-4}alkoxy- C_{2-4}alkylamine such as 2-methoxyethylamine, a phenyl-C_{1-4}alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

[0088] A suitable pharmaceutically acceptable pro-drug of a compound of the formula I or II 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 C_{1-10}alkanoyl 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-(C_{1-4}alkyl)piperazin-1-ylmethyl.

[0089] The *in vivo* effects of a compound of the formula I or II 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 or II. As stated hereinbefore, the *in vivo* effects of a compound of the formula I or II may also be exerted by way of metabolism of a precursor compound (a pro-drug).

Synthesis

[0090] The compounds of the present invention can be prepared by any suitable technique known in the art. Particular processes for the preparation of these compounds are described further in the accompanying examples.

[0091] 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.

[0092] 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.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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 *t*-butoxycarbonyl 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 palladium-on-carbon, 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.

[0097] 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 palladium-on-carbon.

[0098] 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 *t*-butyl 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 palladium-on-carbon.

[0099] Resins may also be used as a protecting group.

[00100] The methodology employed to synthesise a compound of formula I or II will vary depending on the nature of Y, R_1, L, Ring A, Ring B and any substituent groups associated therewith. Suitable processes for their preparation are described further in the accompanying Examples.

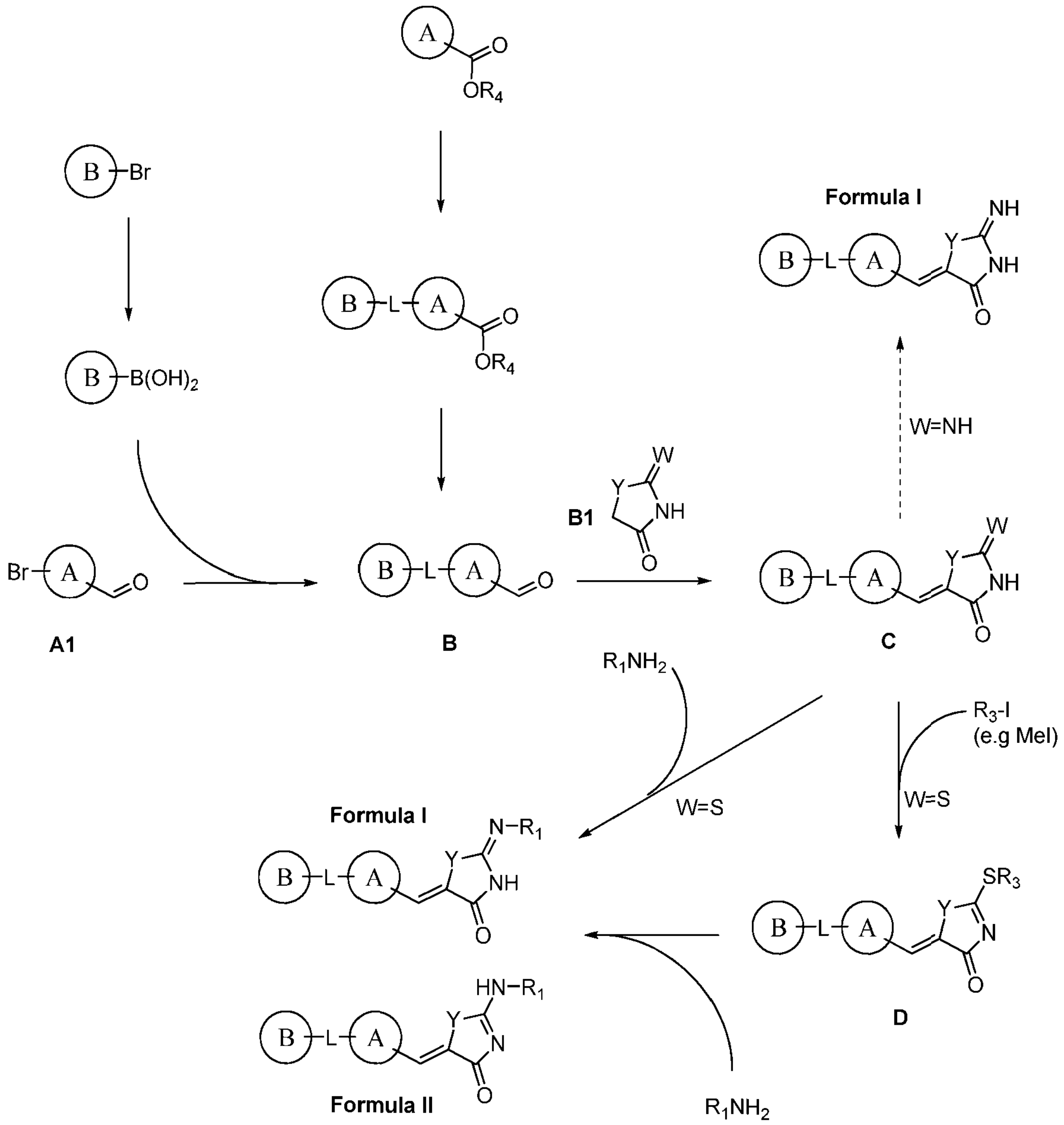
[00101] Once a compound of formula I or II has been synthesised by any one of the processes defined herein, the processes may then further comprise the additional steps of:

(i) removing any protecting groups present;
(ii) converting the compound formula I or II into another compound of formula I or II;
(iii) forming a pharmaceutically acceptable salt, hydrate or solvate thereof; and/or
(iv) forming a prodrug thereof.

[00102] An example of (ii) above is when a compound of formula I or II is synthesised and then one or more of the groups R_1, or $R_{a\text{-}j}$ may be further reacted to change the nature of the group and provide an alternative compound of formula I or II. For example, the compound can be reacted to covert R_1 into a substituent group other than hydrogen.

[00103] The resultant compounds of formula I or II can be isolated and purified using techniques well known in the art.

[00104] Scheme 1 below depicts a generalised scheme illustrating how the compounds of formula I and II may be synthesised.



Scheme 1 – Generic reaction scheme for the synthesis of compounds of formula I and II

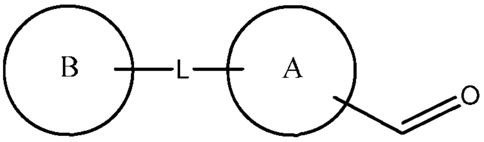
[00105] Y, R_1, Ring A, L, and Ring B each have any one of the meanings defined herein, and W, R_2, and R_3 are as defined further below. Compound B represents a common intermediate from which a variety of compounds of formula I and II can be made.

[00106] When compound B is reacted with a compound B1 in which W is NH, a compound of formula I in which R_1 is NH is formed.

[00107] Alternative derivatives of formula I or II can be formed by reacting compound B with a compound B1 in which W is S to provide a compound of formula C in which W is S. This compound can then be further reacted to introduce the desired substituted amine moiety. This further reaction can be carried out either with or without an initial alkylation step (the reaction with R_3I shown in the Scheme 1 above).

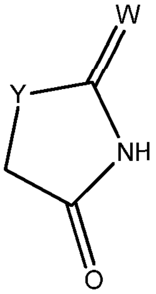
[00108] The present invention provides a process for preparing a compound of formula I or II (as defined herein), the process comprising the steps of:

reacting a compound of formula B:



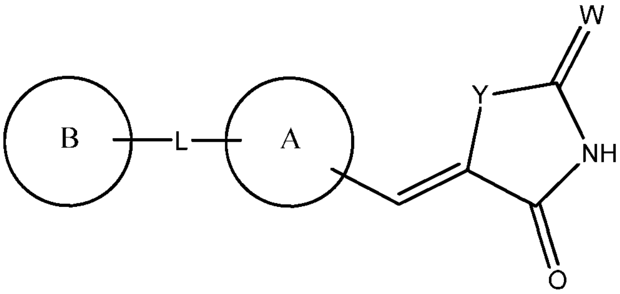
Formula B

with a compound of formula B1:



Formula B1

to form a compound of formula C:



Formula C

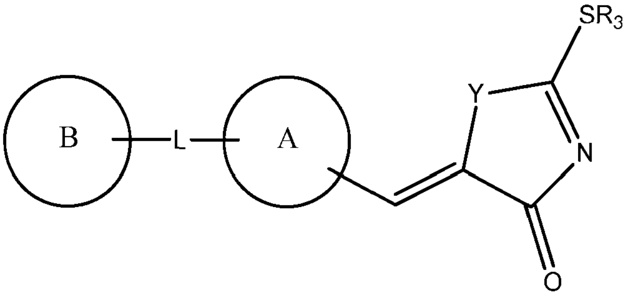
wherein either:

(a) W is NH, and the compound of formula C is a compound of formula I where R_1 is hydrogen;

or

(b) W is S and the compound of formula C is an intermediate compound which is then:

(i) further reacted with a compound of the formula R_3-LG to form an activated intermediate compound of formula D, wherein LG is any suitable leaving group (e.g. halide, tosyl, mesyl, etc.), and R_3 is any group which renders $-SR_3$ a suitable leaving group from compound D:



Formula D

and

compound D is then further reacted with an amine of the formula R_1NH_2;

or

(ii) *compound C is reacted with an amine of the formula* R_1NH_2;

wherein Y, R_1, Ring A, L, and Ring B each have any one of the meanings defined herein;

and optionally thereafter (and if necessary):

(i) removing any protecting groups present into R_1;

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

(iii) forming a pharmaceutically acceptable salt, hydrate or solvate thereof; and/or

(iv) forming a prodrug thereof.

[00109] Suitably one or more of the following features apply in relation to the reaction between the compounds of formulae B and B1:

- The reaction takes place in a suitable solvent, such as a protic solvent (suitably an alcoholic solvent such as ethanol).
- The reaction takes place in the presence of a suitable base, suitably an amine base, such as piperidine.
- The reaction takes place at a suitable temperature. A suitable temperature may be, for example, a temperature above 30°C, suitably above 40°C, or more suitably above 65°C.

- The reaction takes place over a suitable time period (such as between 5 and 48 hours, or between 16 and 24 hours).

[00110] The product of the reaction between intermediate compounds of formulae B and B1 (i.e. the compound of fomula C) is suitably isolated from the reaction mixture. In a particular embodiment, the compound of formula V is isolated by cooling the reaction mixture to approximately room temperature (i.e. between 15 and 30°C) and adding water to precipitate the product. The precipitated product is then suitably filtered, and optionally washed with further water and/or ethanol (preferably ice-cooled ethanol). The solid is then suitably collected and dried.

[00111] In a particular embodiment, W is NH and the compound of formula C is a compound of formula I in which R_1 is NH.

[00112] In another embodiment, W is S. Where the compound of formula C is characterised by W being S, further reaction is necessary to produce a compound of formula I or II.

[00113] In a particular embodiment, the intermediate compound of formula C is reacted to form the activated intermediate compound of formula D before being further reacted with an amine of the formula R_1NH_2 as described above. In general, this process was found to utilise milder reaction conditions and reduced the presence of by-products. Suitably compound C is activated through reaction with an electrophilic R_3-containing compound.

[00114] In a particular embodiment, compound C is reacted with a compound defined by R_3-LG, wherein LG is any suitable leaving group (e.g. halide, tosyl, mesyl, etc.), and R_3 is any group which renders $-SR_3$ a suitable leaving group from compound D. Suitably R_3 is (1-12C)alkyl, (2-12C)alkenyl, (2-12C)alkynyl, (2-12C)alkanoyl, aryl(1-3C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl(1-3C)alkyl. Suitably LG is halide. In a particular embodiment, compound C is alkylated with R_3-LG to produce the compound of formula D, wherein R_3 is (1-12C)alkyl. LG is suitably halide, most suitably chloro, bromo, or iodo. In a particular embodiment, the intermediate compound of Formula C is alkylated by reacting the compound of formula C with an alkyl halide, such as methyl iodide, to yield an alkylated (e.g. methylated) compound of formula D.

[00115] Suitably one or more of the following features apply in relation to the reaction of the compound of formula C to yield the activated intermediate compound of formula D:

- The reaction takes place in a suitable solvent, such as a protic solvent (suitably an alcoholic solvent such as methanol).
- The reaction takes place in the presence of a suitable base, suitably an amine base, such as diisopropylethyl amine.
- The reaction takes place at a suitable temperature, for example, a temperature of between 10 and 35°C (e.g at room temperature).
- The reaction takes place over a suitable time period (such as between 5 and 48 hours, or between 10 and 24 hours).

[00116] The intermediate compound of formula D is suitably isolated from the reaction mixture. In a particular embodiment, the compound of formula D is isolated by adding water to precipitate the product. The precipitated product is then suitably filtered, and optionally washed with further water and/or ethanol (preferably ice-cooled ethanol). The solid is then suitably collected and dried.

[00117] Compound D is further reacted with an amine defined of the formula R_1NH_2.

[00118] Suitably one or more of the following features apply in relation to the reaction of the compound of formula D with R_1NH_2:

- The reaction takes place in a suitable solvent, such as a protic solvent (suitably an alcoholic solvent such as ethanol).
- The reaction takes place in the presence of a suitable base, suitably an amine base, such as diisopropylethyl amine.
- The reaction takes place at a suitable temperature, for example, a temperature of between 70 and 200°C (e.g between 120-160°C).
- The reaction takes place over a suitable time period (such as between 10 and 30 minutes under microwave heating).

[00119] The product of the reaction between the compound of formula D and R_1NH_2 is suitably isolated from the reaction mixture. In a particular embodiment, the product is isolated by adding water to precipitate the product. The precipitated product is then suitably filtered, and optionally washed with further water and/or ethanol (preferably ice-cooled ethanol). The solid is then suitably collected and dried.

[00120] In another embodiment, the compound of formula C, where W is S, is treated directly with the amine R_1NH_2 without any intervening activation (e.g. *S*-alkylation) step. Suitably one or more of the following features apply in relation to the direct reaction of the compound of formula V with R_1NH_2:

- The reaction takes place in a solvent, suitably a protic solvent, suitably an alcoholic solvent, most suitably ethanol.
- The reaction takes place in the presence of a base (i.e. distinct from the compound R_1NH_2), suitably an amine base, such as diisopropylethyl amine.
- The reaction takes place at a suitable temperature, for example between 70 and 200°C or, more suitably, 120-160°C.
- The reaction takes place in a sealed vessel under exposure to microwaves.
- The reaction takes place for a suitable time period (for example, between 10 and 30 minutes under microwave heating).

[00121] The product of the direct reaction between the compound of formula C and R_1NH_2 is suitably isolated from the reaction mixture. In a particular embodiment, the product is isolated by adding water to precipitate the product. The precipitated product is then suitably filtered, and optionally washed with further water and/or ethanol (preferably ice-cooled ethanol). The solid is then suitably collected and dried.

[00122] In a further aspect of the invention, there is provided a compound of formula I or II obtainable by a process as defined herein.

[00123] In a further aspect of the invention, there is provided a compound of formula I or II obtained by a process as defined herein.

[00124] In a further aspect of the invention, there is provided a compound of formula I or II directly obtained by a process as defined herein.

[00125] In a further aspect of the present invention there is provided a novel intermediate compound of formula B, B1, C or D as defined herein.

Biological Activity

[00126] The biological assay described in Example 75 herein may be used to measure the pharmacological effects of the compounds of the present invention.

[00127] Although the pharmacological properties of the compounds of the formulae I and II vary with structural change, as expected, the compounds of the invention were found to be active in the assay described in Example 75.

[00128] In general, the compounds of the invention demonstrate a percentage inhibition of 40% or more at a concentration of 1 µM in the PIM1 kinase assay described in Example 75.

[00129] Preferred compounds of the invention demonstrate a percentage inhibition of 60% or more at a concentration of 1 µM in the PIM1 kinase assay described in Example 75. Most preferred compounds of the invention demonstrate a percentage inhibition of 75% or more at a concentration of 1 µM in the PIM1 kinase assay described in Example 75.

Pharmaceutical Compositions

[00130] 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.

[00131] 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).

[00132] 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.

[00133] 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.

[00134] 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.

[00135] The size of the dose for therapeutic or prophylactic purposes of a compound of the formula I or II 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.

[00136] 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

[00137] The present invention provides a method of inhibiting PIM Kinase, *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.

[00138] The present invention provides 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.

[00139] The present invention provides 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, or a pharmaceutical composition as defined herein.

[00140] The present invention provides 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, or a pharmaceutical composition as defined herein.

[00141] The present invention provides a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein for use in therapy.

[00142] The present invention provides a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein for use in the treatment of a proliferative condition.

[00143] The present invention provides 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.

[00144] The present invention provides a compound, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein for use in the production of a PIM kinase inhibitory effect.

[00145] The present invention provides 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 proliferative condition.

[00146] The present invention provides 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 cancer. Suitably, the medicament is for use in the treatment of human cancers.

[00147] The present invention provides 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 in the production of a PIM kinase inhibitory effect.

[00148] 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.

[00149] The anti-proliferative effects of the compounds of the present invention have particular application in the treatment of human cancers by virtue of their PIM kinase inhibitory properties.

[00150] The anti-cancer effect may arise through one or more mechanisms, including but not limited to, the regulation of cell proliferation, the inhibition of angiogenesis (the formation of new blood vessels), the inhibition of metastasis (the spread of a tumour from its origin), the inhibition of invasion (the spread of tumour cells into neighbouring normal structures), or the promotion of apoptosis (programmed cell death).

[00151] In an embodiment of the invention, the cancer is selected from the group consisting of haematological cancers (e.g. AML, ALL, and lymphomas), and cancers of the liver, pancreas, prostate, breast and head & neck.

Routes of Administration

[00152] 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).

[00153] 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, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

Combination Therapies

[00154] The antiproliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

(i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661) and bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase];

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* (Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 *tyrosine kinase inhibitors such as* lapatinib); *inhibitors of the hepatocyte growth factor* family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R115777) and lonafarnib (SCH66336)), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function *and angiostatin*)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan;

(viii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(ix) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(x) immunotherapy approaches, including for example *ex-vivo* and *in-vivo* approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

[00155] Such conjoint treatment 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.

[00156] 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 another anti-tumour agent.

[00157] According to this aspect of the invention there is provided a combination for use in the treatment of 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 any one of the anti-tumour agents listed under (i) – (ix) above.

[00158] 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 under (i) – (ix) herein above.

[00159] 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.

[00160] 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 under (i) – (ix) herein above), in association with a pharmaceutically acceptable diluent or carrier.

EXAMPLES

General Experimental Details

[00161] All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen or argon before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers (A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, Organometallics, 1996, 15, 1518). Water was purified by an Elix® UV-10 system. All other solvents and reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Pet ether refers to the fraction of petroleum spirit boiling between 30 and 40 ºC. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), or 1% aq. $KMnO_4$. Flash column chromatography was performed on Kieselgel 60 silica on a glass column, or on a Biotage SP4 flash column chromatography platform. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer either as KBr discs or thin films using NaCl plates. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Advance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (J, reported unaveraged) in Hz. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m x 0.25 mm) using amyl acetate as a lock mass.

[00162] Reverse phase HPLC was carried out on a Gilson system (215 Liquid Handler, 306 Pumps, 811C Mixer, 170 DAD, UniPoint software), using an XTerra RP18 Cartridge, 5 μm, 4.6 x 150 mm stationary phase (Waters part no. 186000580). The mobile phase was a water / acetonitrile gradient , doped with TFA (0.1% v/v).

[00163] Microwave syntheses were carried out in a Biotage Initiator, irradiating for the times shown, and at the temperatures indicated.

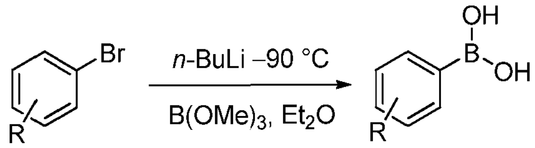
[00164] Where the preparation of chemical building blocks or reagents is not specifically described, these were either purchased from commercial vendors, or prepared using procedures described in the literature.

Synthetic Scheme

[00165] The general synthetic scheme is shown above in Scheme 1.

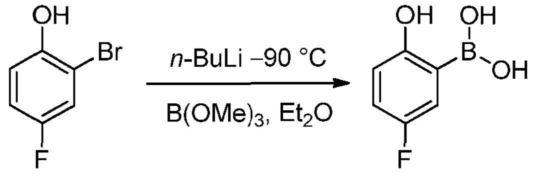
[00166] Various general methods were used for the preparation of the examples described herein. The following procedures describe representative examples.

General Procedure *BA* - preparation of boronic acid precursors



[00167] To a solution of the requisite aryl halide (1.0 eq.) in Et_2O (ca. 8mL / mmol halide) at -90 °C was added dropwise *n*-BuLi (1.6 M in hexanes, 2.1 eq.) and the resulting solution was allowed to warm to room temperature and stirred for 2 h. The mixture was then re-cooled to -90 °C before rapid addition of $B(OMe)_3$ (1.67 eq.) with vigorous stirring. The reaction was stirred at -90 °C for 30 minutes, then warmed to room temperature and stirred for 12 h. The reaction was cooled to 0 °C before dropwise addition of HCl (2 $M_{(aq)}$). The reaction mixture was stirred at 0 °C for 30 min before separation and extraction of the aqueous phase with Et_2O (3 times). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product.

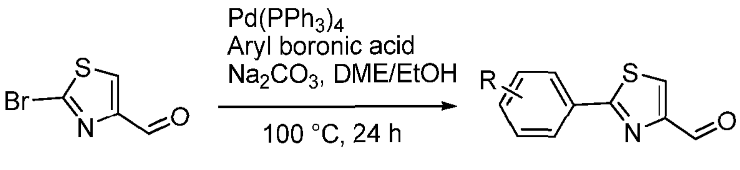
Example preparation: (5-fluoro-2-hydroxyphenyl)boronic acid



[00168] To a solution of 2-bromo-4-fluorophenol (5.00 g, 26.2 mmol) in Et_2O (200 mL) at -90 °C was added dropwise *n*-BuLi (1.6 M in hexanes, 35.2 mL, 56.3 mmol) and the resulting solution was allowed to warm to room temperature and stirred for 2 h. The mixture was then re-cooled to -90 °C before rapid addition of $B(OMe)_3$ (6.3 mL, 43.7 mmol) with vigorous stirring. The reaction was stirred at -90 °C for 30 minutes, then warmed to room temperature and stirred for 12 h. The reaction was cooled to 0 °C before dropwise addition of HCl (2 $M_{(aq)}$, 10 mL). The reaction mixture was stirred at 0 °C for 30 min before separation and extraction of the aqueous phase with Et_2O (3 x 100 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a light brown solid (3.28 g, 80%). The product was used without further purification in the next step. An analytical sample was purified by recrystallisation from benzene/pentane.

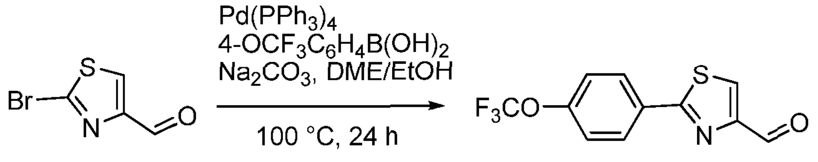
[00169] ^1H NMR (400 MHz, MeOD): δ = 6.93 (app. br. s, 2 H), 6.73 (dd, J = 9.0, 4.2 Hz, 1 H) ppm; m/z LRMS (ESI$^-$): 155.1 (15%) $[M - H]^+$, 335 (100%).

General Procedure SC1: Suzuki coupling of 2-bromothiazole-4-carboxaldehyde with aryl boronic acids



[00170] To a microwave vial equipped with a magnetic stirrer bar was added 2-bromothiazole-4-carboxaldehyde (1 eq.), $Pd(PPh_3)_4$ (0.10 eq.), sodium carbonate (3 eq.) and the appropriate aryl boronic acid (1.2 eq.). The reaction vessel was fitted with a rubber septum and purged with N_2, and to this was added degassed ethanol and 1,2-dimethoxyethane (1:1, 0.1 M overall concentration) via syringe. The reaction vessel was then sealed and heated at 100 °C for 24 hours. After cooling to room temperature the reaction mixture was diluted with ethyl acetate and passed through a short pad of pressed Celite, eluting with ethyl acetate. The solution was concentrated *in vacuo* and purified by flash column chromatography.

Example preparation: 2-(4-(Trifluoromethoxy)phenyl)thiazole-4-carbaldehyde

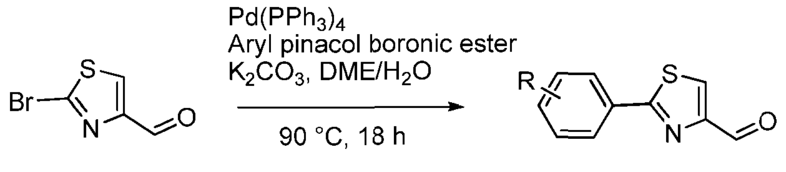


[00171] To a microwave vial equipped with a magnetic stirrer bar was added 2-bromothiazole-4-carboxaldehyde (100 mg, 0.52 mmol), $Pd(PPh_3)_4$ (60.0 mg, 0.052 mmol), sodium carbonate (166 mg, 1.56 mmol) and 4-(trifluoromethoxy)phenylboronic acid (127 mg, 0.62 mmol). The reaction vessel was fitted with a rubber septum and purged with N_2, and to this was added degassed ethanol (2.6 mL) and 1,2-dimethoxyethane (2.6 mL) via syringe. The reaction vessel was then sealed and heated at 100 °C for 24 hours. After cooling to room temperature the reaction mixture was diluted with ethyl acetate and passed through a short pad of pressed Celite®, eluting with ethyl acetate. The solution was concentrated *in vacuo* and purified by flash column chromatography to give the title compound.

[00172] Flash column chromatography (SiO2, petrol:EtOAc 10:1), 132 mg, 91%, white crystalline solid.

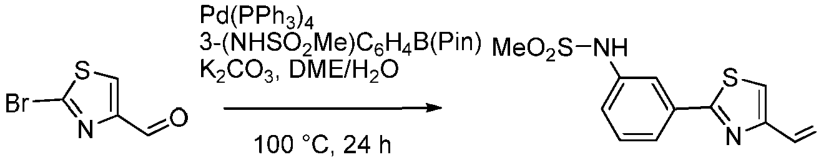
[00173] ^1H NMR (400 MHz, $CDCl_3$): δ = 10.11 (s, 1 H), 8.21 (s, 1 H), 8.08 - 8.05 (m, 2 H), 7.35 - 7.33 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 199.4, 169.3, 166.5, 150.4, 149.9, 131.1, 128.5, 128.2, 127.7, 122.4, 121.9, 120.0 (q, J = 257 Hz) ppm; m/z LRMS (ESI^+): 633.05 $[2(M + MeOH) + Na]^+$ (100%).

General Procedure SC2: Suzuki coupling of 2-bromothiazole-4-carboxaldehyde with aryl pinacol boronic esters



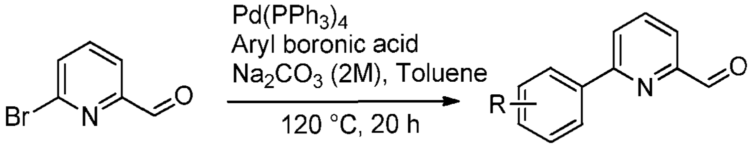
[00174] To a microwave vial equipped with a magnetic stirrer bar was added 2-bromothiazole-4-carboxaldehyde (1 eq.), $Pd(PPh_3)_4$ (0.10 eq.), potassium carbonate (2.5 eq.) and the appropriate aryl pinacol boronic ester (1.2 eq.). The reaction vessel was fitted with a rubber septum and purged with N_2, and to this was added degassed water and 1,2-dimethoxyethane (1:2, 0.1 M overall concentration) via syringe. The reaction vessel was then sealed and heated at 90 °C for 18 hours. After cooling to room temperature the reaction mixture was diluted with ethyl acetate and passed through a short pad of pressed Celite, eluting with ethyl acetate. The solution was concentrated *in vacuo* and purified by flash column chromatography.

Example preparation: *N*-(3-(4-Formylthiazol-2-yl)phenyl)methane- sulfonamide



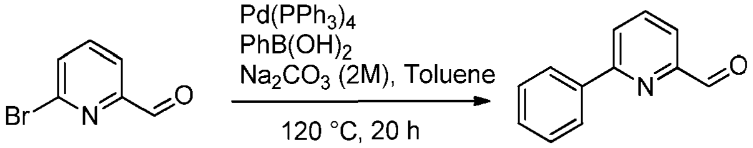
[00175] To a microwave vial equipped with a magnetic stirrer bar was added 2-bromothiazole-4-carboxaldehyde (100 mg, 0.52 mmol), $Pd(PPh_3)_4$ (60.0 mg, 0.052 mmol.), potassium carbonate (180 mg, 1.30 mmol) and 3-(methanesulfonylamino)phenylboronic acid pinacol ester (170 mg, 0.30 mmol). The reaction vessel was fitted with a rubber septum and purged with N_2, and to this was added degassed water (1.75 mL) and 1,2-dimethoxyethane (3.5 mL) via syringe. The reaction vessel was then sealed and heated at 90 °C for 18 hours. After cooling to room temperature the reaction mixture was diluted with ethyl acetate and passed through a short pad of pressed Celite, eluting with ethyl acetate. The solution was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, petrol:EtOAc 1:1) to give the title compound as a tan solid (73 mg, 50%); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 10.02$ (br s, 1 H), 9.99 (s, 1 H), 8.80 (s, 1 H), 7.90 (s, 1 H), 7.74 - 7.71 (m, 1 H), 7.52 (app t, $J = 8.0$ Hz, 1 H), 7.41 - 7.37 (m, 1 H), 3.06 (s, 3 H) ppm; *m/z* LRMS (ESI$^-$): 281 (100%) [M - H]$^-$; HRMS (ESI$^-$): calc. for $C_{11}H_9N_2O_3S_2^-$ [M - H]$^-$ 281.0060, found 281.0055.

General Procedure SC3: Suzuki coupling of 6-bromo-2-pyridine- carboxaldehyde with aryl boronic acids



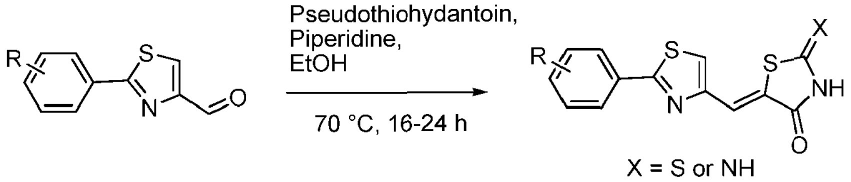
[00176] To a microwave vial equipped with a magnetic stirrer bar was added 6-bromo-2-pyridinecarboxaldehyde (1 eq.), $Pd(PPh_3)_4$ (0.10 eq.) and the appropriate aryl boronic acid (1.2 eq.). The reaction vessel was fitted with a rubber septum and purged with N_2, and to this was added degassed aqueous sodium carbonate (2M, 8 eq.) and toluene (5 ml/mmol bromide) via syringe. The reaction vessel was then sealed and heated at 120 °C for 20 hours. After cooling to room temperature the reaction mixture was diluted with ethyl acetate and passed through a short pad of pressed Celite, eluting with ethyl acetate. The solution was concentrated *in vacuo* and purified by flash column chromatography.

Example preparation: 6-Phenyl-pyridine-2-carboxaldehyde



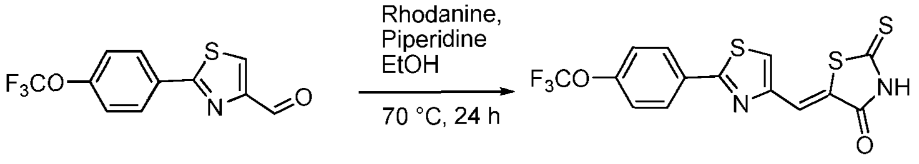
[00177] To a microwave vial equipped with a magnetic stirrer bar was added 6-bromo-2-pyridinecarboxaldehyde (100 mg, 0.54 mmol), $Pd(PPh_3)_4$ (62 mg, 0.054 mmol) and phenyl boronic acid (79 mg, 0.65 mmol). The reaction vessel was fitted with a rubber septum and purged with N_2, and to this was added degassed aqueous sodium carbonate (2M, 2.15 mL, 4.30 mmol)) and toluene (2.8 mL) via syringe. The reaction vessel was then sealed and heated at 120 °C for 20 hours. After cooling to room temperature the reaction mixture was diluted with ethyl acetate and passed through a short pad of pressed Celite, eluting with ethyl acetate. The solution was concentrated *in vacuo* and purified by flash column chromatography (Biotage, SiO_2, gradient elution petrol:Et_2O 98:2 to 90:10) to give the title compound (85 mg, 86%) as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 10.18$ (s, 1 H), 8.11 - 8.08 (m, 2 H), 7.98 - 7.88 (m, 3 H), 7.55 - 7.45 (m, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 194.0$, 157.9, 152.7, 138.1, 137.8, 129.7, 129.0, 127.0, 124.5, 119.8 ppm;

General procedure C1: Condensation of aldehydes with rhodanine or pseudothiohydantoin



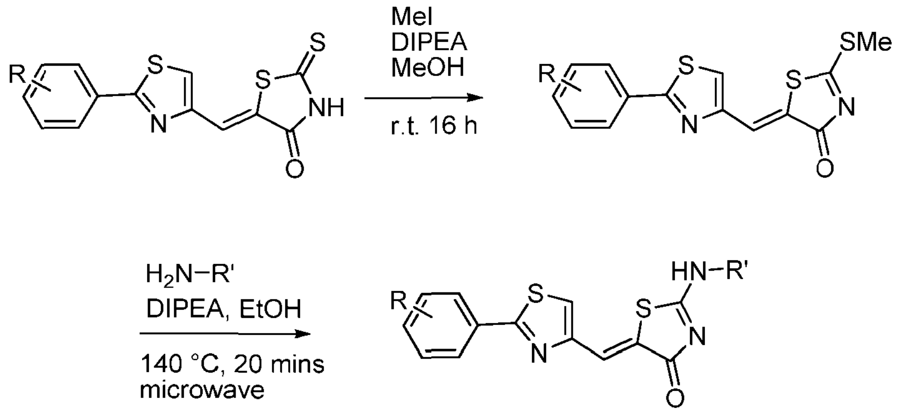
[00178] To a round-bottomed flask equipped with a magnetic stirrer bar was added the appropriate aldehyde (1 eq.), piperidine (0.1 eq.) and rhodanine or pseudothiohydantoin (1 eq.). The flask was sealed, purged with N_2 and ethanol (1-3 mL) was added via syringe. The reaction was then stirred at 70 °C for 16-24 hours and cooled to room temperature. Water was added and the resulting precipitate filtered, washing with water, ice-cooled ethanol and diethyl ether. The remaining solid was collected and dried under vacuum to give the desired product.

Example preparation: (*Z*)-2-Thioxo-5-((2-(4-(trifluoromethoxy)phenyl) thiazol-4-yl) methylene)thiazolidin-4-one



[00179] To a round-bottomed flask equipped with a magnetic stirrer bar was added 2-(4-(trifluoromethoxy)phenyl)thiazole-4-carbaldehyde (129 mg, 0.47 mmol), piperidine (4.6 µL, 0.047 mmol) and rhodanine (62 mg, 0.47 mmol). The flask was sealed, purged with N_2 and ethanol (3 mL) was added via syringe. The reaction was then stirred at 70 °C for 16 hours and cooled to room temperature. Water (10 mL) was added and the resulting precipitate filtered, washing with water, ice-cooled ethanol and diethyl ether. The remaining solid was collected and dried under vacuum to give the desired product (80 mg, 44%); ^{1}H NMR (400 MHz, d_6-DMSO): δ = 8.44 (s, 1 H), 8.15 (d, *J* = 8.7 Hz, 2 H), 7.68 (s, 1 H), 7.61 (d, *J* = 8.3 Hz, 2 H) ppm; *m/z* LRMS (ESI$^-$): 387 (100%) [M - H]$^-$; HRMS (ESI$^-$): calc. for $C_{14}H_6F_3N_2O_2S_3^-$ [M - H]$^-$ 386.9549, found 386.9548.

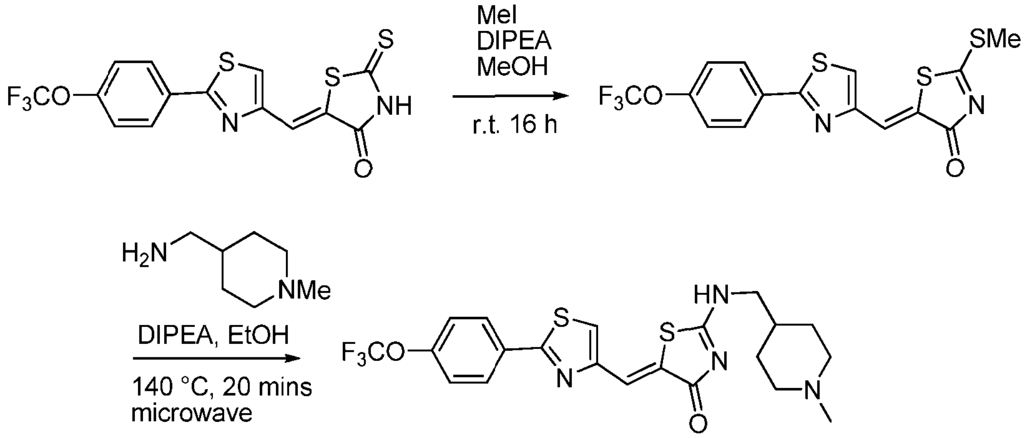
General procedure HG1: Reaction of amines with thiones via the corresponding thioether



[00180] To a round-bottomed flask equipped with a magnetic stirrer bar was added the appropriate thioxothiazolidindione (TTZD; 1 eq.), iodomethane (1.4 eq.), diisopropylethyl amine (1.2 eq.) and methanol (1-3 mL). The flask was sealed and purged with N_2 and the reaction stirred at room temperature for 16 hours. Water was added and the resulting precipitate filtered, washing with water, ice-cooled ethanol and diethyl ether. The remaining solid was collected and dried under vacuum to give the desired product.

[00181] To a microwave vial equipped with a magnetic stirrer bar was added the appropriate methylated TTZD (1 eq.), the requisite amine (1.5 eq.), diisopropylethyl amine (2.5 eq.) and ethanol (1.5 mL). The vial was sealed and heated in a microwave at 140 °C for 20 minutes. The reaction was cooled to room temperature, diluted with water and left to stand at room temperature until a precipitate formed. This was then filtered, washing with water, ice-cooled ethanol and diethyl ether. The remaining solid was collected and dried under vacuum to give the desired product.

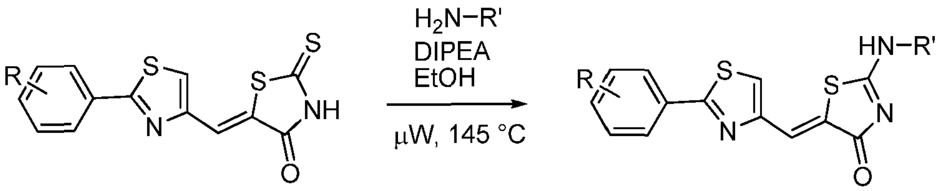
Example preparation: (*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoro methoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5 H)-one



[00182] To a round-bottomed flask equipped with a magnetic stirrer bar was added (*Z*)-2-thioxo-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4-one (80 mg, 0.21 mmol), iodomethane (0.018 mL, 0.29 mmol), diisopropylethyl amine (0.044 mL, 0.25 mmol) and methanol (3 mL). The flask was sealed and purged with N_2 and the reaction stirred at room temperature for 16 hours. Water (10 mL) was added and the resulting precipitate filtered, washing with water, ice-cooled ethanol and diethyl ether. The remaining solid was collected and dried under vacuum to give (*Z*)-2-(methylthio)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one (76 mg, 90%).

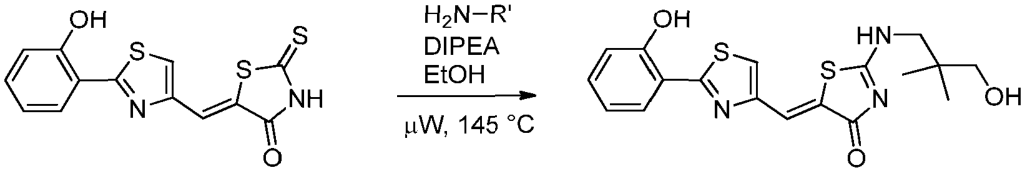
[00183] To a microwave vial equipped with a magnetic stirrer bar was added (*Z*)-2-(methylthio)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one (40 mg, 0.099 mmol), (1-methylpiperidin-4-yl)methanamine (20 mg, 0.15 mmol), diisopropylethyl amine (0.043 mL, 0.25 mmol) and ethanol (1.5 mL). The vial was sealed and heated in a microwave at 140 °C for 20 minutes. The reaction was cooled to room temperature, diluted with water and left to stand at room temperature until a precipitate formed. This was then filtered, washing with water, ice-cooled ethanol and diethyl ether. The remaining solid was collected and dried under vacuum to give the title compound (12 mg, 25%) as a pale yellow solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.59 (br. s, 1 H), 8.24 (s, 1 H), 8.14 (d, J = 8.7 Hz, 2 H), 7.58 (m, 3 H), 3.41 - 3.29 (m, 2 H), 2.75 (d, J = 11.4 Hz, 2 H), 2.14 (s, 3 H), 1.81 (t, J = 11.1 Hz, 2 H), 1.64 (d, J = 12.1 Hz, 2 H), 1.60 - 1.53 (m, 1 H), 1.26 - 1.16 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d^6-DMSO): δ = 179.6, 176.0, 165.6, 151.4, 149.8, 131.6, 131.2, 128.3, 124.7, 121.9, 120.1, 120.0 (q, J = 258 Hz), 54.9, 49.6, 46.1, 34.9, 29.4 ppm; *m/z* LRMS (ESI$^-$): 481.11 (100%) [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{21}H_{22}F_3N_4O_2S_2^+$ [M + H]$^+$ 483.1131, found 483.1129.

General procedure HG2: Direct reaction of amines with thiones



[00184] To a microwave vial equipped with a magnetic stirrer bar was added the appropriate thioxothiazolidindione (TTZD; 1 eq.), the requisite amine (1.5 eq.), diisopropylethyl amine (2.5 eq.) and ethanol (1 mL). The vial was sealed and heated in a microwave at 145 °C for 45 minutes. The reaction was cooled to room temperature, diluted with water and left to stand at room temperature until a precipitate formed. This was then filtered and washed with water. The remaining solid was collected and oven dried to give the desired product.

Example preparation: (Z)-2-((3-hydroxy-2,2-dimethylpropyl)amino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one



[00185] To a microwave vial equipped with a magnetic stirrer bar was added (*Z*)-5-((2-(2-Hydroxyphenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one (40 mg, 0.12 mmol), 3-amino-2,2-dimethylpropan-1-ol (18.5 mg, 0.18 mmol), diisopropylethyl amine (52 µL, 0.30 mmol) and ethanol (0.8 mL). The vial was sealed and heated in a microwave at 145 °C for 45 minutes. The reaction was cooled to room temperature, diluted with water and left to stand at room temperature until a precipitate formed. This was then filtered, washing with water. The remaining solid was collected and oven dried to give the desired product (17 mg, 36%) as a cream solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 11.21 (br. s, 1 H), 9.45 (t, J = 5.9 Hz, 1 H), 8.30 (dd, J = 7.9, 1.5 Hz, 1 H), 8.17 (s, 1 H), 7.59 (s, 1 H), 7.41 - 7.34 (m, 1 H), 7.08 (d, J = 8.0 Hz, 1 H), 7.02 (app. t, J = 7.5 Hz, 1 H), 4.74 (t, J = 5.8 Hz, 1 H), 3.42 (d, J = 5.8 Hz, 2 H), 3.17 (d, J = 5.9 Hz, 2 H), 0.87 (s, 6 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.6, 176.9, 162.8, 155.2, 149.1, 131.5, 130.1, 127.5, 124.7, 120.6, 119.5, 119.1, 116.5, 67.6, 51.3, 37.1, 22.2 ppm; *m/z* LRMS (ESI$^-$): 388 (100%) [M – H]$^-$; HRMS (ESI$^+$): calc. for $C_{18}H_{20}N_3O_3S_2^+$ [M + H]$^+$ 390.0941, found 390.0953.

[00186] *The following compounds were prepared using similar general methods and employing appropriate starting materials, which were either purchased from commercial sources or prepared according to literature procedures.*

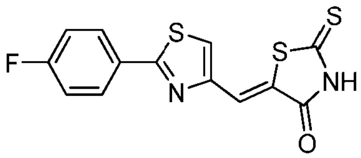
Example 1: Preparation of (*Z*)-5-((2-(4-fluorophenyl)thiazol-4-yl)methylene)-2-iminothiazolidin-4-one

2-(4-Fluorophenyl)thiazole-4-carbaldehyde

[00187] Prepared following *General Procedure SC1 above.*

[00188] Flash column chromatography (SiO_2, petrol:EtOAc 10:1), 22 mg, 41%, white solid; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.16 (s, 1 H), 8.35 - 8.30 (m, 2 H), 7.57 - 7.38 (m, 3 H) ppm; *m/z* LRMS (ESI$^+$): 533.00 [2M + 3MeOH + Na]$^+$ (100%)

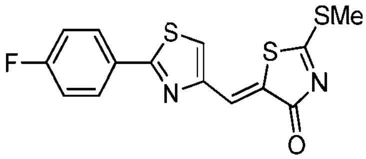
(*Z*)-5-((2-(4-Fluorophenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one



[00189] Prepared following *General Procedure C1*

[00190] 17 mg, 50%, yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 8.56 (s, 1 H), 8.31 - 7.59 (m, 5 H) ppm; *m/z* LRMS (ESI$^-$): 321 (100%) [M - H]$^-$

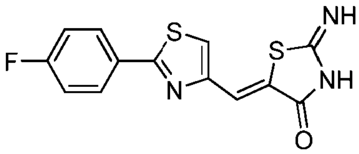
(*Z*)-5-((2-(4-Fluorophenyl)thiazol-4-yl)methylene)-2-(methylthio)thiazol-4(5*H*)-one



[00191] Prepared according to *General Procedure HG1*

[00192] 70 mg, 67%, light orange solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 8.40 (s, 1 H), 8.10 - 8.07 (m, 2 H), 7.83 (s, 1 H), 7.45 - 7.40 (m, 2 H), 2.82 (s, 3 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 196.0, 179.0, 167.0, 163.6 (d, J = 250 Hz), 150.3, 128.9 (d, J = 8.6 Hz), 128.7, 128.0, 125.8, 122.1, 116.6 (d, J = 23 Hz), 15.5 ppm

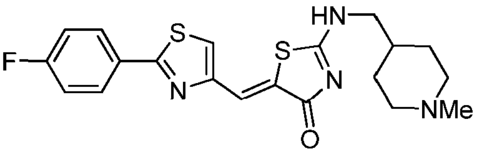
(*Z*)-5-((2-(4-Fluorophenyl)thiazol-4-yl)methylene)-2-iminothiazolidin-4-one



[00193] Prepared following *General Procedure C1*

[00194] 59 mg, 54%, beige solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.32 (br. s, 1 H), 9.09 (br. s, 1 H), 8.19 (s, 1 H), 8.10 - 8.06 (m, 2 H), 7.59 (s, 1 H), 7.45 - 7.41 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 180.4, 178.2, 166.2, 163.5 (d, J = 248 Hz), 151.2, 131.5, 129.1 (d, J = 3.8 Hz), 128.6 (d, J = 8.6 Hz), 124.3, 120.4, 116.5 (d, J = 22.0 Hz) ppm; *m/z* LRMS (ESI$^-$): 304 (100%) [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{13}H_9FN_3OS_2^+$ [M + H]$^+$ 306.0166, found 306.0171.

Example 2 : Preparation of (*Z*)-5-((2-(4-fluorophenyl)thiazol-4-yl)methylene)-2-((1-methylpiperidin-4-yl)methylamino)thiazol-4(5*H*)-one



[00195] Prepared following *General Procedure HG1*

[00196] 14 mg, 16%, peach solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.58 (br. s, 1 H), 8.19 (s, 1 H), 8.10 - 8.06 (m, 2 H), 7.58 (s, 1 H), 7.45 - 7.40 (m, 2 H), 3.40 - 3.35 (m, 2 H), 2.76 (d, J = 11.3 Hz, 2 H), 2.14 (s, 3 H), 1.81 (t, J = 11.6 Hz, 2 H), 1.64 (d, J = 12.8 Hz, 2 H), 1.59 - 1.52 (m, 1 H), 1.26 - 1.16 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.7, 176.0, 166.1, 163.5 (d, J = 249 Hz), 151.2, 131.0, 129.1, 128.6 (d, J

= 8.6 Hz), 124.2, 120.2, 116.5 (d, *J* = 22.0 Hz), 54.8, 49.6, 46.1, 34.9, 29.4; *m/z* LRMS (ESI$^-$): 415 (100%) [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{20}H_{22}FN_4OS_2^+$ [M + H]$^+$ 417.1214, found 417.1210.

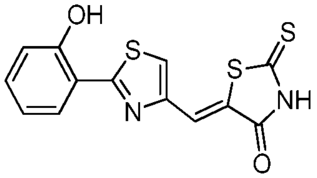
Example 3: Preparation of (*Z*)-5-((2-(2-hydroxyphenyl)thiazol-4-yl) methylene)-2-iminothiazolidin-4-one

2-(2-Hydroxyphenyl)thiazole-4-carboxaldehyde

[00197] Prepared following *General Procedure SC1*

[00198] Flash column chromatography (SiO_2, petrol:EtOAc 4:1), 70 mg, 65% pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.63 (s, 1 H), 10.07 (s, 1 H), 8.14 (s, 1 H), 7.65 (dd, *J* = 7.7, 1.5 Hz, 1 H), 7.40 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 1 H), 7.12 (dd, *J* = 8.3, 1.1 Hz, 1 H), 6.97 (app td, *J* = 7.7, 1.1 Hz, 1 H) ppm; *m/z* LRMS (ESI$^+$): 260 (100%) [M + MeOH + Na]$^+$; HRMS (ESI$^-$): calc. for $C_{10}H_6NO_2S^-$ [M - H]$^-$ 204.0125, found 204.0118.

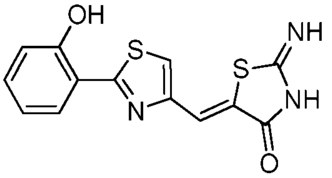
(*Z*)-5-((2-(2-Hydroxyphenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one



[00199] Prepared following *General Procedure C1* using 2-(2-hydroxyphenyl)thiazole-4-carboxaldehyde

[00200] 29 mg, 31%, yellow solid; 95:5 *Z:E;* ^{1}H NMR (500 MHz, d_6-DMSO): δ = 8.39 (s, 1 H), 8.26 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.70 (s, 1 H), 7.42 - 7.37 (m, 1 H), 7.13 - 7.07 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 199.7, 169.5, 163.5, 155.3, 148.2, 131.8, 128.4, 127.5, 126.8, 122.9, 119.8, 118.9, 116.5 ppm; *m/z* LRMS (ESI$^-$): 319 (100%) [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{13}H_8N_2NaO_2S_3^+$ [M + Na]$^+$ 342.9640, found 342.9634.

(*Z*)-5-((2-(2-Hydroxyphenyl)thiazol-4-yl)methylene)-2-iminothiazolidin-4-one



[00201] Prepared following *General Procedure C1* using 2-(2-hydroxyphenyl)thiazole-4-carboxaldehyde

[00202] 100 mg, 97%, brown solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 11.22 (s, 1 H), 9.29 (s, 1 H), 9.09 (s, 1 H), 8.27 (d, *J* = 7.8 Hz, 1 H), 8.16 (s, 1 H), 7.61 (s, 1 H), 7.37 (app t, *J* = 7.8 Hz, 1 H), 7.08 (d, *J* = 7.8 Hz, 1 H), 7.01 (app t, *J* = 7.8 Hz, 1 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 180.5, 178.2, 162.9, 155.3, 149.0, 131.5, 130.7, 127.4, 124.8, 120.8, 119.5, 119.1, 116.6 ppm; *m/z* LRMS (ESI$^-$): 302 (100%) [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{13}H_9N_3NaO_2S_2^+$ [M + Na]$^+$ 326.0028, found 326.0034.

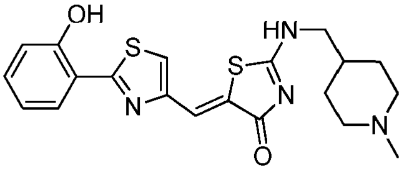
Example 4: Preparation of (*Z*)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)-2-(((1-methyl piperidin-4-yl)methyl)amino)thiazol-4(5 H)-one

[00203] Prepared following *General Procedure HG1* using (*Z*)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one.

(Z)-5-((2-(2-Hydroxyphenyl)thiazol-4-yl)methylene)-2-(methylthio)thiazol-4(5 H)-one

[00204] 47 mg, 75%, yellow solid; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 11.25 (s, 1 H), 8.41 (s, 1 H), 7.88 (s, 1 H), 8.27 (d, *J* = 8.2 Hz, 1 H), 7.41 - 7.36 (m, 1 H), 7.11 - 7.05 (m, 2 H), 2.84 (s, 3 H) ppm; *m/z* LRMS (ESI$^+$): 691 (100%) [2M + Na]$^+$; HRMS (ESI$^+$): calc. for $C_{14}H_{10}N_2NaO_2S_3^+$ [M + Na]$^+$ 356.9797, found 356.9796.

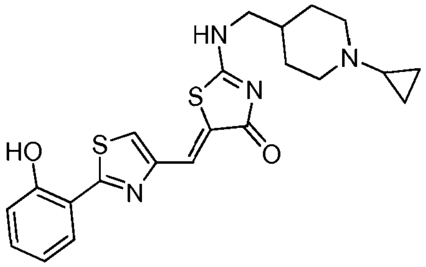
(*Z*)-5-((2-(2-Hydroxyphenyl)thiazol-4-yl)methylene)-2-(((1-methyl piperidin-4-yl)methyl)amino)thiazol-4(5 H)-one



[00205] 7 mg, 13%, pale yellow solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.57 (s, 1 H), 8.28 (d, *J* = 7.5 Hz, 1 H), 8.15 (s, 1 H), 7.59 (s, 1 H), 7.40-7.33 (m, 2 H), 7.07 (d, *J* = 7.7 Hz, 1 H), 6.99 (app t, *J* = 7.2 Hz, 1 H), 3.25 - 3.17 (m, 2 H), 2.77 (d, *J* = 11.0 Hz, 2 H), 2.15 (s, 3 H), 1.84 (t, *J* = 11.0 Hz, 2 H), 1.66 (d, *J* = 12.6 Hz, 2 H), 1.61 - 1.52 (m, 1

H), 1.27 - 1.16 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.9, 176.2, 162.9, 155.5, 149.0, 131.5, 130.2, 127.4, 124.6, 120.6, 119.3, 119.1, 116.6, 54.9, 49.6, 46.1, 34.8, 29.4 ppm; *m/z* LRMS (ESI$^+$): 415 (100%) $[M + H]^+$; HRMS (ESI$^+$): calc. for $C_{20}H_{23}N_4O_2S_2^+$ $[M + H]^+$ 415.1527, found 415.1254.

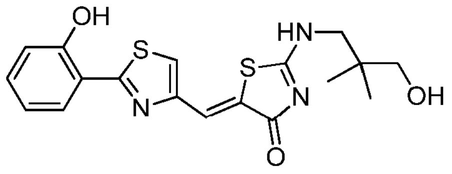
Example 5: Preparation of (Z)-2-(((1-cyclopropylpiperidin-4-yl)methyl)amino)-5-((2-(2-hydroxyphenyl) thiazol-4-yl)methylene)thiazol-4(5H)-one



[00206] Prepared following *General Procedure HG1* using (*Z*)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one

[00207] 51 mg, 30%, orange solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 11.25 (br. s, 1 H), 9.57 (t, *J* = 5.2 Hz, 1 H), 8.28 (d, *J* = 8.0 Hz, 1 H), 8.16 (s, 1 H), 7.59 (s, 1 H), 7.37 (t, *J* = 7.0 Hz, 1 H), 7.10 (d, *J* = 8.3 Hz, 1 H), 7.05 – 6.98 (m, 1 H), 2.94 (d, *J* = 11.0 Hz, 2 H), 2.17 – 2.12 (m, 1 H), 1.71 – 1.60 (m, 4 H), 1.26 – 1.12 (m, 5 H; obscured by diethyl ether impurity), 0.42 – 0.38 (m, 2 H), 0.30 – 0.27 (m, 2 H); ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.8, 176.2, 162.8, 155.2, 149.0, 131.5, 130.2, 127.5, 124.7, 120.6, 119.5, 119.1, 166.6, 52.9, 49.5, 40.1, 29.2, 5.6; *m/z* LRMS (ESI$^-$): 439. (100%) $[M-H]^-$;

Example 6: Preparation of (*Z*)-2-((3-hydroxy-2,2-dimethylpropyl)amino)-5-((2-(2-hydroxyphenyl) thiazole-4-yl)methylene)thiazol-4(5*H*)-one

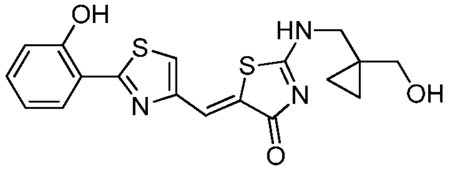


[00208] Prepared following *General Procedure HG1* using (*Z*)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one

[00209] 17 mg, 36%, cream solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 11.21 (br. s, 1 H), 9.45 (t, *J* = 5.9 Hz, 1 H), 8.30 (dd, *J* = 7.9, 1.5 Hz, 1 H), 8.17 (s, 1 H), 7.59 (s, 1 H), 7.41 - 7.34 (m, 1 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 7.02 (app. t, *J* = 7.5 Hz, 1 H), 4.74 (t, *J* = 5.8 Hz, 1 H), 3.42 (d, *J* = 5.8 Hz, 2 H), 3.17 (d, *J* = 5.9 Hz, 2 H), 0.87 (s, 6 H) ppm; ^{13}C

NMR (125 MHz, d_6-DMSO): δ = 179.6, 176.9, 162.8, 155.2, 149.1, 131.5, 130.1, 127.5, 124.7, 120.6, 119.5, 119.1, 116.5, 67.6, 51.3, 37.1, 22.2 ppm; *m*/*z* LRMS (ESI$^-$): 388 (100%) [M – H]$^-$; HRMS (ESI$^+$): calc. for $C_{18}H_{20}N_3O_3S_2^+$ [M + H]$^+$ 390.0941, found 390.0953.

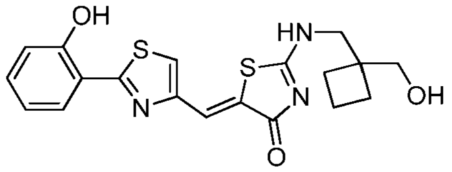
Example 7: Preparation of (*Z*)-2-(((1-(hydroxymethyl)cyclopropyl)methyl) amino)-5-((2-(2-hydroxy phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one



[00210] Prepared following *General Procedure HG1* using (*Z*)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one

[00211] 25 mg, 71%, cream solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.57 (br. s, 1 H), 8.29 (dd, *J* = 7.9, 1.5 Hz, 1 H), 8.15 (s, 1 H), 7.59 (s, 1 H), 7.40 - 7.33 (m, 1 H), 7.08 (d, *J* = 8.2 Hz, 1 H), 7.01 (app. t, *J* = 7.6 Hz, 1 H), 4.67 (br. s., 1 H), 3.54 (s, 2 H), 3.32 (s, 2 H), 0.53 - 0.49 (m, 2 H), 0.48 - 0.44 (m, 2 H); ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.7, 176.3, 162.8, 155.3, 149.1, 131.5, 130.3, 127.5, 124.6, 120.5, 119.4, 119.1, 116.6, 64.2, 48.4, 22.5, 8.5 ppm; *m*/*z* LRMS (ESI$^-$): 386 [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{18}H_{17}N_3NaO_3S_2^+$ [M + Na]$^+$ 410.0604, found 410.0610.

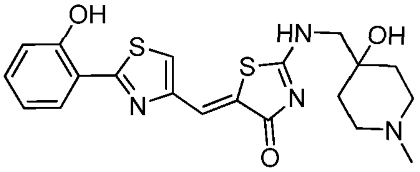
Example 8: Preparation of (*Z*)-2-(((1-(hydroxymethyl)cyclobutyl)methyl) amino)-5-((2-(2-hydroxy phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one



[00212] Prepared following *General Procedure HG1* using (*Z*)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one

[00213] 15 mg, 42%, cream solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 11.21 (br. s., 1 H), 9.53 - 9.45 (m, 1 H), 8.29 (d, *J* = 7.9 Hz, 1 H), 8.16 (s, 1 H), 7.60 (s, 1 H), 7.41 - 7.34 (t, *J* = 7.6 Hz, 1 H), 7.11 – 7.07 (m, 1 H), 7.02 (app. t, *J* = 7.5 Hz, 1 H), 4.76 (t, *J* = 5.3 Hz, 1 H), 3.62 (d, *J* = 5.3 Hz, 2 H), 3.41 (d, *J* = 5.3 Hz, 2 H), 1.90 – 1.70 (m, 6 H); ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.7, 176.9, 162.8, 155.2, 149.1, 131.5, 130.2, 127.5, 124.7, 120.6, 119.5, 119.1, 116.5, 64.9, 49.2, 43.5, 25.7, 14.6 ppm; *m/z* LRMS (ESI$^-$): 400 [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{19}H_{19}N_3NaO_3S_2^+$ [M + Na]$^+$ 424.0760, found 424.0765.

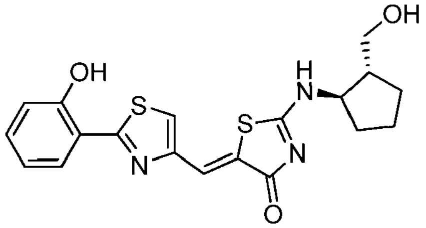
Example 9: Preparation of (Z)-2-((4-hydroxy-1-methylpiperidin-4-yl)methylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one



[00214] Prepared following *General Procedure HG1*

[00215] 15 mg, 20%, orange solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.57 (br. s, 1 H), 8.28 (d, *J* = 7.5 Hz, 1 H), 8.04 (s, 1 H), 7.59 (s, 1 H), 7.40 - 7.33 (m, 2 H), 7.07 (d, *J* = 7.7 Hz, 1 H), 6.99 (app t, *J* = 7.2 Hz, 1 H), 3.53 (app. br. s, 2 H), 2.38 - 2.45 (m, 4 H), 2.15 (s, 3 H), 1.52 - 1.54 (m, 2 H), 1.45 - 1.49 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.9, 177.1, 172.1, 163.0, 149.0, 131.4, 130.5, 127.4, 124.3, 120.4, 119.3, 119.2, 116.8, 67.8, 50.8, 45.9, 34.2, 30.7 ppm; *m/z* LRMS (ESI$^-$): 429 (100%) [M-H]$^-$;

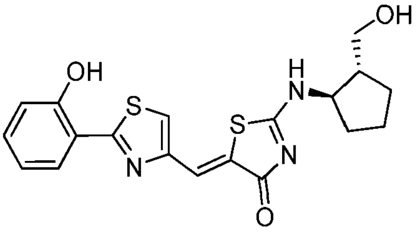
Example 10: Preparation of (Z)-2-((1R,2R)-2-(hydroxymethyl) cyclopentylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one



[00216] Prepared following *General Procedure HG1*

[00217] 19 mg, 17%, orange solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 11.22 (br. s, 1 H), 9.60 (d, *J* = 7.3 Hz, 1 H), 8.28 (dd, *J* = 7.9, 1.7 Hz, 1 H), 8.16 (s, 1 H), 7.60 (s, 1 H), 7.39 - 7.34 (m, 1 H), 7.07 (d, *J* = 7.9 Hz, 1 H), 7.01 (app. t, *J* = 7.9 Hz, 1 H), 4.68 (br. s, 1 H), 4.20 – 4.13 (m, 1 H), 3.47 - 3.41 (m, 1 H), 2.07 – 1.95 (m, 3 H), 1.88 - 1.79 (m, 1 H), 1.71 - 1.56 (m, 3 H), 1.44 - 1.37 (m, 1 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.2, 175.0, 162.8, 155.2, 149.0, 131.5, 130.1, 127.5, 124.6, 120.5, 119.8, 119.5, 116.6, 62.6, 58.0, 47.9, 30.7, 27.3, 22.6 ppm; *m/z* LRMS (ESI$^-$): 400 (100%) [M-H]$^-$;

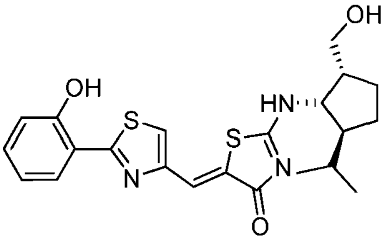
Example 11: Preparation of (Z)-2-((1R,2R)-2-(hydroxymethyl)cyclopentyl amino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one (racemic)



[00218] Prepared following *General Procedure HG1*

[00219] 91 mg, 96%, yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.60 (d, *J* = 7.3 Hz, 1 H), 8.28 (dd, *J* = 7.9, 1.65 Hz, 1 H), 8.16 (s, 1 H), 7.60 (s, 1 H), 7.39 - 7.34 (m, 1 H), 7.07 (d, *J* = 7.9 Hz, 1 H), 7.01 (t, *J* = 7.9 Hz, 1 H), 4.68 (br. s, 1 H), 4.20 - 4.13 (m, 1 H), 3.47 - 3.41 (m, 1 H), 2.07 – 1.95 (m, 2 H), 1.88 - 1.79 (m, 1 H), 1.71 - 1.56 (m, 4 H), 1.44 - 1.37 (m, 1 H) ppm;^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.7, 175.1, 162.9, 155.7, 148.9, 131.5, 130.1, 127.4, 124.6, 120.5, 119.2, 119.1, 116.6, 62.6, 58.0, 47.9, 30.7, 27.3, 22.6 ppm; *m/z* LRMS (ESI$^-$): 400 (100%) [M-H]$^-$;

Example 12: Preparation of (Z)-2-((1S,2R,5S)-2-(hydroxymethyl)-5-isopropylcyclopentylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one



[00220] The amine building block ((1S,2R,3R)-2-amino-3-isopropylcyclopentyl)methanol was prepared according to the following procedure.

[00221] (1S,2R,3R)-tert-Butyl-2-((3,4-dimethoxybenzyl)(1-phenylethyl) amino)-3-isopropylcyclopentanecarboxylate (292 mg, 0.589 mmol) was dissolved in a 5:1 CH_2Cl_2 / water mixture (15 mL) before addition of DDQ (538 mg, 2.36 mmol). The resulting solution was heated to 50 °C for 10 h, cooled down, diluted in CH_2Cl_2 and treated with $NaHCO_3$ aq. sat. sol. (10 mL). The aqueous layer was extracted further with CH_2Cl_2; the combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The desired product was obtained after purification on SiO_2 (5:1, petrol/EtOAc) as a colourless oil (181 mg, 89%).

[00222] A solution of the prepared amine (140 mg, 0.405 mmol), in THF was cooled down to 0 °C before portion-wise addition of $LiAlH_4$ (31 mg, 0.810 mmol). After the end of gas evolution, the mixture was refluxed for 9 h, then cooled down to 0 °C before careful addition of NH_4Cl aq. sat. sol. The aqueous layer was extracted with Et_2O and EtOAc; the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The desired product was obtained after purification on SiO_2 (3:1, petrol/EtOAc) was a colourless oil (92 mg, 87%).

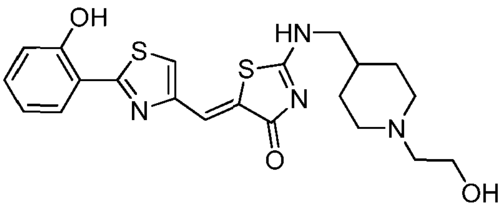
[00223] The prepared amino-alcohol (86 mg, 0.331 mmol) was dissolved in MeOH before addition of Pd/C (10%) followed by atmospheric H_2. After 8 h, the reaction was opened to air, filtered through Celite and concentrated in vacuo. The desired product was purified on SiO_2 (CH_2Cl_2, then 9:1 CH_2Cl_2/MeOH) and obtained as a glassy solid (27 mg, 54%).

[00224] ^1H NMR (400 MHz, MeOD): δ = 3.80 (dd, J = 11.4, 4.8 Hz, 1 H), 3.65 (dd, J = 11.4, 7.8 Hz, 1 H), 3.48 (dd, J = 7.3, 4.9 Hz, 1 H), 2.25 (m, 1 H), 1.84 – 1.74 (m, 4 H), 1.57 (m, 1 H), 1.45 (m, 1 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H) ppm; m/z LRMS (ESI^+): 158.2 (100%) $[M + H]^+$.

[00225] The title compound was prepared from ((1S,2R,3R)-2-amino-3-isopropylcyclopentyl)methanol and the appropriate thione following *General Procedure HG1*

[00226] 10 mg, 10%, yellow solid; ^1H NMR (400 MHz, d_6-DMSO): δ = 8.17 (d, *J* = 8.9 Hz, 1 H), 7.93 (s, 1 H), 7.67 (s, 1 H), 7.36 (app. t, *J* = 8.9 Hz, 1 H), 7.06 – 6.97 (m, 2 H), 4.50 - 4.46 (m, 1 H), 3.63 - 3.59 (m, 1 H), 3.50 - 3.45 (m, 1 H), 2.38 - 2.31 (m, 1 H), 1.99 - 1.78 (m, 4 H), 1.70 - 1.63 (m, 1 H), 1.59 - 1.50 (m, 1 H), 1.41 - 1.31 (m, 1 H), 1.00 – 0.95 (m, 6 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.7, 175.1, 162.8, 155.2, 149.1, 131.5, 130.3, 127.5, 124.6, 120.4, 119.5, 119.1, 116.5, 60.8, 59.7, 51.6, 44.9, 30.7, 27.4, 26.7, 21.0, 19.8 ppm; *m/z* LRMS (ESI^-): 442 (100%) $[M-H]^-$;

Example 13: Preparation of (Z)-2-((1-(2-hydroxyethyl)piperidin-4-yl) methylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one



[00227] Prepared following *General Procedure HG1*

[00228] 96 mg, 73%, yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.56 (s, 1 H), 8.28 (dd, J = 7.9, 1.6 Hz, 1 H), 8.15 (s, 1 H), 7.59 (s, 1 H), 7.36 (app. t, J = 8.5 Hz, 1 H), 7.07 (d, J = 8.1 Hz, 1 H), 6.99 (app. t, J = 7.3 Hz, 1 H), 4.40 (s, 1 H), 3.50 - 3.46 (m, 3 H), 2.89 - 2.87 (m, 2 H), 2.39 - 2.36 (m, 2 H), 1.98 - 1.92 (m, 2 H), 1.67 - 1.57 (m, 4 H), 1.26 - 1.18 (m, 2 H) ppm; *m/z* LRMS (ESI$^-$): 443 (100%) [M-H]$^-$;

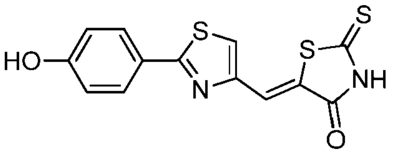
Example 14: Preparation of (*Z*)-5-((2-(4-hydroxyphenyl)thiazol-4-yl)methylene)-2-iminothiazolidin-4-one

2-(4-Hydroxyphenyl)thiazole-4-carboxaldehyde

[00229] Prepared following *General Procedure SC1*

[00230] Flash column chromatography (SiO_2, petrol:EtOAc 4:1), 64 mg, 68% pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.07 (s, 1 H), 8.12 (s, 1 H), 7.90 (d, J = 8.5 Hz, 2 H), 6.94 (d, J = 8.5 Hz, 2 H), 4.08 (s, 1 H) ppm; *m/z* LRMS (ESI$^+$): 260 (100%) [M + MeOH + Na]$^+$; HRMS (ESI$^-$): calc. for $C_{10}H_6NO_2S^-$ [M - H]$^-$ 204.0125, found 204.0118.

(*Z*)-5-((2-(4-Hydroxyphenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one

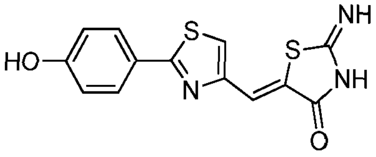


[00231] Prepared following *General Procedure C1* using 2-(4-hydroxyphenyl)thiazole-4-carboxaldehyde

[00232] 37 mg, 32%, yellow solid; 85:15 *Z*:*E*; ^{1}H NMR (500 MHz, d_6-DMSO): δ = 13.65 (s, 1 H), 10.21 (s, 1 H), 8.29 (s, 1 H), 7.87 (d, J = 8.7 Hz, 2 H), 7.64 (s, 1 H), 6.97

(d, J = 8.7 Hz, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 199.7, 168.5, 160.3, 150.0, 128.3, 128.1, 127.1, 126.4, 123.3, 122.8, 116.2 ppm; *m/z* LRMS (ESI$^-$): 319 (100%) [M - H]$^-$; HRMS (ESI$^-$): calc. for $C_{13}H_7N_2O_2S_3^-$ [M - H]$^-$ 318.9675, found 318.9671.

(*Z*)-5-((2-(4-Hydroxyphenyl)thiazol-4-yl)methylene)-2-iminothiazolidin-4-one



[00233] Prepared following *General Procedure C1* using 2-(4-hydroxyphenyl)thiazole-4-carboxaldehyde

[00234] 31 mg, 33%, pale brown solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 10.16 (br s, 1 H), 9.28 (br s, 1 H), 9.05 (br s, 1 H), 8.05 (s, 1 H), 7.86 (d, J = 8.1 Hz, 2 H), 7.54 (s, 1 H), 6.92 (d, J = 8.1 Hz, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 180.5, 178.3, 167.6, 160.0, 150.8, 131.2, 128.0, 123.7, 122.8, 120.6, 116.0 ppm; *m/z* LRMS (ESI$^-$): 302 (100%) [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{13}H_9N_3NaO_2S_2^+$ [M + Na]$^+$ 326.0028, found 326.0035.

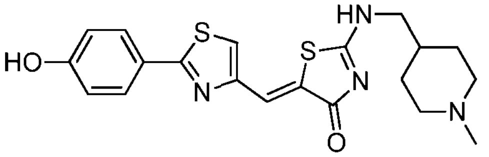
Example 15: Preparation of (*Z*)-5-((2-(4-hydroxyphenyl)thiazol-4-yl)methylene)-2-(((1-methyl piperidin-4-yl) methyl)amino)thiazol-4(5 H)-one

[00235] Prepared following *General Procedure HG1* using (*Z*)-5-((2-(4-hydroxyphenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one

(Z)-5-((2-(4-Hydroxyphenyl)thiazol-4-yl)methylene)-2-(methylthio)thiazol-4(5 H)-one

[00236] 45 mg, 71%, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.21 (br s, 1 H), 8.30 (s, 1 H), 7.88 (d, J = 8.6 Hz, 2 H), 7.81 (s, 1 H), 6.94 (d, J = 8.6 Hz, 2 H), 2.83 (s, 3 H) ppm; *m/z* LRMS (ESI$^-$): 333 (100%) [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{14}H_{10}N_2NaO_2S_3^+$ [M + Na]$^+$ 356.9797, found 356.9796.

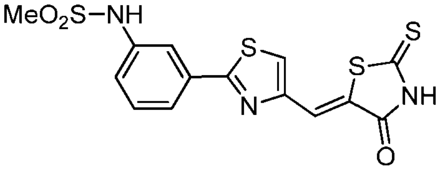
(*Z*)-5-((2-(4-Hydroxyphenyl)thiazol-4-yl)methylene)-2-(((1-methyl piperidin-4-yl) methyl)amino)thiazol-4(5 H)-one



[00237] 20 mg, 39%, pale yellow solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 10.15 (br s, 1 H), 9.53 (br s, 1 H), 8.05 (s, 1 H), 7.87 (d, *J* = 8.1 Hz, 2 H), 7.53 (s, 1 H), 6.92 (d, *J* = 8.1 Hz, 2 H), 3.31 - 3.25 (m, 2H), 2.75 (d, *J* = 10.2 Hz, 2 H), 2.14 (s, 3 H), 1.90 – 1.78 (m, 2 H), 1.73 – 1.60 (m, 2 H), 1.58 - 1.50 (m, 1 H), 1.27 - 1.15 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 179.8, 176.2, 167.6, 160.0, 150.8, 130.7, 128.0, 123.7, 122.6, 120.4, 116.0, 54.9, 49.6, 46.1, 34.9, 29.4 ppm; *m/z* LRMS (ESI$^+$): 415 (100%) [M + H]$^+$; HRMS (ESI$^+$): calc. for $C_{20}H_{23}N_4O_2S_2^+$ [M + H]$^+$ 415.1527, found 415.1264.

Example 16: Preparation of (*Z*)-*N*-(3-(4-((2-imino-4-oxothiazolidin-5-ylidene)methyl)thiazol-2-yl)phenyl)methanesulfonamide

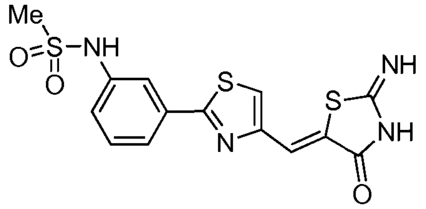
(*Z*)-*N*-(3-(4-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol-2-yl)phenyl) methanesulfonamide



[00238] Prepared following *General Procedure C1 using* *N*-(3-(4-formylthiazol-2-yl)phenyl)methanesulfonamide.

[00239] 50 mg, 57%, yellow solid; 92:8 *Z*:*E*; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 10.19 (s, 1 H), 8.42 (s, 1 H), 7.92 (s, 1 H), 7.73 (d, *J* = 7.9 Hz, 1 H), 7.68 (s, 1 H), 7.56 (app t, *J* = 7.9 Hz, 1 H), 7.40 (d, *J* = 7.9 Hz, 1 H), $SO_2C\underline{H}_3$ resonance obscured by solvent signal ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 199.6, 169.5, 167.7, 150.3, 139.5, 133.0, 130.6, 127.8, 127.7, 122.5, 121.6, 121.5, 116.7 ppm, SO$_2$*Me* resonance obscured by solvent signal; *m/z* LRMS (ESI$^-$): 396 (100%) [M - H]$^-$; HRMS (ESI$^-$): calc. for $C_{14}H_{10}N_3O_3S_4^-$ [M - H]$^-$395.9610, found 395.9607.

(*Z*)-*N*-(3-(4-((2-Imino-4-oxothiazolidin-5-ylidene)methyl)thiazol-2-yl)phenyl)methanesulfonamide



[00240] Prepared following *General Procedure C1*

[00241] 50 mg, 49%, beige solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 10.05 (br. s, 1 H), 9.32 (br. s, 1 H), 9.08 (br. s, 1 H), 8.21 (s, 1 H), 7.82 (s, 1 H), 7.78 (d, *J* = 7.8 Hz, 1 H), 7.60 (s, 1 H), 7.54 (app. t, *J* = 7.9 Hz, 1 H), 7.38 (d, *J* = 8.1 Hz, 1 H), 3.09 (s, 3 H) ppm; ^{13}C NMR (125 MHz, d^6-DMSO): δ = 180.4, 178.2, 166.9, 151.3, 139.4, 133.4, 131.6, 130.4, 124.4, 121.5, 121.3, 120.5, 117.3 ppm, SO_2*Me* signal obscured by solvent peak; *m/z* LRMS (ESI$^-$): 379 (100%) [M - H]$^-$; HRMS (ESI$^-$): calc. for $C_{14}H_{11}N_4O_3S_3^-$ [M - H]$^-$ 378.9999, found 378.9995.

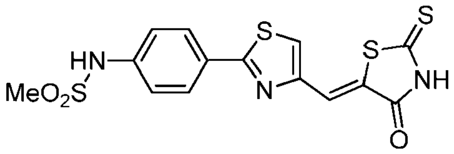
Example 17: Preparation of (*Z*)-*N*-(4-(4-((2-imino-4-oxothiazolidin-5-ylidene)methyl)thiazol-2-yl) phenyl)methanesulfonamide

***N*-(4-(4-Formylthiazol-2-yl)phenyl)methanesulfonamide**

[00242] Prepared following *General Procedure SC2*

[00243] Flash column chromatography (SiO_2, petrol:EtOAc 1:1), 105 mg, 71%, tan solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.23 (br s, 1 H), 9.96 (s, 1 H), 8.73 (s, 1 H), 7.99 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 3.10 (s, 3 H) ppm; *m/z* LRMS (ESI$^-$): 281 (100%) [M - H]$^-$; HRMS (ESI$^-$): calc. for $C_{11}H_9N_2O_3S_2^-$ [M - H]$^-$ 281.0060, found 281.0055.

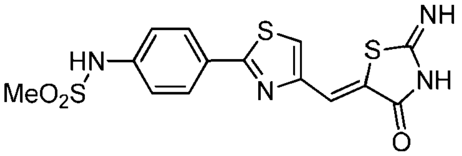
(*Z*)-*N*-(4-(4-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol-2-yl) phenyl)methanesulfonamide



[00244] Prepared following *General Procedure C1* using *N*-(4-(4-formylthiazol-2-yl)phenyl)methanesulfonamide

[00245] 65 mg, 75%, orange solid; 95:5 *Z*:*E*; ^{1}H NMR (500 MHz, d_6-DMSO): δ = 10.27 (s, 1 H), 8.35 (s, 1 H), 7.99 (d, *J* = 8.5 Hz, 2 H), 7.66 (s, 1 H), 7.39 (d, *J* = 8.5 Hz, 2 H), 3.12 (s, 3 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 199.6, 169.4, 167.8, 150.2, 141.1, 127.7, 127.4, 127.2, 127.0, 122.6, 119.1 ppm, SO_2Me resonance obscured by solvent signal; *m*/*z* LRMS (ESI$^-$): 396 (100%) [M - H]$^-$; HRMS (ESI$^-$): calc. for $C_{14}H_{10}N_3O_3S_4^-$ [M - H]$^-$ 395.9610, found 395.9607.

(*Z*)-*N*-(4-(4-((2-Imino-4-oxothiazolidin-5-ylidene)methyl)thiazol-2-yl) phenyl)methanesulfonamide



[00246] Prepared following *General Procedure C1* using *N*-(4-(4-formylthiazol-2-yl)phenyl)methanesulfonamide

[00247] 34 mg, 36%, tan solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 10.16 (br s, 1 H), 9.30 (br s, 1 H), 9.02 (br s, 1 H), 8.13 (s, 1 H), 7.99 (d, *J* = 8.3 Hz, 2 H), 7.57 (s, 1 H), 7.34 (d, *J* = 8.3 Hz, 2 H), 3.10 (s, 3 H) ppm; ^{13}C NMR (100 MHz, d_6-DMSO): δ = 180.5, 178.3, 166.7, 151.0, 140.9, 131.6, 127.6, 127.5, 123.6, 120.4, 119.0 ppm, SO_2Me resonance obscured by solvent signal; *m*/*z* LRMS (ESI$^-$): 379 (100%) [M - H]$^-$; HRMS (ESI$^-$): calc. for $C_{14}H_{11}N_4O_3S_3^-$ [M - H]$^-$ 378.9999, found 379.0001.

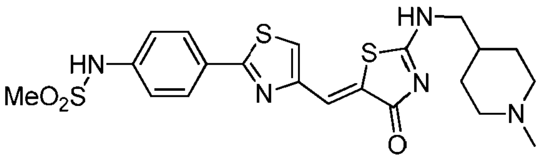
Example 18: Preparation of (*Z*)-*N*-(4-(4-((2-(((1-methylpiperidin-4-yl)methyl) amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl) methanesulfonamide

[00248] Prepared following *General Procedure HG1* using (*Z*)-*N*-(4-(4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol-2-yl) phenyl)methanesulfonamide

(Z)-*N*-(4-(4-((2-(Methylthio)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl) methanesulfonamide

[00249] 77 mg, 75%, yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 10.26 (br s, 1 H), 8.37 (s, 1 H), 8.02 (d, *J* = 8.3 Hz, 2 H), 7.84 (s, 1 H), 7.38 (d, *J* = 8.3 Hz, 2 H), 3.12 (s, 3 H), 2.82 (s, 3 H) ppm; *m*/*z* LRMS (ESI$^+$): 434 (100%) [M + Na]$^+$; HRMS (ESI$^+$): calc. for $C_{15}H_{13}N_3NaO_3S_4^+$ [M + Na]$^+$ 433.9732, found 433.9732.

(*Z*)-*N*-(4-(4-((2-(((1-Methylpiperidin-4-yl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)methanesulfonamide



[00250] 25 mg, 42%, yellow solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): $\delta = 8.08$ (s, 1 H), 7.94 (d, $J = 8.4$ Hz, 2 H), 7.54 (s, 1 H), 7.26 (d, $J = 8.4$ Hz, 2 H), 3.40 - 3.33 (m, 2 H), 3.02 (s, 3 H), 2.76 (d, $J = 10.2$ Hz, 2 H), 2.14 (s, 3 H), 1.83 (app. t, $J = 11.5$ Hz, 2 H), 1.65 (app. d, $J = 11.5$ Hz, 2 H), 1.59 - 1.51 (m, 1 H), 1.28 - 1.14 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): $\delta = 179.7$, 176.2, 166.8, 151.0, 141.7, 131.1, 127.5, 127.0, 123.3, 120.2, 119.0, 54.8, 49.5, 46.0, 34.8, 29.3 ppm, SO_2Me resonance obscured by solvent signal; *m*/*z* LRMS (ESI$^+$): 492 (100%) $[M + H]^+$; HRMS (ESI$^+$): calc. for $C_{21}H_{26}N_5O_3S_3^+$ $[M + H]^+$ 492.1192, found 492.1187.

Example 19: Preparation of (*Z*)-*N*-(3-(4-((2-imino-5-oxo-1,3-dithiolan-4-ylidene)methyl)thiazol-2-yl) phenyl)-*N*-methylmethanesulfonamide

***N*-(3-Bromophenyl)-*N*-methylmethanesulfonamide**

[00251] Pyridine (2.3 mL, 29.1 mmol) was added to a solution of 3-bromoaniline (0.63 mL, 5.81 mmol), in CH_2Cl_2 (29 mL) at room temperature. After 5 min mesyl chloride (0.90 mL, 11.6 mmol) was added dropwise. After 16 h 1M HCl (20 mL) was added and the mixture diluted with CH_2Cl_2 (50 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give *N*-(3-bromophenyl)methanesulfonamide which required no further purification.

[00252] *N*-(3-Bromophenyl)methanesulfonamide (~1.45 g, 5.81 mmol) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 418 mg, 10.4 mmol) in DMF (11.6 mL) at 0 °C. Following complete addition the cooling bath was removed and the reaction allowed to warm to room temperature. After 30 min methyl iodide (0.43 mL, 6.97 mmol) was added in one portion. After 2 h water (5 mL) was added dropwise and the solution extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, gradient elution petrol:Et_2O 1:1 to 1:3) gave the title compound (1.26 g, 82% over two steps) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ

= 7.53 (app t, *J* = 2.0 Hz, 1 H), 7.46 - 7.42 (m, 1 H), 7.38 - 7.34 (m, 1 H), 7.28 (s, 1 H), 3.32 (s, 3 H), 2.87 (s, 3 H) ppm; *m*/*z* (ESI$^+$) 551 (100%) [2M+Na]$^+$.

N-Methyl-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methanesulfonamide

[00253] Prepared according to *General Procedure BA* using the appropriate aryl halide

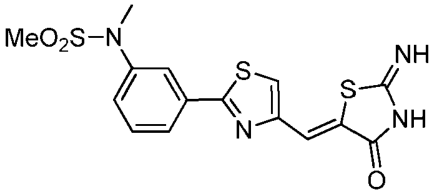
[00254] 1.27 g, 86%, yellow solid; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76 - 7.71 (m, 1 H), 7.55 - 7.51 (m, 1 H), 7.43 - 7.38 (m, 2 H), 3.35 (s, 3 H), 2.87 (s, 3 H), 1.35 (s, 12 H) ppm; *m*/*z* LRMS (ESI$^+$): 645 (80%) [2M + Na]$^+$.

N-(3-(4-Formylthiazol-2-yl)phenyl)-N-methylmethanesulfonamide

[00255] Prepared following *General Procedure SC2* using *N*-methyl-*N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methanesulfonamide

[00256] 210 mg, 68%, tan solid; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 10.11 (s, 1 H), 8.22 (s, 1 H), 8.07 (s, 1 H), 7.91 - 7.87 (m, 1 H), 7.58 - 7.53 (m, 2 H), 3.42 (s, 3 H), 2.91 (s, 3 H) ppm; *m*/*z* LRMS (ESI$^+$): 679 (100%) [2(M + MeOH) + Na]$^+$.

(Z)-N-(3-(4-((2-Imino-5-oxo-1,3-dithiolan-4-ylidene)methyl)thiazol-2-yl) phenyl)-N-methylmethanesulfonamide

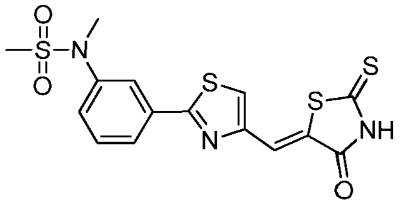


[00257] Prepared following *General Procedure C1* using *N*-(3-(4-formylthiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide

[00258] 20 mg, 30%, tan solid; ^{1}H NMR (500 MHz, d$_6$-DMSO): δ = 9.30 (br s, 1 H), 9.12 (br s, 1 H), 8.23 (s, 1 H), 7.99 - 7.95 (m, 2 H), 7.63 - 7.61 (m, 2 H), 7.61 (s, 1 H), 3.34 (s, 3 H), 3.04 (s, 3 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 180.4, 178.1, 166.5, 151.3, 142.6, 133.3, 131.6, 130.2, 128.0, 124.7, 124.6, 124.0, 120.4, 37.7, 35.2 ppm; *m*/*z* LRMS (ESI$^+$): 417 (100%) [M + Na]$^+$; HRMS (ESI$^+$): calc. for $C_{15}H_{14}N_4NaO_3S_3^+$ [M + Na]$^+$ 417.0120, found 417.0116.

Example 20: Preparation of (*Z*)-*N*-methyl-*N*-(3-(4-((2-(((1-methylpiperidin-4-yl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)methanesulfonamide

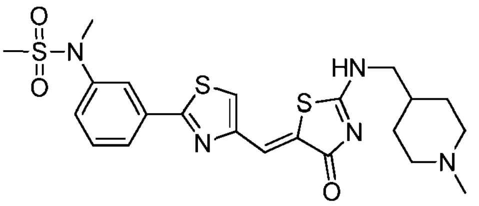
(*Z*)-*N*-Methyl-*N*-(3-(4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol -2-yl)phenyl)methanesulfonamide



[00259] Prepared following *General Procedure C1* using *N*-(3-(4-formylthiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide

[00260] 55 mg, 80%, yellow solid; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.44 (s, 1 H), 8.01 - 8.00 (m, 1 H), 7.97 (app td, *J* = 7.0, 1.5 Hz, 1 H), 7.70 (s, 1 H), 7.67 - 7.61 (m, 2 H), 3.04 (s, 3 H) ppm, 1 x 3H singlet obscured by residual water in solvent; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 199.5, 169.4, 167.3, 150.3, 142.6, 132.8, 130.4, 128.0, 127.9, 127.7, 124.7, 124.1, 122.4, 37.5, 35.4 ppm; *m*/*z* LRMS (ESI$^-$): 410 (100%) [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{15}H_{13}N_3NaO_3S_4^+$ [M + Na]$^+$ 433.9732, found 433.9732.

(*Z*)-*N*-Methyl-*N*-(3-(4-((2-(((1-methylpiperidin-4-yl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)methanesulfonamide

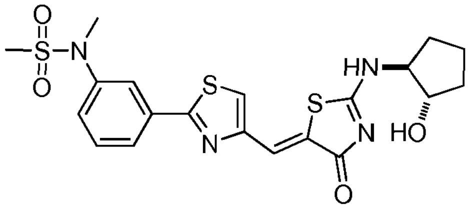


[00261] Prepared following *General Procedure HG1* using (Z)-N-methyl-N-(3-(4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol -2-yl)phenyl)methanesulfonamide

[00262] 34 mg, 58%, beige solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.63 - 9.58 (m, 1 H), 8.23 (s, 1 H), 8.00 – 7.91 (m, 2 H), 7.64 - 7.61 (m, 2 H), 7.60 (s, 1 H), 3.41 - 3.38 (m, 2 H), 3.03 (s, 3 H), 2.80 - 2.73 (m, 2 H), 2.15 (s, 3 H), 1.88 - 1.79 (m, 2 H), 1.69 - 1.61 (m, 2 H), 1.61 - 1.51 (m, 1 H), 1.27 - 1.18 (m, 2 H) ppm, 1 x 3H resonance obscured by trace H_2O resonance; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 179.7, 176.0, 166.5, 151.3, 142.6, 133.3, 131.0, 130.2, 127.9, 124.7, 124.6, 124.2, 120.3, 54.8, 49.6, 46.1, 37.7, 35.3, 29.4 ppm, SO$_2$*Me* resonance obscured by solvent signal; *m*/*z* LRMS

(ESI$^+$): 506 [M + H]$^+$; HRMS (ESI$^+$): calc. for $C_{22}H_{28}N_5O_3S_3^+$ [M + H]$^+$ 506.1349, found 506.1351.

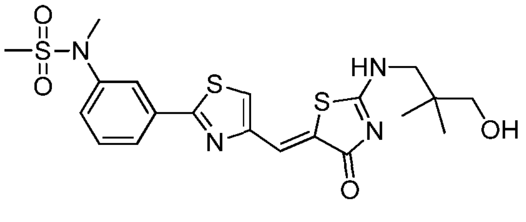
Example 21: Preparation of *N*-(3-(4-((*Z*)-(2-(((1*R*,2*S*)-2-hydroxycyclopentyl) amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide



[00263] Prepared following *General Procedure HG1* using (Z)-N-methyl-N-(3-(4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol -2-yl)phenyl)methanesulfonamide

[00264] 35 mg, 63%, pale yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.57 - 9.54 (m, 1 H), 8.24 (s, 1 H), 8.00 - 7.97 (m, 1 H), 7.96 - 7.94 (m, 1 H), 7.64 - 7.61 (m, 2 H), 7.60 (s, 1 H), 5.05 (d, *J* = 4.5 Hz, 1 H), 4.18 - 4.11 (m, 1 H), 4.03 - 3.99 (m, 1 H), 3.03 (s, 3 H), 2.10 - 2.05 (m, 1 H), 1.91 - 1.84 (m, 1 H), 1.73 - 1.66 (m, 2 H), 1.56 - 1.48 (m, 2 H) ppm, 1 x 3H resonance obscured by trace H_2O resonance; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.7, 175.2, 166.5, 151.3, 142.6, 133.3, 130.9, 130.2, 127.8, 124.7, 124.6, 124.4, 120.2, 75.7, 63.0, 37.7, 35.3, 32.0, 29.2, 20.3 ppm; *m*/*z* LRMS (ESI$^-$): 477 [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{20}H_{22}N_4NaO_4S_3^+$ [M + Na]$^+$ 501.0695, found 501.0700.

Example 22: Preparation of *N*-(3-(4-((*Z*)-(2-((3-hydroxy-2,2-dimethylpropyl) amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide

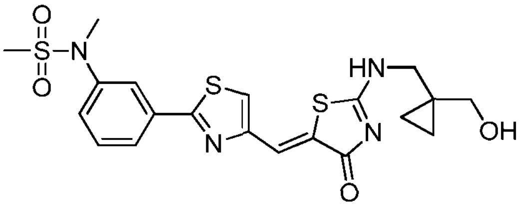


[00265] Prepared following *General Procedure HG1* using (Z)-N-methyl-N-(3-(4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol -2-yl)phenyl)methanesulfonamide

[00266] 15 mg, 26%, cream solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.51 - 9.46 (m, 1 H), 8.24 (s, 1 H), 8.02 - 7.98 (m, 1 H), 7.96 - 7.94 (m, 1 H), 7.65 - 7.62 (m, 2 H), 7.60 (s, 1 H), 4.74 (t, *J* = 5.9 Hz, 1 H), 3.43 (d, *J* = 5.9 Hz, 2 H), 3.17 (d, *J* = 5.6 Hz, 2 H), 3.03 (s, 3 H), 0.87 (s, 6 H) ppm, SO_2*Me* resonance obscured by trace H_2O

resonance; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.5, 176.8, 166.6, 151.3, 142.6, 133.3, 130.9, 130.2, 127.9, 124.7, 124.6, 124.4, 120.3, 67.6, 51.4, 37.7, 37.1, 35.3, 22.2 ppm; *m/z* LRMS (ESI$^-$): 479 [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{20}H_{24}N_4NaO_4S_3^+$ [M + Na]$^+$ 503.0852, found 503.0850.

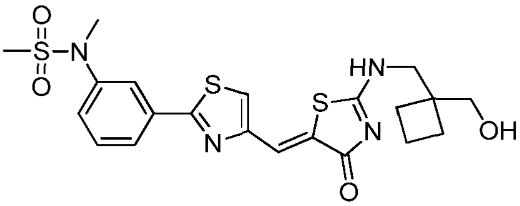
Example 23: Preparation of (*Z*)-*N*-(3-(4-((2-(((1-(hydroxymethyl) cyclopropyl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide



[00267] Prepared following *General Procedure HG1* using (Z)-N-methyl-N-(3-(4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol -2-yl)phenyl)methanesulfonamide

[00268] 10 mg, 18%, cream solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.61 (t, *J* = 5.5 Hz, 1 H), 8.23 (s, 1 H), 8.01 - 7.97 (m, 1 H), 7.96 (s, 1 H), 7.64 - 7.61 (m, 2 H), 7.60 (s, 1 H), 4.66 (t, *J* = 5.7 Hz, 1 H), 3.55 (d, *J* = 5.7 Hz, 2 H), 3.32 (d, *J* = 5.8 Hz, 2 H), 3.03 (s, 3 H), 0.53 - 0.49 (m, 2 H), 0.47 - 0.43 (m, 2 H) ppm, 1 x 3H resonance obscured by trace H_2O resonance; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.6, 176.2, 166.5, 151.3, 142.7, 133.3, 131.0, 130.2, 127.9, 124.7, 124.6, 124.3, 120.2, 64.3, 48.4, 37.7, 35.3, 22.5, 8.5 ppm; *m/z* LRMS (ESI$^-$): 477 [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{20}H_{22}N_4NaO_4S_3^+$ [M + Na]$^+$ 501.0695, found 501.0695.

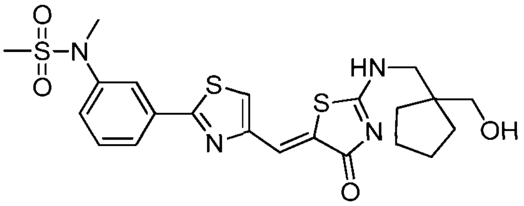
Example 24: Preparation of (*Z*)-*N*-(3-(4-((2-(((1-(hydroxymethyl) cyclobutyl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide



[00269] Prepared following *General Procedure HG1* using (Z)-N-methyl-N-(3-(4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol -2-yl)phenyl)methanesulfonamide

[00270] 17 mg, 29%, cream solid; ^{1}H NMR (500 MHz, d_6-DMSO): δ = 9.53 (br. s, 1 H), 8.24 (s, 1 H), 8.01 - 7.98 (m, 1 H), 7.96 - 7.95 (m, 1 H), 7.64 - 7.62 (m, 2 H), 7.61 (s, 1 H), 4.75 (t, *J* = 5.4 Hz, 1 H), 3.63 (d, *J* = 5.4 Hz, 2 H), 3.41 (d, *J* = 5.3 Hz, 2 H), 3.35 (s, 3 H), 3.03 (s, 3 H), 1.83 - 1.78 (m, 6 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 179.6, 176.8, 166.6, 151.3, 142.7, 133.3, 130.9, 130.2, 127.9, 124.7, 124.4, 120.3, 64.9, 59.8, 49.2, 43.6, 37.7, 35.3, 25.6, 14.6 ppm; *m*/*z* LRMS (ESI$^-$): 491 [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{21}H_{24}N_4NaO_4S_3^+$ [M + Na]$^+$ 515.0852, found 515.0851.

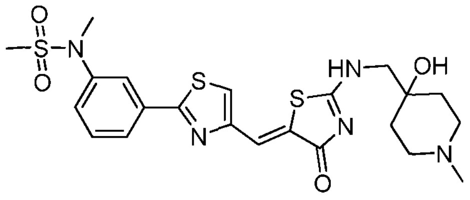
Example 25: Preparation of (*Z*)-*N*-(3-(4-((2-(((1-(hydroxymethyl)cyclopentyl) methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide



[00271] Prepared following *General Procedure HG1* using (Z)-N-methyl-N-(3-(4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol -2-yl)phenyl)methanesulfonamide

[00272] 41 mg, 85%, beige solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.52 (br. s, 1 H), 8.24 (s, 1 H), 8.02 - 7.98 (m, 1 H), 7.95 (s, 1 H), 7.64 - 7.61 (m, 2 H), 7.60 (s, 1 H), 4.82 - 4.77 (m, 1 H), 3.53 (s, 2 H), 3.24 (d, *J* = 3.2 Hz, 2 H), 3.03 (s, 3 H), 1.59 - 1.54 (m, 4 H), 1.48 - 1.35 (m, 4 H) ppm, 1 x 3H resonance obscured by trace H_2O resonance; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 179.5, 176.8, 166.6, 151.3, 142.6, 133.3, 130.9, 130.2, 127.9, 124.7, 124.7, 124.4, 120.3, 65.3, 49.6, 48.6, 37.7, 35.3, 32.0, 24.9 ppm; *m*/*z* LRMS (ESI$^-$): 505 (100%) [M – H$^-$]; HRMS (ESI$^+$): calc. for $C_{22}H_{27}N_4O_4S_3^+$ [M + H]$^+$ 507.1189, found 507.1200.

Example 26: Preparation of (Z)-N-(3-(4-((2-((4-hydroxy-1-methylpiperidin-4-yl)methylamino)-4-oxothiazol-5(4H)-ylidene)methyl)thiazol-2-yl)phenyl)-N-methylmethanesulfonamide



[00273] Prepared following *General Procedure HG1*

[00274] 96 mg, 95%, orange solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.80 (br. s, 1 H), 8.24 (s, 1 H), 7.98 (br. s, 2 H), 7.63 - 7.60 (m, 3 H), 5.22 (br s, 1 H), 3.60 (s, 2 H), 3.36 (s, 3 H), 3.18 – 3.19 (m, 2 H), 3.03 – 3.05 (m, 5 H), 2.71 (s, 3 H), 1.86 - 1.68 (m, 4 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ =179.6, 177.2, 166.5, 151.3, 142.7, 133.3, 131.1, 130.2, 128.0, 124.7, 124.6, 124.1, 120.3, 49.3, 42.5, 37.7, 35.4, 35.3, 31.5, 30.7 ppm; *m/z* LRMS (ESI$^+$): 522.17 (100%) [M+H]$^+$;

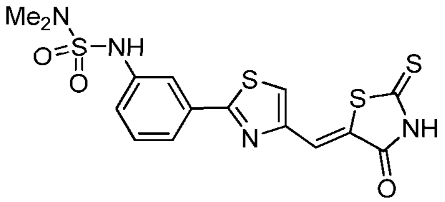
Example 27: Preparation of (*Z*)-2-imino-5-((2-(3-*N,N*-dimethylsulfamoylamino)thiazol-4-yl)methylene)thiazolidin-4-one

2-(3-*N,N*-Dimethylsulfamoylamino)thiazole-4-carbaldehyde

[00275] Prepared following *General Procedure SC1*

[00276] Flash column chromatography (SiO$_2$, petrol:EtOAc 2:1), 45 mg, 28%, white crystalline solid; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 10.10 (s, 1 H), 8.21 (s, 1 H), 7.72 (d, *J* = 7.7 Hz, 1 H), 7.46 - 7.34 (m, 2 H), 2.91 (s, 6 H) ppm

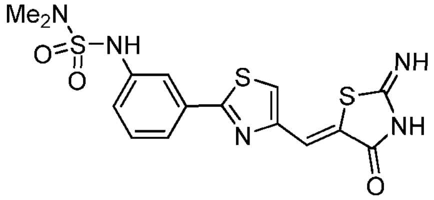
(*Z*)-5-((2-(3-*N,N*-Dimethylsulfamoylamino)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one



[00277] Prepared following *General Procedure C1*

[00278] 13 mg, 21%, dark yellow solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 10.32 (s, 1 H), 8.41 (s, 1 H), 7.97 (s, 1 H), 7.67 - 7.65 (m, 2 H), 7.51 (app. t, *J* = 7.9 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 2.79 (s, 6 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 199.7, 169.7, 167.9, 150.4, 139.7, 132.8, 130.3, 127.8, 127.7, 122.4, 121.3, 121.2, 115.9, 37.7 ppm; *m/z* LRMS (ESI$^-$): 425 (100%) [M - H]$^-$; HRMS (ESI$^-$): calc. for $C_{15}H_{13}N_4O_3S_4^-$ [M - H]$^-$ 424.9876, found 424.9875 .

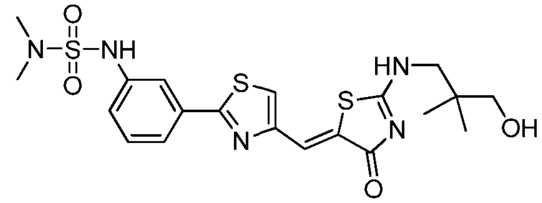
(*Z*)-2-Imino-5-((2-(3-*N,N*-dimethylsulfamoylamino)thiazol-4-yl)methylene)thiazolidin-4-one



[00279] Prepared following *General Procedure C1*

[00280] 29 mg, 29%, beige solid; ^1H NMR (400 MHz, d_6-DMSO): δ = 10.22 (br. s, 1 H), 9.32 (br. s, 1 H), 9.07 (br. s, 1 H), 8.20 (s, 1 H), 7.79 - 7.78 (m, 1 H), 7.73 (d, *J* = 7.9 Hz, 1 H), 7.60 (s, 1 H), 7.50 (app. t, *J* = 7.9 Hz, 1 H), 7.35 - 7.33 (m, 1 H), 2.76 (s, 6 H) ppm; *m/z* LRMS (ESI$^-$): 408 (100%) [M - H]$^-$

Example 28: Preparation of N-(3-(4-((Z)-(2-((3-hydroxy-2,2-dimethylpropyl) amino)-4-oxothiazol-5(4H)-ylidene)methyl)thiazol-2-yl)phenyl)-N,N-dimethylsulfonamide



[00281] Prepared following *General Procedure HG2*

[00282] 7 mg, 15%, tan solid; ^1H NMR (400 MHz, d_6-DMSO): δ = 10.22 (br. s, 1H), 9.45 (br. s, 1H), 8.23-8.17 (m, 1H), 7.80-7.75 (m, 2H), 7.63-7.57 (m, 1H), 7.51 (app. t, J = 8.1Hz, 1H), 7.35 (d, J = 8Hz, 1H), 4.74 (t, J = 5.5Hz, 1H), 3.42 (d, J = 5.8Hz, 2H), 3.17 (d, J = 5.6Hz, 2H), 2.74 (s, 6H), 0.90 (s, 6H); *m/z* LRMS (ESI$^-$): 494 (100%) [M – H$^-$]; HRMS (ESI$^+$): calc. for $C_{20}H_{26}N_5O_4S_3^+$ [M + H]$^+$ 496.1141, found 496.1135.

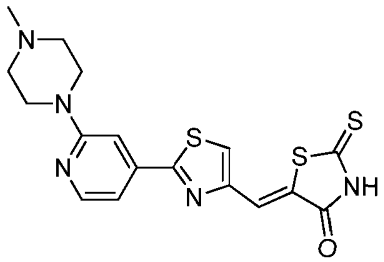
Example 29: Preparation of (*Z*)-2-imino-5-((2-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)thiazol-4-yl)methylene)thiazolidin-4-one

2-(2-(4-Methylpiperazin-1-yl)pyridin-4-yl)thiazole-4-carboxaldehyde

[00283] Prepared following *General Procedure SC2*

[00284] Flash column chromatography (SiO_2, EtOAc:MeOH 1:1), 57%, ^{1}H NMR (400 MHz, d_6-DMSO): δ = 10.01 (s, 1 H), 8.87 (s, 1 H), 8.32 (s, 1 H), 8.27 (d, J = 5.1 Hz, 1 H), 7.19 (d, J = 5.1 Hz, 1 H), 3.63 - 3.55 (m, 4 H), 2.45 - 2.40 (m, 4 H), 2.23 (s, 3 H) ppm; *m/z* LRMS (ESI$^+$): 321 (75%) [M + MeOH + H$^+$].

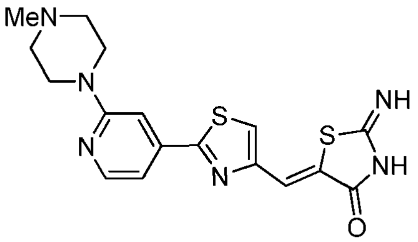
(*Z*)-5-((2-(2-(4-Methylpiperazin-1-yl)pyridin-4-yl)thiazol-4-yl)methylene)-2-thioxo thiazolidin-4-one



[00285] Prepared following *General Procedure C1* using 2-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)thiazole-4-carboxaldehyde

[00286] 58 mg, 32%, brown solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 8.36 - 8.31 (m, 2 H), 7.47 (s, 1 H), 7.32 (s, 1 H), 7.29 (d, J = 5.1 Hz, 1 H), 3.75 - 3.70 (m, 4 H), 2.87 - 2.82 (m, 4 H), 2.53 (s, 3 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 202.3, 175.0, 165.9, 159.2, 151.3, 149.1, 140.6, 132.2, 126.6, 119.3, 110.0, 103.7, 53.2, 44.1, 43.3 ppm; *m/z* LRMS (ESI$^+$): 404 (100%) [M + H]$^+$; HRMS (ESI$^+$): calc. for $C_{17}H_{18}N_5OS_3^+$ [M + H]$^+$ 404.0668, found 404.0668.

(*Z*)-2-Imino-5-((2-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)thiazol-4-yl)methylene)thiazolidin-4-one



[00287] Prepared following *General Procedure C1*

[00288] 47 mg, 37%, cream solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.33 (br. s, 1 H), 9.10 (br. s, 1 H), 8.32 – 8.25 (m, 2 H), 7.61 (s, 1 H), 7.26 - 7.23 (m, 2 H), 3.60 - 3.58 (m, 4 H), 2.45 - 2.43 (m. 4 H), 2.24 (s, 3 H) ppm; *m/z* LRMS (ESI$^-$): 385 (100%) [M - H]$^-$

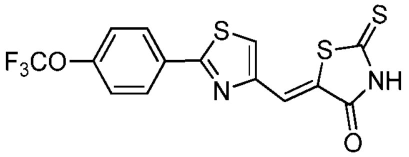
Example 30: Preparation of (*Z*)-2-(((1-methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one

2-(4-(Trifluoromethoxy)phenyl)thiazole-4-carbaldehyde

[00289] Prepared following *General Procedure SC1*

[00290] White crystals 2.20 g, 70% Yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.10 (s, 1 H), 8.20 (s, 1 H), 8.05 (d, *J* = 8.7 Hz, 2 H), 7.33 (d, *J* = 8.7 Hz, 2 H) ppm; ^{13}C NMR (101 MHz, d_6-DMSO): δ= 184.7, 167.8, 155.8, 150.9, 131.1, 128.5, 127.3, 121.4 ppm $F_3\underline{C}O$- resonance not visible; *m/z* LRMS (ESI) 271.99 (100%) [M - H]$^-$

(*Z*)-2-Thioxo-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4-one



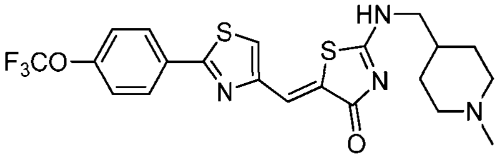
[00291] Prepared following *General Procedure C1*

[00292] Yellow powder 2.60 g, 83%; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 8.46 (s, 1 H), 8.18 (d, *J* = 8.1 Hz, 2 H), 7.70 (s, 1 H), 7.64 (d, *J* = 8.8 Hz, 2 H) ppm, *m/z* LRMS (ESI) 386.94 (100%) [M - H]$^-$

(*Z*)-2-(Methylthio)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one

[00293] Yellow powder 2.50 g, 94% yield; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 8.44 (s, 1 H), 8.15 (d, *J* = 8.8 Hz, 2 H), 7.84 (s, 1 H), 7.58 (d, *J* = 8.8 Hz, 2 H), 2.82 (s, 3 H) ppm; *m/z* LRMS (ESI) 401 (10%) [M - H]$^-$

(*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one



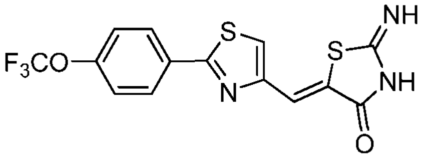
[00294] Prepared following *General Procedure HG1*

[00295] Cream powder 2.28 g, 85%; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.60 (s, 1 H), 8.23 (s, 1 H), 8.13 (d, *J* = 8.5 Hz, 2 H), 7.60 - 7.55 (m, 3 H), 3.42 – 3.37 (m, 2H), 2.79 - 2.72 (m, 2 H), 2.14 (s, 3 H), 1.86 - 1.74 (m, 2 H), 1.68 - 1.60 (m, 2 H), 1.60 - 1.49 (m, 1 H), 1.27 - 1.15 (m, 2 H) ppm; *m/z* LRMS (ESI) 481.06 (100%) $[M - H]^-$

[00296] In an different preparation the following data were also recorded ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.6, 176.0, 165.6, 151.4, 149.8, 131.6, 131.2, 128.3, 124.7, 121.9, 120.1, 120.0 (q, *J* = 258 Hz), 54.9, 49.6, 46.1, 34.9, 29.4 ppm; *m/z* LRMS (ESI$^-$): 481 (100%) $[M - H]^-$; HRMS (ESI$^+$): calc. for $C_{21}H_{22}F_3N_4O_2S_2^+$ $[M + H]^+$ 483.1131, found 483.1129.

Example 31: Preparation of (*Z*)-2-imino-5-((2-(4-(trifluoromethoxy)phenyl) thiazol-4-yl)methylene)thiazolidin-4-one

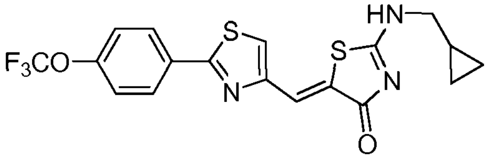
(*Z*)-2-Imino-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene) thiazolidin-4-one



[00297] Prepared following *General Procedure C1*

[00298] 65 mg, 55%, cream solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.33 (br. s, 1 H), 9.10 (br. s, 1 H), 8.42 (s, 1 H), 8.16 - 8.13 (m, 2 H), 7.61 - 7.57 (m, 3 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 180.4, 178.1, 165.7, 151.4, 149.8, 131.7, 131.6, 128.3, 124.8, 121.9, 120.3, 120.0 (q, *J* = 257 Hz) ppm; *m/z* LRMS (ESI$^-$): 370 (100%) $[M - H]^-$; HRMS (ESI$^+$): calc. for $C_{14}H_9F_3N_3O_2S_2^+$ $[M + H]^+$ 372.0083, found 372.0083.

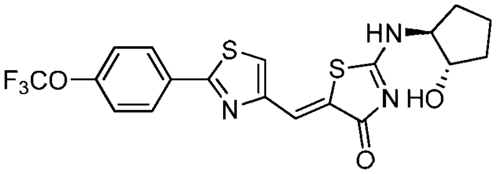
Example 32: Preparation of (*Z*)-2-(cyclopropylmethylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one



[00299] Prepared following *General Procedure HG1*

[00300] 59 mg, 74%, cream solid; ^1H NMR (400 MHz, d_6-DMSO): δ = 9.71 (br. s, 1 H), 8.24 (s, 1 H), 8.16 - 8.13 (m, 2 H), 7.59 - 7.57 (m, 3 H), 3.41 - 3.30 (m, 2 H), 1.12 - 1.05 (m, 1 H), 0.54 - 0.50 (m, 2 H), 0.30 - 0.27 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.6, 175.6, 165.6, 151.4, 149.8, 131.6, 131.3, 128.3, 124.7, 121.9, 120.1, 120.0 (q, J = 256 Hz), 48.7, 10.3, 3.5 ppm; *m/z* LRMS (ESI$^-$): 424 (100%) $[M - H]^-$; HRMS (ESI$^+$): calc. for $C_{18}H_{14}F_3N_3NaO_2S_2^+$ $[M + Na]^+$ 448.0372, found 448.0372.

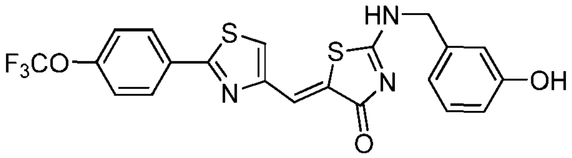
<u>Example 33: Preparation of (*Z*)-2-((1*S*,2*S*)-2-hydroxycyclopentylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one</u>



[00301] Prepared following *General Procedure HG1*

[00302] 60 mg, 65%, peach solid; ^1H NMR (400 MHz, d_6-DMSO): δ = 9.54 (d, *J* = 5.7 Hz, 1 H), 8.23 (s, 1 H), 8.13 (d, *J* = 8.8 Hz, 2 H), 7.59 - 7.56 (m, 3 H), 5.05 (d, *J* = 4.4 Hz, 1 H), 4.18 – 4.10 (m, 1 H), 4.02 – 3.96 (m, 1 H), 2.12 - 2.04 (m, 1 H), 1.91 - 1.84 (m, 1 H), 1.76 - 1.63 (m, 2 H), 1.56 - 1.48 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.6, 175.3, 165.6, 151.4, 149.8, 131.6, 131.1, 128.3, 124.7, 121.9, 120.1, 120.0 (q, *J* = 256 Hz), 75.7, 62.9, 32.0, 29.2, 20.3 ppm; *m/z* LRMS (ESI$^-$): 454 (100%) $[M - H]^-$; HRMS (ESI$^+$): calc. for $C_{19}H_{16}F_3N_3NaO_3S_2^+$ $[M + Na]^+$ 478.0477, found 478.0474.

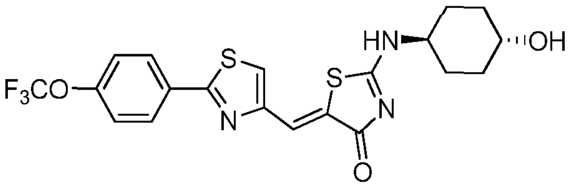
Example 34: Preparation of (*Z*)-2-(3-hydroxybenzylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one



[00303] Prepared following *General Procedure HG1*

[00304] 43 mg, 48%, pale yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.99 (br. s, 1 H), 9.48 (s, 1 H), 8.25 (s, 1 H), 8.14 (d, *J* = 8.7 Hz, 2 H), 7.62 (s, 1 H), 7.57 (d, *J* = 8.2 Hz, 2 H), 7.17 (t, *J* = 7.8 Hz, 1 H), 6.78 – 6.73 (m, 2 H), 6.69 (d, *J* = 8.2 Hz, 1 H), 4.64 (s, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.7, 176.2, 165.7, 157.5, 151.3, 149.8, 138.7, 131.6, 131.2, 129.6, 128.3, 124.9, 121.9, 120.4, 120.0 (q, *J* = 258 Hz), 118.1, 114.4, 114.3, 47.3 ppm; *m*/*z* LRMS (ESI$^-$): 476 (100%) $[M - H]^-$; HRMS (ESI$^-$): calc. for $C_{21}H_{13}F_3N_3O_3S_2^-$ $[M - H]^-$ 476.0356, found 476.0349.

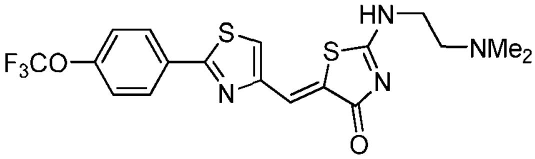
Example 35: Preparation of (*Z*)-2-((1*R*,4*R*)-4-hydroxycyclohexylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one



[00305] Prepared following *General Procedure HG1*

[00306] 71 mg, 74%, white solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.50 (br. s, 1 H), 8.23 (s, 1 H), 8.15 - 8.11 (m, 2 H), 7.58 - 7.56 (m, 3 H), 4.64 (d, *J* = 4.4 Hz, 1 H), 3.86 (m, 1 H), 3.47 - 3.40 (m, 1 H), 1.97 - 1.85 (m, 4 H), 1.28 (m, 4 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.7, 174.7, 165.6, 151.4, 149.8, 131.6, 131.1, 128.3, 124.7, 121.9, 120.1, 120.0 (q, *J* = 256 Hz), 67.7, 53.1, 33.4, 29.7 ppm; *m*/*z* LRMS (ESI$^-$): 468 (100%) $[M - H]^-$; HRMS (ESI$^-$): calc. for $C_{20}H_{17}F_3N_3O_3S_2^-$ $[M - H]^-$ 468.0669, found 468.0663.

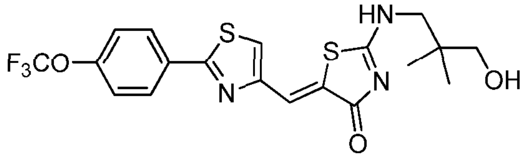
Example 36: Preparation of (*Z*)-2-(2-(dimethylamino)ethylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one



[00307] Prepared following *General Procedure HG1*

[00308] 57 mg, 68%, off-white solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 8.23 (s, 1 H), 8.16 - 8.13 (m, 2 H), 7.59 - 7.57 (m, 3 H), 3.60 (t, *J* = 6.2 Hz, 2 H), 2.46 (t, *J* = 6.2 Hz, 2 H), 2.19 (s, 6 H), ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.6, 175.8, 165.6, 151.4, 149.8, 131.6, 131.4, 128.3, 124.6, 121.9, 120.1, 120.0 (q, *J* = 256 Hz), 57.3, 45.1, 42.2 ppm; *m/z* LRMS (ESI$^-$): 441 (100%) [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{18}H_{18}F_3N_4O_2S_2^+$ [M + H$^+$] 443.0818, found 443.0818.

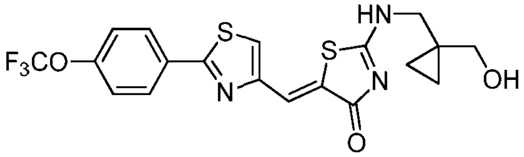
Example 37: Preparation of (*Z*)-2-((3-hydroxy-2,2-dimethylpropyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one



[00309] Prepared following *General Procedure HG1* using (*Z*)-2-thioxo-5-((2-(4-(trifluoromethoxy)phenyl) thiazol-5-yl) methylene)thiazolidin-4-one

[00310] 44 mg, 52%, yellow solid; ^{1}H NMR (500 MHz, d_6-DMSO): δ = 9.46 - 9.42 (m, 1 H), 8.24 (s, 1 H), 8.17 - 8.14 (m, 2 H), 7.60 (s, 1 H), 7.58 (d, *J* = 7.9 Hz, 2 H), 4.72 (t, *J* = 6.0 Hz, 1 H), 3.43 (d, *J* = 5.3 Hz, 2 H), 3.18 (d, *J* = 5.6 Hz, 2 H), 0.87 (s, 6 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.5, 176.8, 165.7, 151.4, 149.8, 131.6, 131.1, 128.3, 124.5, 121.9, 120.2, 120.0 (q, *J* = 257 Hz), 67.6, 51.4, 37.1, 22.2 ppm; *m/z* LRMS (ESI$^-$): 456 [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{19}H_{18}F_3N_3NaO_3S_2^+$ [M + Na]$^+$ 480.0634, found 480.0632.

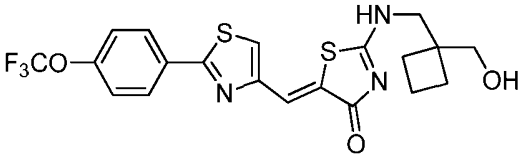
Example 38: Preparation of (*Z*)-2-(((1-(hydroxymethyl)cyclopropyl)methyl) amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one



[00311] Prepared following *General Procedure HG1* using (*Z*)-2-thioxo-5-((2-(4-(trifluoromethoxy)phenyl) thiazol-5-yl) methylene)thiazolidin-4-one

[00312] 61 mg, 72%, yellow solid; ^{1}H NMR (500 MHz, d_6-DMSO): δ = 9.58 - 9.55 (m, 1 H), 8.24 (s, 1 H), 8.17 - 8.14 (m, 2 H), 7.60 - 7.56 (m, 3 H), 4.65 (t, J = 5.8 Hz, 1 H), 3.54 (s, 2H), ~3.3 (m, 2H, obscured by solvent) 0.52 - 0.49 (m, 2 H), 0.48 - 0.44 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.6, 176.2, 165.6, 151.4, 149.8, 131.6, 131.3, 128.3, 124.7, 121.9, 120.1, 120.0 (q, J = 257 Hz), 64.3, 48.4, 22.5, 8.5 ppm; *m*/*z* LRMS (ESI$^-$): 454 [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{19}H_{16}F_3N_3NaO_3S_2^+$ [M + Na]$^+$ 478.0477, found 478.0477.

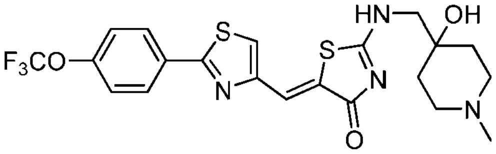
Example 39: Preparation of (*Z*)-2-(((1-(hydroxymethyl)cyclobutyl)methyl) amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one



[00313] Prepared following *General Procedure HG1* using (*Z*)-2-thioxo-5-((2-(4-(trifluoromethoxy)phenyl) thiazol-5-yl) methylene)thiazolidin-4-one

[00314] 55 mg, 63%, yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.50 (br. s, 1 H), 8.24 (s, 1 H), 8.17 - 8.13 (m, 2 H), 7.60 - 7.59 (s, 1 H, partly obscured), 7.59 - 7.56 (m, 2 H), 4.75 (br. s, 1 H), 3.62 (s, 2 H), 3.40 (s, 2 H), 1.83 - 1.78 (m, 6 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.5, 176.8, 165.7, 151.4, 149.8, 131.6, 131.2, 128.3, 124.7, 121.9, 120.1, 120.0 (q, J = 257 Hz), 65.0, 49.2, 43.5, 25.6, 14.6 ppm; *m*/*z* LRMS (ESI$^-$): 468 [M - H]$^-$; HRMS (ESI$^+$): calc. for $C_{20}H_{18}F_3N_3NaO_3S_2^+$ [M + Na]$^+$ 492.0634, found 492.0629.

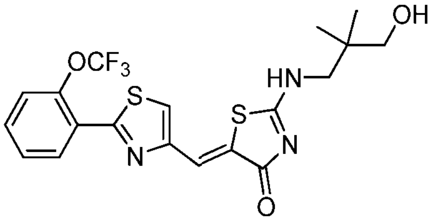
Example 40: Preparation of (Z)-2-((4-hydroxy-1-methylpiperidin-4-yl) methylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene) thiazol-4(5H)-one



[00315] Prepared following *General Procedure HG1* using (*Z*)-2-thioxo-5-((2-(4-(trifluoromethoxy)phenyl) thiazol-5-yl) methylene)thiazolidin-4-one.

[00316] 60 mg, 60%, cream coloured powder. ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.52 (s, 1 H), 8.21 (s, 1 H), 8.16 (d, J = 8.0 Hz, 2 H), 7.56 s, 1 H), 7.55 (d, J = 8.0 Hz, 2 H), 4.60 (s, 1 H), 3.52 (s, 2H), 2.43 – 2.39 (m, 2 H), 2.30-2.23 (m, 2 H), 2.15 (s, 3 H), 1.57 (m, 4 H) ppm; ^{19}F NMR (376 MHz, d_6-DMSO): δ = -56.7 ppm; ^{13}C NMR (100 MHz, d_6-DMSO): δ = 180.5, 176.8, 169.4, 166.2, 152.4, 132.5, 132.3, 129.2, 129.0, 125.5, 122.7, 120.8, 68.5, 51.6, 46.4, 38.9 ppm $F_3\underline{C}O$- resonance not visible, *m/z* LRMS (ESI) 497 (100%) $[M - H]^-$

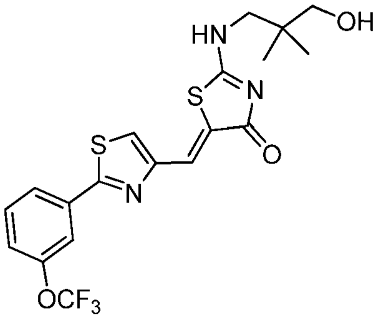
Example 41: Preparation of (Z)-2-(3-hydroxy-2,2-dimethylpropylamino)-5-((2-(2-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one



[00317] Prepared following *General Procedure HG1* using (*Z*)-2-thioxo-5-((2-(4-(trifluoromethoxy)phenyl) thiazol-5-yl) methylene)thiazolidin-4-one.

[00318] 61 mg, 72%, colourless powder. ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.46 (s, 1 H), 8.45 (dd, J = 8.0; 2.0 Hz, 1 H), 8.35 (s, 1 H), 7.65 – 7.72 (m, 3 H), 7.63 (s, 1 H), 4.75 (s, 1 H), 3.43 (s, 2 H), 3.17 (s, 2 H), 0.87 (s, 6 H) ppm; ^{19}F NMR (376 MHz, d_6-DMSO): δ = -55.7 ppm; *m/z* LRMS (ESI) 456 (100%) $[M - H]^-$

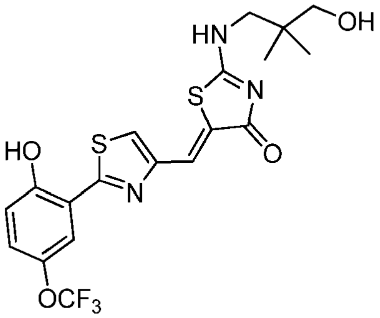
Example 42: Preparation of (Z)-2-((3-hydroxy-2,2-dimethylpropyl)amino)-5-((2-(3-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one



[00319] Prepared following *General Procedure HG1* using (*Z*)-2-thioxo-5-((2-(3-(trifluoromethoxy)phenyl) thiazol-5-yl) methylene)thiazolidin-4-one. The thiocarbonyl species was prepared in a similar manner to other examples using appropriate starting materials and reagents.

[00320] 95 mg, 84%, cream solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.49 (br. s, 1 H), 8.29 (s, 1 H), 8.07 (d, *J* = 7.6 Hz, 1 H), 7.95 (s, 1 H), 7.72 (app. t, *J* = 8.0 Hz, 1 H), 7.64 – 7.55 (m, 2 H), 4.75 (br. s, 1 H), 3.43 (s, 2 H), 3.17 (s, 2 H), 0.87 (s, 6 H); ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.5, 176.7,165.5, 151.4, 148.9, 134.5, 131.8, 131.6, 131.1, 125.6, 125.5, 123.1, 122.0 (q, *J* = 258 Hz), 119.1, 67.6, 51.4, 37.1, 22.2; *m/z* LRMS (ESI$^-$): 456 (100%) [M-H]$^-$;

Example 43: Preparation of (Z)-2-((3-hydroxy-2,2-dimethylpropyl)amino)-5-((2-(2-hydroxy-5-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one



[00321] Prepared following *General Procedure HG1* using the appropriate thiocarbonyl species.

[00322] 45 mg, 59%, orange solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.54 (br. s, 1 H), 8.24 (s, 1 H), 8.13 (d, *J* = 2.4 Hz, 1 H), 7.6 (s, 1 H), 7.41 – 7.36 (m, 1 H), 7.17 – 7.14 (m, 1 H), 4.77 (br. s, 1 H), 3.43 (d, *J* = 5.2 Hz, 2 H), 3.23 (d, *J* = 7.2 Hz, 2 H), 3.17 (br. s, 1 H), 0.87 (s, 6 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.5, 176.7, 161.3, 154.2, 149.3, 140.7, 130.1, 125.8, 124.2, 122.1 (q, *J* = 258 Hz), 120.6, 120.0, 119.9, 118.0, 67.6, 51.3, 37.2, 22.3 ppm; *m/z* LRMS (ESI$^-$): 472 (100%) [M-H]$^-$.

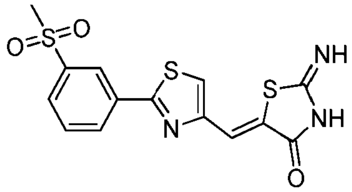
Example 44: Preparation of (Z)-2-imino-5-((2-(3-(methylsulfonyl)phenyl) thiazol-4-yl)methylene) thiazolidin-4-one

2-(3-(Methylsulfonyl)phenyl)thiazole-4-carbaldehyde

[00323] Prepared following *General Procedure SC1*

[00324] 81 mg 80%, white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ = 10.09 (s, 1 H), 8.42 (s, 1 H), 8.36 (d, *J* = 8.0 Hz, 1 H), 8.31 (s, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.87 (app. t, *J* = 8.0 Hz, 1 H), 3.36 (s, 3 H) ppm; *m/z* LRMS (ESI$^+$): 290 [M + Na]$^+$ (100%);

(Z)-2-Imino-5-((2-(3-(methylsulfonyl)phenyl)thiazol-4-yl)methylene) thiazolidin-4-one



[00325] Prepared following *General Procedure C1*

[00326] 40 mg, 39%, orange solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.33 (br s, 1 H), 9.18 (br s, 1 H), 8.42 (s, 1 H), 8.36 (d, *J* = 8.0 Hz, 1 H), 8.31 (s, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.87 (t, *J* = 8.0 Hz, 1 H), 7.63 (s, 1 H), 3.36 (s, 3 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 180.4, 178.0, 165.6, 151.5, 142.1, 133.1, 131.7, 130.9, 130.6, 129.1, 125.4, 124.5, 120.3, 43.4 ppm; *m/z* LRMS (ESI$^-$): 364 (100%) [M-H]$^-$.

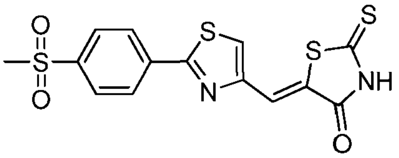
Example 45: Preparation of (*Z*)-2-imino-5-((2-(4-(methylsulfonyl)phenyl) thiazol-4-yl)methylene)-1,3-dithiolan-4-one

2-(4-(Methylsulfonyl)phenyl)thiazole-4-carbaldehyde

[00327] Prepared following *General Procedure C1*

[00328] Flash column chromatography (SiO_2, gradient elution petrol:EtOAc 1:1 to 1:2), 162 mg, 58%, pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.14 (d, *J* = 1.0 Hz, 1 H), 8.29 (d, *J* = 1.0 Hz, 1 H), 8.25 - 8.21 (m, 2 H), 8.10 - 8.06 (m, 2 H), 3.12 (s, 3 H) ppm.

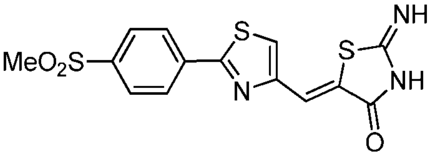
(*Z*)-5-((2-(4-(Methylsulfonyl)phenyl)thiazol-4-yl)methylene)-2-thioxo thiazolidin-4-one



[00329] Prepared following *General Procedure HG1* using 2-(4-(methylsulfonyl)phenyl)thiazole-4-carbaldehyde

[00330] 53 mg, 74%, yellow solid; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.53 (s, 1 H), 8.28 (d, *J* = 8.4 Hz, 2 H), 8.15 (d, *J* = 8.4 Hz, 2 H), 7.72 (s, 1 H), 3.30 (s, 3 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 199.4, 169.4, 166.3, 150.7, 142.4, 136.2, 129.1, 128.3, 128.0, 127.2, 122.3, 43.4 ppm; *m/z* LRMS (ESI$^-$): 381 (100%) [M - H]$^-$; HRMS (ESI$^-$): calc. for $C_{14}H_9N_2O_3S_4^-$ [M - H]$^-$ 380.9501, found 380.9501.

(*Z*)-2-Imino-5-((2-(4-(methylsulfonyl)phenyl)thiazol-4-yl)methylene)-1,3-dithiolan-4-one



[00331] Prepared following *General Procedure C1* using 2-(4-(methylsulfonyl)phenyl)thiazole-4-carbaldehyde

[00332] 14 mg, 55%, cream solid; ^{1}H NMR (500 MHz, d$_6$-DMSO): δ = 9.33 (br s, 1 H), 9.12 (br s, 1 H), 8.33 (s, 1 H), 8.26 (d, *J* = 8.5 Hz, 2 H), 8.10 (d, *J* = 8.5 Hz, 2 H), 7.63 (s, 1 H), 3.31 (s, 3 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 180.3, 178.0, 165.4, 151.7, 142.2, 136.6, 131.9, 128.1, 127.0, 125.8, 120.2, 43.4 ppm; *m/z* LRMS (ESI$^+$): 388 (100%) [M + Na]$^+$; HRMS (ESI$^+$): calc. for $C_{14}H_{11}N_3NaO_3S_3^+$ [M + Na]$^+$ 387.9855, found 387.9854.

Example 46: Preparation of (*Z*)-2-imino-5-((2-(3-(piperidin-1-yl)phenyl)thiazol-4-yl)methylene)-1,3-dithiolan-4-one

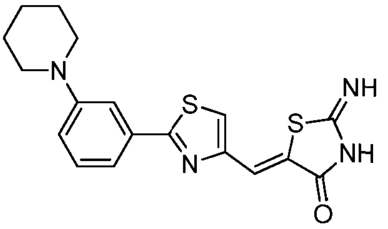
2-(3-(Piperidin-1-yl)phenyl)thiazole-4-carboxaldehyde

[00333] Prepared following *General Procedure SC2*

[00334] Flash column chromatography (SiO$_2$, petrol:EtOAc 4:1), 93%; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.98 (s, 1 H), 8.76 (s, 1 H), 7.49 - 7.47 (m, 1 H), 7.36 (d, *J* = 3.2 Hz, 1 H), 7.35 (s, 1 H), 7.15 - 7.11 (m, 1 H), 3.26 - 3.21 (m, 4 H), 1.68 - 1.62 (m, 4

H), 1.61 - 1.54 (m, 2 H) ppm.

(*Z*)-2-Imino-5-((2-(3-(piperidin-1-yl)phenyl)thiazol-4-yl)methylene)-1,3-dithiolan-4-one

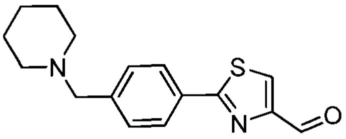


[00335] Prepared following *General Procedure C1* using 2-(3-(piperidin-1-yl)phenyl)thiazole-4-carboxaldehyde

[00336] 12 mg, 14%, cream solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.28 (br s, 1 H), 9.09 (br s, 1 H), 8.16 (s, 1 H), 7.58 (s, 1 H), 7.46 (s, 1 H), 7.42 – 7.32 (m, 2H), 7.12 (d, *J* = 7.0 Hz, 1 H), 3.27-3.23 (m, 4 H), 1.68 - 1.62 (m, 4 H), 1.61-1.55 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 180.5, 178.2, 168.1, 152.1, 151.0, 133.1, 131.4, 129.9, 123.9, 120.6, 118.2, 116.2, 112.9, 49.3, 25.1, 23.8 ppm; *m*/*z* LRMS (ESI$^+$): 393 (100%) [M + Na]$^+$; HRMS (ESI$^+$): calc. for $C_{18}H_{18}N_4NaOS_2^+$ [M + Na]$^+$ 393.0814, found 393.0814.

Example 47: Preparation of (Z)-2-imino-5-((2-(4-(piperidin-1-ylmethyl) phenyl)thiazol-4-yl)methylene)thiazolidin-4-one

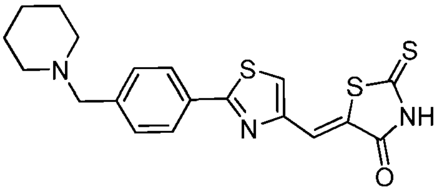
2-(4-(Piperidin-1-ylmethyl)phenyl)thiazole-4-carbaldehyde



[00337] Prepared following *General Procedure SC1*

[00338] 110 mg, 76%, white solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 10.10 (s, 1 H), 8.17 (s, 1 H), 7.95 (d, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 3.56 (s, 2 H), 2.41 (br. s, 4 H), 1.71 (br. s, 4 H), 1.46 (br. s, 2 H) ppm; *m*/*z* LRMS (ESI$^+$): 309 [M + Na]$^+$ (100%);

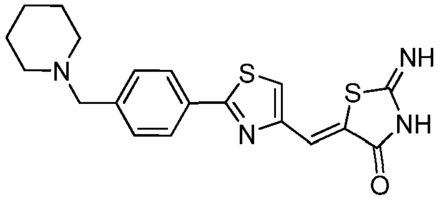
(Z)-5-((2-(4-(Piperidin-1-ylmethyl)phenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one



[00339] Prepared following *General Procedure C1*

[00340] 42 mg, 35%, brown solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 8.22 (s, 1 H), 8.03 (d, *J* = 8.1 Hz, 2 H), 7.59 (d, *J* = 8.1 Hz, 2 H), 7.42 (s, 1 H), 3.90 (s, 2 H), 2.80 – 2.55 (m, 4 H), 1.70 – 1.51 (m, 4 H), 1.45 – 1.33 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 206.5, 167.2, 151.3, 132.1, 131.8, 131.1, 126.5, 125.6, 119.6, 60.5, 52.9, 43.8, 30.7, 24.0, 22.2 ppm; *m/z* LRMS (ESI$^-$): 400 (100%) [M-H]$^-$.

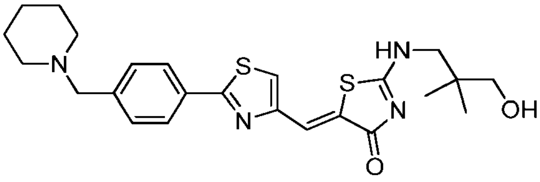
(Z)-2-Imino-5-((2-(4-(piperidin-1-ylmethyl)phenyl)thiazol-4-yl)methylene) thiazolidin-4-one



[00341] Prepared following *General Procedure C1*

[00342] 29 mg, 26%, brown solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.07 (br. s, 1 H), 8.76 (br. s, 1 H), 8.17 (s, 1 H), 7.97 (d, *J* = 8.5 Hz, 2 H), 7.58 (s, 1 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 3.91 (s, 2 H), 2.35 – 2.33 (m, 4 H), 1.52 - 1.50 (m, 4 H), 1.41 - 1.40 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 187.8, 182.8, 180.4, 178.2, 167.3, 151.1, 131.5, 129.6, 126.2, 123.9, 120.5, 62.2, 56.0, 53.8, 18.6 ppm; *m/z* LRMS (ESI$^-$): 383.1 (100%) [M-H]$^-$;

Example 48: Preparation of (Z)-2-((3-hydroxy-2,2-dimethylpropyl)amino)-5-((2-(4-(piperidin-1-ylmethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one



[00343] Prepared following *General Procedure HG2* using (*Z*)-5-((2-(4-(piperidin-1-ylmethyl)phenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one

[00344] 30 mg, 65%, grey solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.43 (t, J = 5.8 Hz, 1 H), 8.17 (s, 1 H), 7.98 (d, J = 8.0 Hz, 2 H), 7.57 (s, 1 H), 7.47 (d, J = 8.0 Hz, 2 H), 4.74 (t, J = 5.8 Hz, 1 H), 3.51 (s, 2 H), 3.42 (d, J = 5.8 Hz, 2 H), 3.17 (d, J = 5.8 Hz, 2 H), 2.40 - 2.29 (m, 4 H), 1.55 - 1.47 (m, 4 H), 1.44 - 1.36 (m, 2 H), 0.87 (s, 6 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 179.5, 176.9, 167.3, 151.2, 142.0, 131.1, 130.9, 129.5, 126.2, 123.8, 120.3, 67.6, 62.3, 53.9, 51.3, 37.0, 25.6, 24.0, 22.2 ppm.

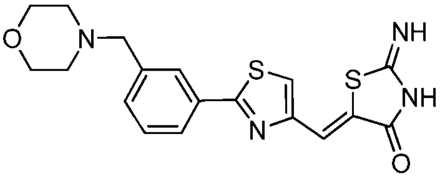
Example 49: Preparation of (Z)-2-imino-5-((2-(3-(morpholinomethyl) phenyl)thiazol-4-yl)methylene)thiazolidin -4-one

2-(3-(Morpholinomethyl)phenyl)thiazole-4-carbaldehyde

[00345] Prepared following *General Procedure SC1*

[00346] 120 mg, 84%, white solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 10.08 (s, 1 H), 8.17 (s, 1H), 7.97 (s, 1 H), 7.86 (d, J = 7.3 Hz, 1 H), 7.67 (app. t, J = 7.3 Hz, 1 H), 7.46 (d, J = 7.3 Hz, 1 H), 3.74 - 3.64 (m, 8 H), 2.56 – 2.44 (m, 2 H) ppm; *m/z* LRMS (ESI$^+$): 311 [M + Na]$^+$ (100%).

(Z)-2-Imino-5-((2-(3-(morpholinomethyl)phenyl)thiazol-4-yl)methylene)thiazolidin -4-one

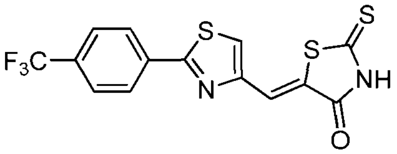


[00347] Prepared following *General Procedure C1*

[00348] 18 mg, 29%, brown solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.3 – 9.1 (m, 2 H), 8.19 (s, 1 H), 7.96 (d, J = 7.3 Hz, 1 H), 7.88 (s, 1 H), 7.60 (s, 1 H), 7.55 - 7.50 (m, 2 H), 3.61-3.58 (m, 6 H), 2.50 – 2.30 (m, 4 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 180.4, 178.2, 167.4, 151.2, 139.3, 132.4, 131.5, 131.3, 129.3, 126.8, 124.8, 124.1, 120.5, 66.2, 61.9, 53.1 ppm; *m/z* LRMS (ESI$^-$): 385 (100%) [M-H]$^-$.

Example 50: Preparation of (*Z*)-2-imino-5-((2-(4-(trifluoromethyl)phenyl) thiazol-4-yl)methylene) thiazolidin-4-one

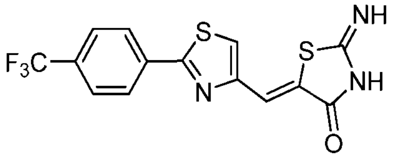
(*Z*)-2-Thioxo-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazolidin-4-one



[00349] Prepared following *General Procedure C1*

[00350] 94 mg, 45%, yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 8.49 (s, 1 H), 8.21 (d, *J* = 8.2 Hz, 2 H), 7.96 (d, *J* = 8.2 Hz, 2 H), 7.69 (s, 1 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 199.4, 169.3, 166.4, 150.6, 135.5, 130.6 (q, *J* = 32.2 Hz), 128.8, 127.8, 127.1, 126.6, 123.9 (q, *J* = 272.0 Hz), 122.3 ppm; *m/z* LRMS (ESI$^-$): 371 (100%) [M - H]$^-$.

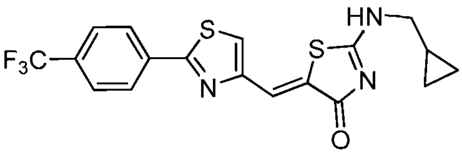
(*Z*)-2-Imino-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene) thiazolidin-4-one



[00351] Prepared following *General Procedure C1*

[00352] White solid 704 mg, 51%; ^{1}H NMR (500 MHz, d_6-DMSO): δ = 9.34 (s, 1 H), 9.19 (s, 1 H), 8.31 (s, 1 H), 8.22 (d, *J* = 8.2 Hz, 2 H), 7.93 (d, *J* = 8.2 Hz, 2 H), 7.62 (s, 1 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 180.4, 178.0, 165.6, 151.6, 136.0, 131.8, 130.5, 127.0, 126.4, 125.5, 122.8, 120.2 ppm; *m/z* LRMS (ESI$^+$): 378 (100%) [M + Na]$^+$.

Example 51: Preparation of (Z)-2-(cyclopropylmethylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one

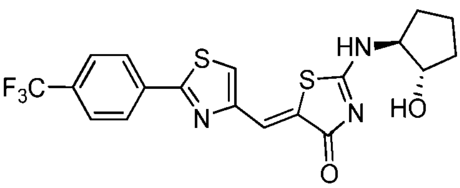


[00353] Prepared following *General Procedure HG1*

[00354] 47 mg, 45%, white solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.75 (br. s, 1 H), 8.30 (s, 1 H), 8.23 (d, *J* = 8.2 Hz, 2 H), 7.94 (d, *J* = 8.2 Hz, 2 H), 7.62 (s, 1 H), 3.39 (d, *J* = 6.7 Hz, 2 H), 1.13 - 1.04 (m, 1 H), 0.54-0.50 (m, 2 H), 0.31-0.27 (m, 2 H) ppm;

^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.6, 175.5, 165.5, 151.6, 135.9, 131.4, 130.5, 127.0, 126.3, 125.3, 124.1 (q, *J* = 270 Hz), 120.0, 48.8, 10.3, 3.5 ppm; *m/z* LRMS (ESI$^-$): 408 (100%) [M-H]$^-$.

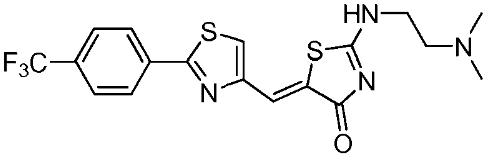
Example 52: Preparation of (Z)-2-((1R,2S)-2-hydroxycyclopentylamino)-5-((2-(4-(trifluoromethyl)phenyl) thiazol-4-yl)methylene)thiazol-4(5H)-one



[00355] Prepared following *General Procedure HG1*

[00356] 47 mg, 40%, pink solid; ^1H NMR (400 MHz, d_6-DMSO): δ = 9.59 (d, *J* = 5.4 Hz, 1 H), 8.31 (s, 1 H), 8.23 (d, 8.7 Hz, 2 H), 7.93 (d, *J* = 8.7 Hz, 2 H), 7.62 (s, 1 H), 5.05 (d, *J* = 4.3 Hz, 1 H), 4.18 - 4.12 (m, 1 H), 4.03 - 3.98 (m, 1 H), 2.13 - 2.04 (m, 1 H), 1.92 - 1.83 (m, 1 H), 1.74 - 1.65 (m, 2 H), 1.57 - 1.48 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.6, 175.2, 165.5, 151.5, 136.0, 131.3, 130.6, 126.5, 126.3, 125.4, 124.1 (q, *J* = 270 Hz), 120.0, 75.7, 63.0, 32.1, 29.2, 20.2 ppm; *m/z* LRMS (ESI$^-$): 438 (100%) [M-H]$^-$.

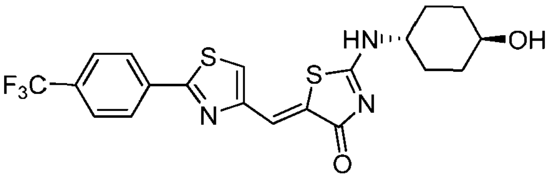
Example 53: Preparation of (Z)-2-(2-(dimethylamino)ethylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one



[00357] Prepared following *General Procedure HG1*

[00358] 44 mg, 43%, yellow solid; ^1H NMR (400 MHz, d_6-DMSO): δ = 9.60 (br. s, 1 H), 8.30 (s, 1 H), 8.23 (d, *J* = 8.4 Hz, 2 H), 7.93 (d, *J* = 8.4 Hz, 2 H), 7.61 (s, 1 H), 3.60 (t, *J* = 6.7 Hz, 2 H), 2.47 (t, *J* = 6.7 Hz, 2 H), 2.19 (s, 6 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.6, 175.7, 165.5, 151,6, 136.0, 131.5, 130.4, 127.1, 126.3, 125.3, 124.1. (q, *J* = 273 Hz), 120.0, 57.3, 45.1, 42.3 ppm; *m/z* LRMS (ESI$^-$): 425 (100%) [M-H]$^-$.

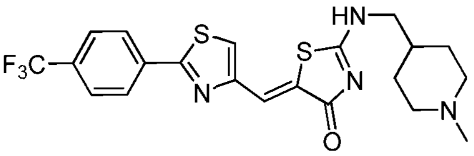
Example 54: Preparation of (Z)-2-((1r,4r)-4-hydroxycyclohexylamino)-5-((2-(4-(trifluoromethyl)phenyl) thiazol-4-yl)methylene)thiazol-4(5H)-one



[00359] Prepared following *General Procedure HG1*

[00360] 88 mg, 68%, white solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.55 (d, *J* = 7.4 Hz, 1 H), 8.30 (s, 1 H), 8.22 (d, *J* = 8.3 Hz, 2 H), 7.93 (d, *J* = 8.3 Hz, 2 H), 7.61 (s, 1 H), 4.65 (d, *J* = 4.11, 1 H), 3.90 - 3.83 (m, 1 H), 3.47 - 3.39 (m, 1H), 1.97 - 1.94 (m, 2 H), 1.88 - 1.85 (m, 2 H), 1.39 - 1.25 (m, 4 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 179.7, 174.6, 165.5, 151.6, 136.0, 131.2, 127.2, 126.9, 126.3, 125.4, 123.9 (q, *J* = 272 Hz), 120.0, 67.7, 53.2, 33.5, 30.7 ppm; *m/z* LRMS (ESI$^-$): 434 (100%) [M-H]$^-$.

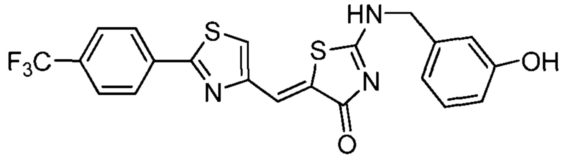
Example 55: Preparation of (Z)-2-((1-methylpiperidin-4-yl)methylamino)-5-((2-(4-(trifluoromethyl)phenyl) thiazol-4-yl)methylene)thiazol-4(5H)-one



[00361] Prepared following *General Procedure HG1*

[00362] 35 mg, 40%, yellow solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 8.30 (s, 1 H), 8.21 (d, *J* = 8.2 Hz, 2 H), 7.92 (d, *J* = 8.2 Hz, 2 H), 7.61 (s, 1 H), 3.40 (d, *J* = 7.7 Hz, 2 H), 2.76 - 2.74 (m, 2 H), 2.13 (s, 3 H), 1.84 -1.78 (m, 2 H), 1.66 - 1.63 (m, 2 H), 1.58 - 1.55 (m, 1 H), 1.25 - 1.17 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 179.6, 175.9, 165.5, 151.6, 136.0, 131.3, 130.4, 127.1, 126.4, 126.3, 125.4, 125.0, 123.9 (q, *J* = 273 Hz), 120.1, 54.8, 49.6, 46.0, 30.7, 29.3 ppm; *m/z* LRMS (ESI$^-$): 465 (100%) [M - H]$^-$;

Example 56: Preparation of (Z)-2-(3-hydroxybenzylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl) methylene) thiazol-4(5H)-one



[00363] Prepared following *General Procedure HG1*

[00364] 70 mg, 68%, yellow solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.48 (s, 1 H), 8.31 (s, 1 H), 8.22 (d, *J* = 8.1 Hz, 2 H), 7.93 (d, *J* = 8.1 Hz, 2 H), 7.65 (s, 1 H), 7.17 (app. t, *J* = 8.0 Hz, 1 H), 6.77 - 6.75 (m, 2 H), 6.70 (d, *J* = 8.3 Hz, 1 H), 4.65 (s, 2 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 206.5, 179.6, 165.6, 157.6, 151.5, 138.7, 136.0, 131.3, 130.1, 129.6, 125.5, 125.0, 123.8 (q, *J* = 273 Hz), 120.7, 120.4, 118.2, 118.1, 114.4, 30.7 ppm; *m/z* LRMS (ESI$^-$): 460 (100%) [M-H]$^-$.

Example 57: Preparation of (Z)-5-((2-(4-fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-(3-hydroxy-2,2-dimethylpropylamino)thiazol-4(5H)-one

(4-Fluoro-2-hydroxyphenyl)boronic acid

[00365] The title compound was prepared from the corresponding halide following general procedure *BA* and obtained after recrystallisation from benzene/pentane as a beige powder (1.23 g, 38%).

[00366] ^{1}H NMR (400 MHz, acetone): δ = 7.80 (dd, *J* = 8.0, 7.5 Hz, 1 H), 6.88 (ddd, *J* = 10.5, 8.8, 2.2 Hz, 1 H), 6.74 (dd, *J* = 10.6, 2.2 Hz, 1 H) ppm; *m/z* LRMS (ESI$^-$): 155 (9%) [M - H]$^+$, 335 (100%).

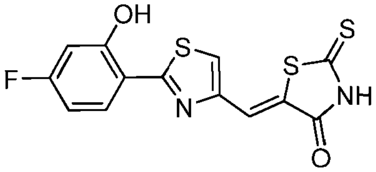
2-(4-Fluoro-2-hydroxyphenyl)thiazole-4-carbaldehyde

[00367] Prepared following *General Procedure SC1*

[00368] Flash column chromatography (SiO$_2$, petrol:EtOAc 1:6), 205 mg, 36%, bright yellow oil

[00369] ^{1}H NMR (400 MHz, CDCl$_3$): δ = 10.04 (s, 1 H), 8.12 (s, 1 H), 7.61 (dd, *J* = 8.7, 6.1 Hz, 1 H), 7.34 – 7.32 (m, 1 H), 6.80 (dd, *J* = 10.3, 2.6 Hz, 1 H), 6.68 (ddd, *J* = 10.4, 8.7, 2.6 Hz, 1 H) ppm; *m/z* LRMS (ESI$^+$): 248 (100%) [M + Na]$^+$.

(*Z*)-5-((2-(4-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one



[00370] Prepared following *General Procedure C1*

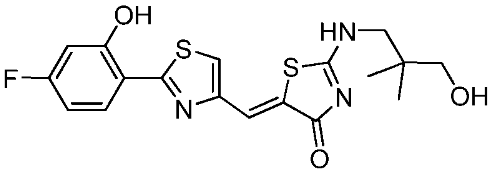
[00371] 35 mg, 32%, bright yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 11.81 (s, 1 H), 8.37 (s, 1 H), 8.27 (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.68 (s, 1 H), 7.01 (dd, *J* = 10.3, 2.6 Hz, 1 H), 6.85 (dd, *J* = 10.4, 2.5 Hz, 1 H) ppm; *m/z* LRMS (ESI$^-$): 337 (100%) [M - H]$^+$.

(*Z*)-5-((2-(4-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-(methylthio)thiazol-4(5H)-one

[00372] Prepared following *General Procedure HG2*

[00373] 26 mg, 74%, bright yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 11.82 (s, 1 H), 8.38 (s, 1 H), 8.29 (dd, *J* = 8.7, 6.8 Hz, 1 H), 7.86 (s, 1 H), 6.95 – 6.91 (m, 1 H), 6.83 (dd, *J* = 10.4, 2.5 Hz, 1 H) 2.83 (s, 3H) ppm; *m/z* LRMS (ESI$^-$): 351 (100%) [M - H]$^+$.

(Z)-5-((2-(4-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-(3-hydroxy-2,2-dimethylpropylamino)thiazol-4(5H)-one



[00374] Prepared following *General Procedure HG1*

[00375] 9.6 mg, 18%, white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.77 (s, 1 H), 9.44 (s, 1 H), 8.30 (dd, *J* = 7.9, 5.5 Hz, 1 H), 8.14 (s, 1 H), 7.58 (s, 1 H), 6.85 (m, 2 H), 4.73 (s, 1 H) 3.40 (s, 2 H), 3.16 (app. d, *J* = 4.4 Hz, 2 H), 0.86 (s, 6 H) ppm; *m/z* LRMS (ESI$^-$): 406 (100%) [M-H]$^-$

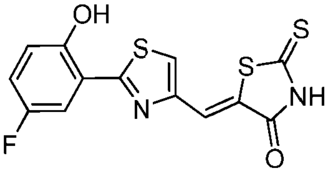
Example 58: Preparation of (Z)-5-((2-(5-fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-((1S,2S)-2-(hydroxymethyl)cyclopentylamino)thiazol-4(5H)-one

2-(5-Fluoro-2-hydroxyphenyl)thiazole-4-carbaldehyde

[00376] Prepared following *General Procedure SC1*

[00377] Flash column chromatography (SiO_2, petrol:EtOAc 1:6), 280 mg, 65%, bright yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.43 (s, 1 H), 10.08 (s, 1 H), 8.18 (s, 1 H), 7.35 (dd, *J* = 8.7, 2.9 Hz, 1 H), 7.15 – 7.06 (m, 2 H) ppm; *m/z* LRMS (ESI$^+$): 248 (100%) [M + Na]$^+$.

(*Z*)-5-((2-(5-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-thioxothiazolidin-4-one



[00378] Prepared following *General Procedure C1*

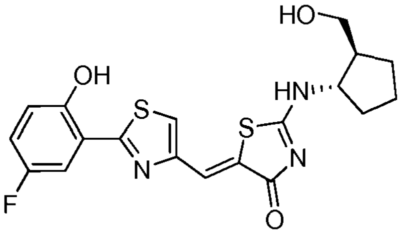
[00379] 110 mg, 51%, bright yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 11.33 (s, 1 H), 8.42 (s, 1 H), 7.92 (dd, *J* = 8.7, 2.9 Hz, 1 H), 7.69 (s, 1 H), 7.29 – 7.25 (m, 1 H), 7.10 – 7.06 (m, 1 H) ppm; *m/z* LRMS (ESI$^+$): 337 (100%) [M - H]$^+$.

(*Z*)-5-((2-(5-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-(methylthio)thiazol-4(5H)-one

[00380] Prepared following *General Procedure HG2*

[00381] 72 mg, 63%, bright yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 11.32 (s, 1 H), 8.44 (s, 1 H), 7.92 (dd, *J* = 9.6, 3.3 Hz, 1 H), 7.86 (s, 1 H), 7.27 (ddd, *J* = 9.0, 8.0, 3.3 Hz, 1 H), 7.08 (dd, *J* = 9.1, 4.7 Hz, 1 H), 2.83 (s, 3H) ppm; *m/z* LRMS (ESI$^-$): 351 (100%) [M - H]$^+$.

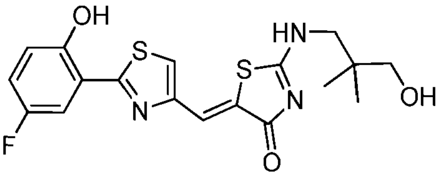
(Z)-5-((2-(5-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-((1S,2S)-2-(hydroxymethyl)cyclopentylamino)thiazol-4(5H)-one



[00382] Prepared following *General Procedure HG1*

[00383] 35 mg, 37%, yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.63 (s, 1 H), 8.22 (s, 1 H), 8.00 - 7.95 (m, 1 H), 7.60 (s, 1 H), 7.27 - 7.21 (m, 1 H), 7.10 - 7.06 (m, 1 H), 4.69 (s, 1 H), 4.19 - 4.14 (m, 1 H), 3.47 - 3.41 (m, 2 H), 2.07 - 1.95 (m, 2 H), 1.87 - 1.79 (m, 1 H), 1.70 - 1.55 (m, 4 H), 1.45 - 1.35 (m, 1 H) ppm; *m/z* LRMS (ESI$^-$): 418 (100%) [M-H]$^-$;

Example 59: Preparation of (Z)-5-((2-(5-fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-(3-hydroxy-2,2-dimethylpropylamino)thiazol-4(5H)-one



[00384] Prepared following *General Procedure HG1*

[00385] 18 mg, 19%, grey solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.28 (s, 1 H), 9.50 – 9.48 (m, 1 H), 8.21 – 8.19 (m, 1 H), 8.01 – 7.99 (m, 1 H), 7.61 – 7.59 (m, 1 H), 7.25 – 7.23 (m, 1 H), 7.08 – 7.06 (m, 1 H), 4.74 (s, 1 H) 3.42 (s, 2 H), 3.16 (s, 2 H), 0.86 (s, 6 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.6, 176.9, 161.5, 155.3 (d, *J* = 237 Hz), 151.7, 149.2, 130.3, 125.5, 120.5, 120.0, 119.9 (d, J = 8.5 Hz), 118.2 (d, *J* = 23 Hz), 112.6 (d, *J* = 24 Hz), 67.6, 51.3, 37.1, 22.2 ppm; *m/z* LRMS (ESI$^-$): 406 (100%) [M-H]$^-$.

Example 60: Preparation of (*Z*)-5-((2-(3-fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-((3-hydroxy-2,2-dimethylpropyl)amino)thiazol-4(*5H*)-one

(3-Fluoro-2-hydroxyphenyl)boronic acid

[00386] The title compound was prepared from the corresponding halide following general procedure *BA* and obtained after recrystallisation from benzene/pentane as a brown powder (237 mg, 29%).

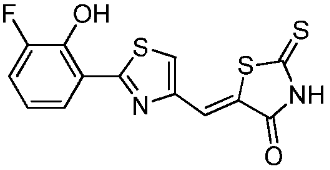
[00387] ^{1}H NMR (400 MHz, d_6-acetone): δ = 8.39 (s, 1 H), 7.42 (dd, *J* = 8.1, 3.2 Hz, 1 H), 7.25 (app. td, *J* = 8.7, 3.2 Hz, 1 H), 7.03 (dd, *J* = 8.9, 4.2 Hz, 1 H), 5.82 (s, 2 H) ppm.

2-(3-Fluoro-2-hydroxyphenyl)thiazole-4-carbaldehyde

[00388] Prepared following *General Procedure SC1*.

[00389] White powder 160 mg, 16%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.77 (s, 1 H), 10.09 (s, 1 H), 8.18 (s, 1 H), 7.46 - 7.42 (m, 1 H), 7.25 - 7.19 (m, 1 H), 6.94 - 6.88 (m, 1 H); *m/z* LRMS (ESI) 222 (100%) $[M - H]^+$.

(*Z*)-5-((2-(3-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-(thioxo)thiazolidin-4-one



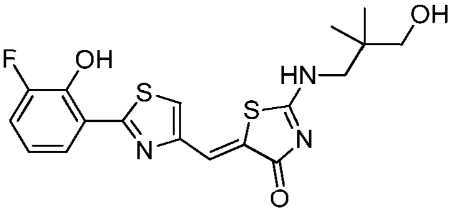
[00390] Prepared following *General Procedure C1*

[00391] Yellow powder 230 mg, 63%; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 11.58 (br. s, 1 H), 8.45 (s, 1 H), 8.11 - 8.05 (m, 1 H), 7.70 (s, 1 H), 7.46 - 7.35 (m, 1 H), 7.19 - 7.07 (m, 1 H) ppm; *m/z* LRMS (ESI) 336 (100%) $[M - H]^-$

(*Z*)-5-((2-(3-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-(methylthio))thiazol-4(*5H*)-one

[00392] Orange powder 154 mg, 64%; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 11.54 (br. s, 1 H), 8.44 (s, 1 H), 8.08 (d, *J* = 7.9 Hz, 1 H), 7.87 (s, 1 H), 7.40 - 7.35 (m, 1 H), 7.11 - 7.05 (m, 1 H), 2.84 (s, 3 H) ppm.

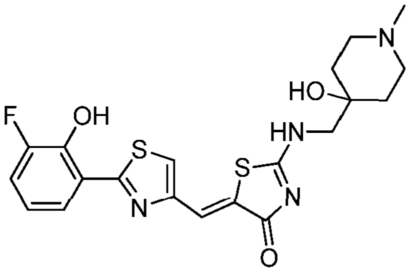
(*Z*)-5-((2-(3-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-((3-hydroxy-2,2-dimethylpropyl)amino)thiazol-4(*5H*)-one



[00393] Prepared following *General Procedure HG1*

[00394] Following purification of the crude product by RP-HPLC, the title compound was isolated as a yellow powder 6 mg, 11%; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 11.54 (s, 1 H), 9.48 (t, *J* = 5.8 Hz, 1 H), 8.23 (s, 1 H), 8.11 - 8.08 (m, 1 H), 7.61 (s, 1 H), 7.41 - 7.35 (m, 1 H), 7.36 (s, 1 H), 7.05 - 6.99 (m, 1 H), ~3.5 (obs, 2 H), 3.17 (s, 2 H), 0.87 (s, 6 H) ppm; *m/z* LRMS (ESI) 406 (100%) $[M - H]^-$.

Example 61: Preparation of (*Z*)-5-((2-(3-fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-((4-hydroxy-1-methylpiperidin-4-yl)methyl)amino)thiazol-4(*5H*)-one

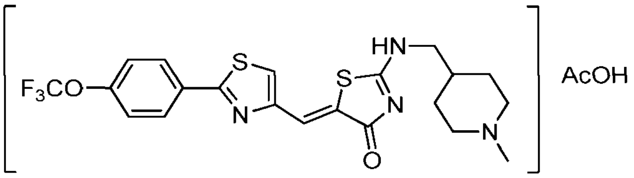


[00395] Prepared following *General Procedure HG1*

[00396] Yellow powder 10 mg, 16%; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.42 (m, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 7.90 – 7.80 (m, 1 H), 7.46 (s, 1 H), 7.15 - 7.09 (m, 1 H), 6.59 - 6.52 (m, 1 H), 4.80 (s, 1 H), 3.53 - 3.49 (m, 2 H), 2.78 - 2.70 (m, 2 H), 2.61 - 2.55 (m, 2 H), 2.38 (s, 3 H), 1.83 - 1.73 (m, 2 H), 1.58 - 1.52 (m, 2 H) ppm; ^{13}C NMR (101 MHz, d_6-DMSO): δ = 180.0, 177.4, 163.3, 148.4, 142.8, 129.6, 123.8, 122.5, 122.1, 120.8, 115.9, 115.7, 67.6, 53.7, 50.4, 48.6, 44.8, 33.3 ppm; *m/z* LRMS (ESI$^-$) 447 (100%) [M - H]$^-$.

General procedure S1: Preparation of salts

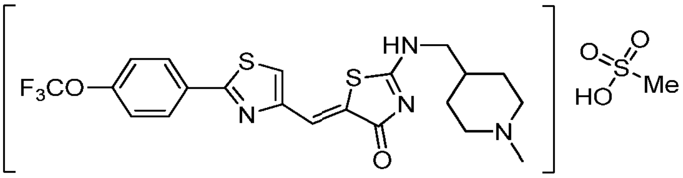
Example 62: Preparation of (*Z*)-2-(((1-methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one acetate



[00397] To a round-bottom flask equipped with a magnetic stirrer bar was added (*Z*)-2-(((1-methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one (500 mg, 1.04 mmol), which was dissolved in methanol (30 mL). Acetic acid (300 uL, 5.2 mmol) was added drop-wise to the reaction mixture over 5 min and after stirring for 30 min the reaction mixture was concentrated under reduced pressure. The crude reaction mixture was triturated with diethyl ether (20 mL) and the precipitate was collected by filtration and washed with diethyl ether (20 mL). The precipitate was concentrated under reduced pressure and excess acetic acid removed by azeotropic distillation with toluene (3 x 20 mL) to yield an off white powder (450 mg, 0.83 mmol, 80%). mp 245-246 °C; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.59 (s, 1 H), 8.23 (s, 1 H), 8.14 (d, *J* = 8.6 Hz, 2 H), 7.60 - 7.56 (m, 3 H), 3.40 (d, *J* = 6.8 Hz, 2 H), 2.80 - 2.75 (m, 2 H), 2.16 (s, 3 H), 1.91 (s, 3 H), 1.90 - 1.83 (m, 2 H), 1.68 - 1.63 (m, 2 H), 1.61 - 1.52 (m, 1 H), 1.27 - 1.18 (m, 2 H) ppm; ^{13}C NMR (101 MHz, d_6-DMSO): δ = 179.7, 176.0, 172.1, 165.7, 151.4, 149.8, 131.6, 131.2, 128.4, 124.8, 121.9, 120.2, 119.0, 54.8, 49.6, 46.0, 34.8, 29.4, 21.1 ppm $F_3\underline{C}O$ resonance not seen; *m/z* LRMS (ESI) 540 (10%) [M - H]$^-$; Anal. Calc. for $C_{23}H_{25}F_3N_4O_4S_2$: C, 50.91; H, 4.64; N, 10.33. Found: C, 50.83; H, 4.58; N, 10.25%.

[00398] *The following compounds were prepared in a similar manner, using appropriate starting materials / reagents.*

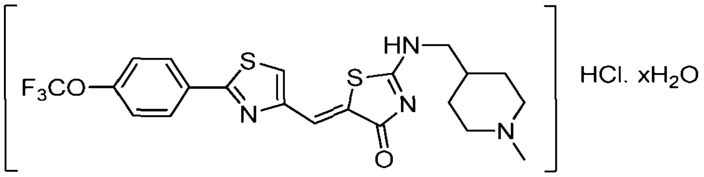
Example 63: Preparation of (*Z*)-2-(((1-methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one methane sulfonate



[00399] Prepared following *General Procedure S1*

[00400] White powder 2.50 g, 100%; mp 205-206 °C; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.75 (s, 1 H), 9.25 (s, 1 H), 8.25 (s, 1 H), 8.14 (d, *J* = 8.4 Hz, 2 H), 7.61 (s, 1 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 3.49 - 3.41 (m, 2 H), 3.00 - 2.90 (m, 2 H), 2.76 (d, *J* = 4.9 Hz, 2 H), 2.39 (s, 3 H), 1.94 - 1.68 (m, 3 H), 1.48 - 1.37 (m, 2 H) ppm; ^{13}C NMR (101 MHz, d_6-DMSO): δ = 179.3, 176.2, 165.7, 151.2, 149.8, 131.5, 130.8, 128.3, 125.0, 121.9, 120.5, 119.0, 53.1, 48.6, 42.7, 39.5, 32.8, 26.8 ppm; *m/z* LRMS (ESI) 577 (100%) [M - H]$^-$; Anal. Calc. for $C_{22}H_{25}F_3N_4O_5S_3$: C, 45.66; H, 4.35; N, 9.68. Found: C, 45.59; H, 4.27; N, 9.58%.

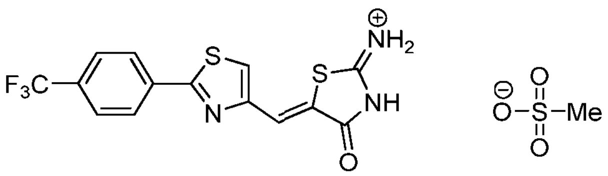
Example 64: Preparation of (*Z*)-2-(((1-methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one hydrochloride . hydrate



[00401] Prepared following *General Procedure S1*

[00402] Yellow powder 1.50 g, 95%; mp 180-181 °C; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 10.20 (br s, 1 H), 9.90 (br s, 1 H), 8.26 (s, 1 H), 8.15 (d, *J* = 8.8 Hz, 2 H), 7.63 (s, 1 H), 7.58 (d, *J* = 8.8 Hz, 2 H), 3.47 - 3.38 (m, 4 H), 2.97 - 2.87 (m, 2 H), 2.70 (d, *J* = 4.7 Hz, 3 H), 1.91 - 1.85 (m, 3 H), 1.55 - 1.45 (m, 2 H) ppm; ^{13}C NMR (101 MHz, d_6-DMSO,): δ = 179.0, 176.0, 165.7, 151.2, 149.8, 131.6, 130.7, 128.3, 125.1, 121.9, 120.6, 119.0, 52.9, 48.7, 42.5, 32.9, 26.7 ppm; *m/z* LRMS (ESI) 517 (50%) $[M - H]^-$; Anal. Calc. for $C_{21}H_{22}ClF_3N_4O_2S_2$: C, 48.60; H, 4.27; N, 10.80. Found: C, 41.75; H, 4.39; N, 9.19%.

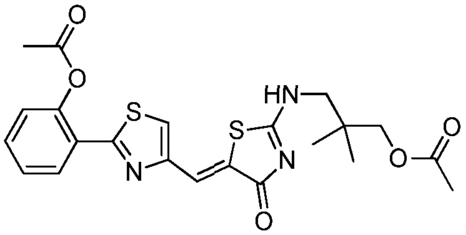
Example 65: Preparation of (*Z*)-2-amino-5-((2-(4-(trifluoromethyl)phenyl) thiazol-4-yl)methylene)thiazol-4(5*H*)-one methane sulfonate



[00403] Prepared following *General Procedure S1*

[00404] White solid, 44 mg, 99%; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.55 (br. s, 1 H), 9.43 (s, 1 H), 8.34 (s, 1 H), 8.22 (d, *J* = 8.3 Hz, 2 H), 7.93 (d, *J* = 8.3 Hz, 2 H), 7.68 (s, 1 H), 2.36 (s, 3 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 178.4, 177.2, 165.8, 151.3, 135.9, 130.5 (q, J = 31 Hz), 127.0, 126.4, 126.1, 122.8, 121.2, 40.1 ppm; *m/z* LRMS (ESI): 450 (100%) $[M - H]^-$.

Example 66: Preparation of the prodrug (Z)-2-(4-((2-((3-acetoxy-2,2-dimethylpropyl)amino)-4-oxothiazol-5(4H)-ylidene)methyl)thiazol-2-yl)phenyl acetate



[00405] To a round-bottomed flask equipped with a magnetic stirrer bar was added (Z)-2-((3-hydroxy-2,2-dimethylpropyl)amino)-5-((2-(2-hydroxyphenyl)thiazole-4-yl)methylene)thiazol-4(5H)-one (0.77 mmol) and pyridine (2.0 mL) followed by dropwise addition of Ac_2O (1.90 mmol). The reaction vessel was fitted with a rubber septum and stirred at room temperature for 16 hours. After that the reaction mixture was diluted with Et_2O (5 mL) and the precipitate filtered off. The solid was washed several times with Et_2O to give the desired product as a white solid (0.35 g, 95%).

[00406] ^1H NMR (400 MHz, d_6-DMSO): δ = 8.47 (d, *J* = 7.9 Hz, 1 H), 7.98 (s, 1 H), 7.64 (s, 1 H), 7.56 (app. t, *J* = 8.1 Hz, 1 H), 7.43 (app. t, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 3.90 (s, 2 H), 3.61 (s, 2 H), 2.48 (s, 3 H), 2.10 (s, 3 H), 1.06 (s, 6 H); ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.6, 177.0, 170.4, 168.9, 161.0,150.1, 147.6, 131.4, 131.0, 128.1, 126.5, 125.3, 124.9, 124.2, 120.2, 69.3, 51.1, 35.6, 22.2, 21.6, 20.7; *m/z* LRMS (ESI^-): 472 (100%) $[M-H]^-$;

Example 67: Preparation of *N*-(4-((*Z*)-((*E*)-2-(3-hydroxy-2,2-dimethylpropylimino)-4-oxothiazolidin-5-ylidene)methyl)thiazol-2-yl)-*N*-methylbenzamide

[00407] Ethyl 2-benzamidothiazole-4-carboxylate

[00408] To a round-bottomed flask equipped with a magnetic stirrer bar was added ethyl 2-aminothiazole-5-carboxylate (200 mg, 1.16 mmol), DIPEA (0.22 mL, 1.28 mmol) and CH_2Cl_2 (5.8 mL). Benzoyl chloride (0.15 mL, 1.28 mmol) was then added dropwise via syringe and the reaction stirred under N_2 at room temperature for 16 hours. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were then dried over Na_2SO_4 and concentrated under reduced pressure.

[00409] Flash column chromatography (SiO_2, petrol:EtOAc 2:1), 235 mg, 73%, white solid; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.87 (br. s, 1 H), 7.93 - 7.90 (m, 3 H), 7.68 - 7.62 (m, 1 H), 7.56 - 7.52 (m, 2 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 1.40 (t, *J* = 7.2 Hz, 3 H) ppm; *m/z* LRMS (ESI^-): 275 (100%) $[M - H]^-$

***N*-(4-Formylthiazol-2-yl)benzamide**

[00410] To a flame dried round-bottomed flask equipped with a magnetic stirrer bar was added ethyl 2-benzamidothiazole-4-carboxylate (235 mg, 0.85 mmol) and anhydrous CH_2Cl_2 (2.8 mL). The solution was cooled to -78℃ and DIBAL (1.19 mL, 1.19 mmol, 1.0 M in CH_2Cl_2) was then added dropwise via syringe. The reaction mixture was stirred for 3 hours at -78℃ then quenched with methanol (2.0 mL). A solution of sat. aq. Rochelle's salt (10 mL) was added and the mixture stirred for 2 hours, then extracted with 3 × 10 mL of diethyl ether. The combined organic layers were then dried over Na_2SO_4 and concentrated under reduced pressure.

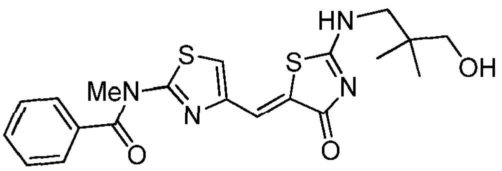
[00411] Flash column chromatography (SiO_2, petrol:EtOAc 2:1), 69 mg, 35%, white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.86 (s, 1 H), 7.95 - 7.93 (m, 2 H), 7.91 (s, 1 H), 7.67 - 7.64 (m, 1 H), 7.58 - 7.54 (m, 2 H) ppm; *m/z* LRMS (ESI$^-$): 231 (100%) $[M - H]^-$

(*Z*)-*N*-(4-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol-2-yl)benzamide

[00412] Prepared following *General Procedure C1*

[00413] 45 mg, 44%, yellow powder; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 8.11 (d, *J* = 7.3 Hz, 2 H), 7.99 (s, 1 H), 7.68 (app. t, *J* = 7.3 Hz, 1 H), 7.61 - 7.57 (m, 3 H) ppm; *m/z* LRMS (ESI$^-$): 346 (100%) $[M - H]^-$

***N*-(4-((*Z*)-((*E*)-2-(3-Hydroxy-2,2-dimethylpropylimino)-4-oxothiazolidin-5-ylidene)methyl)thiazol-2-yl)-*N*-methylbenzamide**



[00414] Prepared following *General Procedure HG1*

[00415] 8 mg, 52%, off-white powder; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.38 (br. s, 1 H), 7.81 (s, 1 H), 7.70 - 7.69 (m, 2 H), 7.60 - 7.52 (m, 3 H), 7.50 (s, 1 H), 4.71 (t, *J* = 5.8 Hz, 1 H), 3.68 (s, 3 H), 3.39 - 3.38 (m, 2 H), 3.14 (d, *J* = 5.8 Hz, 2 H), 0.84 (s, 6 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.7, 176.9, 170.1, 159.8, 144.6, 134.2, 130.9, 129.7, 128.6, 127.6, 120.9, 120.2, 67.6, 51.3, 37.2, 37.1, 22.2 ppm; *m/z* LRMS (ESI$^-$): 429 (100%) $[M - H]^-$

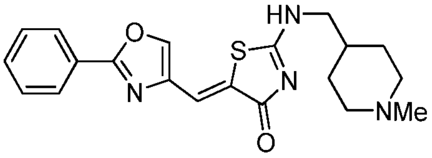
Example 68: Preparation of (*Z*)-2-((1-methylpiperidin-4-yl)methylamino)-5-((2-phenyloxazol-4-yl)methylene)thiazol-4(5H)-one

(Z)-5-((2-Phenyloxazol-4-yl)methylene)-2-thioxothiazolidin-4-one

[00416] Prepared following *General Procedure C1*

[00417] 133 mg, 76%, yellow solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 8.75 (s, 1 H), 8.06 - 8.04 (m, 2 H), 7.61 - 7.57 (m, 4 H) ppm; *m/z* LRMS (ESI$^-$): 287 (100%) $[M - H]^-$

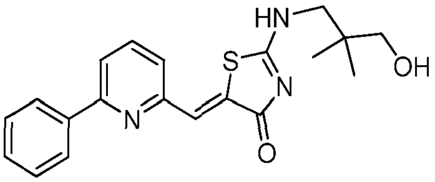
(*Z*)-2-((1-Methylpiperidin-4-yl)methylamino)-5-((2-phenyloxazol-4-yl)methylene)thiazol-4(5H)-one



[00418] Prepared following *General Procedure HG1*

[00419] 26 mg, 52%, cream solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.54 (br. s, 1 H), 8.62 (s, 1H), 8.04 - 8.01 (m, 2 H), 7.63 – 7.58 (m, 3 H), 7.46 (s, 1 H), 3.40 - 3.38 (m, 2 H), 2.78 – 2.70 (m, 2 H), 2.13 (s, 3 H), 1.86 – 1.76 (m, 2 H), 1.68 - 1.60 (m, 2 H), 1.57 - 1.52 (m, 1 H), 1.25 - 1.15 (m, 2 H) ppm; *m/z* LRMS (ESI$^-$): 381 (100%) [M - H]$^-$

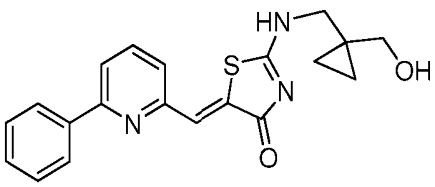
Example 69: Preparation of (2E,5Z)-2-(3-hydroxy-2,2-dimethylpropylimino)-5-((6-phenylpyridin-2-yl)methylene)thiazolidin-4-one



[00420] Prepared following *General Procedure HG1*

[00421] 21 mg, 24%, cream solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.57 (br. s, 1 H), 8.26 - 8.23 (m, 2 H), 8.01 - 7.94 (m, 2 H), 7.75 - 7.72 (m, 1 H), 7.69 (s, 1 H), 7.60 - 7.50 (m, 3 H), 4.76 (br. s, 1 H), 3.45 - 3.40 (m, 2 H), 3.17 (d, J = 4.0 Hz, 2 H), 0.87 (s, 6 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 179.6, 178.3, 156.3, 151.8, 138.4, 138.2, 132.7, 129.5, 128.9, 127.0, 125.9, 120.0, 67.6, 51.4, 37.2, 22.2 ppm; *m/z* LRMS (ESI$^-$): 366 (100%) [M - H]$^-$

Example 70: Preparation of (2E,5Z)-2-((1-(hydroxymethyl)cyclopropyl) methylimino)-5-((6-phenylpyridin-2-yl)methylene)thiazolidin-4-one

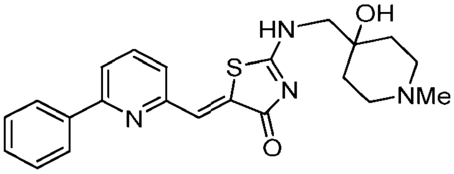


[00422] Prepared following *General Procedure HG1*

[00423] 78 mg, 89%, cream solid; ^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 9.68 (br. s, 1

H), 8.28 - 8.24 (m, 2 H), 8.00 - 7.94 (m, 2 H), 7.75 - 7.72 (m, 1 H), 7.68 (s, 1 H), 7.60 - 7.55 (m, 2 H), 7.55 - 7.50 (m, 1 H), 4.68 (t, *J* = 5.5 Hz, 1 H), 3.56 (s, 2 H), 3.32 (d, *J* = 5.1 Hz, 2 H), 0.53 - 0.44 (m, 4 H) ppm; ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.7, 177.7, 156.3, 151.8, 138.4, 138.2, 132.8, 129.6, 128.9, 127.0, 125.8, 120.0, 64.2, 48.5, 22.5, 8.6 ppm; *m/z* LRMS (ESI$^-$): 364 (100%) [M - H]$^-$

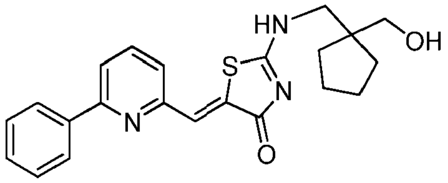
Example 71: Preparation of ((2E,5Z)-2-((4-hydroxy-1-methylpiperidin-4-yl)methylimino)-5-((6-phenylpyridin-2-yl)methylene)thiazolidin-4-one



[00424] Prepared following *General Procedure HG1*

[00425] 44 mg, 45%, cream solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.65 (br. s, 1 H), 8.29 - 8.26 (m, 2 H), 8.00 - 7.95 (m, 2 H), 7.76 - 7.71 (m, 1 H), 7.66 (s, 1 H), 7.60 - 7.56 (m, 2 H), 7.53 - 7.50 (m, 1 H), 4.66 (br. s, 1 H), 3.55 (s, 2 H), 2.46 - 2.42 (m, 2 H), 2.33 - 2.27 (m, 2 H), 2.17 (s, 3 H), 1.58 - 1.50 (m, 4 H); ^{13}C NMR (125 MHz, d_6-DMSO): δ = 179.8, 178.3, 156.2, 151.8, 138.5, 138.4, 133.1, 133.1, 129.5, 128.9, 127.0, 125.8, 125.7, 119.8, 68.0, 54.3, 50.8, 45.9, 34.3 ppm; *m/z* LRMS (ESI$^-$): 407 (100%) [M - H]$^-$

Example 72: Preparation of ((2E,5Z)-2-((1-(hydroxymethyl)cyclopentyl) methylimino)-5-((6-phenylpyridin-2-yl)methylene)thiazolidin-4-one



[00426] Prepared following *General Procedure HG1*

[00427] 44 mg, 47%, cream solid; ^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.59 (br. s, 1 H), 8.24 (d, *J* = 7.2 Hz, 2 H), 8.01 - 7.95 (m, 2 H), 7.74 (dd, *J* = 7.2, 1.0 Hz, 1 H), 7.69 (s, 1 H), 7.59 - 7.52 (m, 3 H), 4.83 (br. s, 1 H), 3.55 (s, 2 H), 3.24 (s, 2 H), 1.57 – 1.55 (m, 4 H), 1.46 – 1.40 (m, 4 H) ppm; *m/z* LRMS (ESI$^+$): 394 (100%) [M + H]$^+$

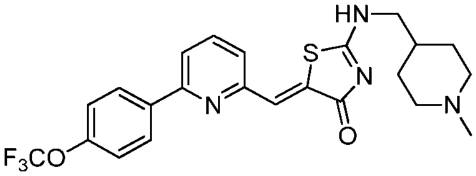
Example 73: Preparation of (*Z*)-2-(((1-methylpiperidin-4-yl)methyl)amino)-5-((6-(4-(trifluoromethoxy) phenyl)pyridin-2-yl)methylene)thiazol-4(5*H*)-one

(*Z*)-2-(Methylthio)-5-((6-(4-(trifluoromethoxy)phenyl)pyridin-2-yl)methylene) thiazol-4(5*H*)-one

[00428] Prepared following *General Procedure HG1 using* (*Z*)-2-thioxo-5-((6-(4-(trifluoromethoxy)phenyl)pyridin-2-yl)methylene) thiazolidin-4-one

[00429] 50 mg, 60%, pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.33 (d, *J* = 8.9 Hz, 2 H), 8.10 - 8.07 (m, 3 H), 7.96 (s, 1 H), 7.92 (dd, *J* = 5.5, 3.1 Hz, 1 H), 7.61 (d, *J* = 8.9 Hz, 2 H), 2.86 (s, 3 H) ppm; *m/z* LRMS (ESI$^+$): 815 (100%) [2M + Na]$^+$; HRMS (ESI$^+$): calc. for $C_{17}H_{11}F_3N_2NaO_2S_2^+$ [M + Na]$^+$ 419.0106, found 419.0099.

(*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((6-(4-(trifluoromethoxy) phenyl)pyridin-2-yl)methylene)thiazol-4(5*H*)-one



[00430] 19 mg, 40%, pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.64 (br s, 1 H), 8.36 (d, *J* = 8.9 Hz, 2 H), 8.06 - 7.97 (m, 2 H), 7.79 (d, *J* = 6.8 Hz, 1 H), 7.70 (s, 1 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 3.43 (d, *J* = 6.5 Hz, 2 H), 2.76 (d, *J* = 10.9 Hz, 2 H), 2.14 (s, 3 H), 1.82 (app t, *J* = 10.9 Hz, 2 H), 1.70 – 1.50 (m, 3 H), 1.29 - 1.15 (m, 2 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 179.7, 177.4, 154.8, 151.9, 149.2, 138.6, 137.4, 133.0, 129.0, 126.2, 125.6, 121.2, 120.2, 54.8, 49.7, 46.1, 34.9, 29.4 ppm $F_3\underline{C}O$ resonance not seen; *m/z* LRMS (ESI$^+$): 953 (100%) [2M + H]$^+$; HRMS (ESI$^+$): calc. for $C_{23}H_{24}F_3N_4O_2S^+$ [M + H]$^+$ 477.1567, found 477.1566.

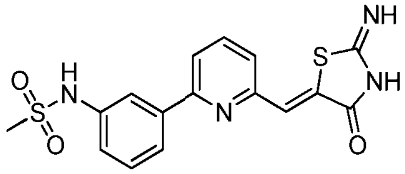
Example 74: Preparation of (*Z*)-*N*-(3-(6-((2-imino-4-oxothiazolidin-5-ylidene)methyl)pyridin-2-yl) phenyl)methanesulfonamide

***N*-(3-(6-Formylpyridin-2-yl)phenyl)methanesulfonamide**

[00431] Prepared following *General Procedure SC3*

[00432] Flash column chromatography (SiO$_2$, gradient elution petrol:EtOAc 1:1 to 1:2), 145 mg, 40%, yellow solid; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 10.17 (s, 1 H), 8.01 - 7.94 (m, 4 H), 7.93 - 7.88 (m, 1 H), 7.53 (app t, *J* = 8.2 Hz, 1 H), 7.41 - 7.36 (m, 1 H), 6.52 (s, 1 H), 3.08 (s, 3 H) ppm; *m/z* LRMS (ESI$^+$): 331 (100%) [M + MeOH + Na]$^+$; HRMS (ESI$^+$): calc. for $C_{13}H_{13}N_2O_3S^+$ [M + H]$^+$ 277.0641, found 277.0636.

(*Z*)-*N*-(3-(6-((2-Imino-4-oxothiazolidin-5-ylidene)methyl)pyridin-2-yl) phenyl)methanesulfonamide



[00433] Prepared following *General Procedure C1 using* *N*-(3-(6-formylpyridin-2-yl)phenyl)methanesulfonamide.

[00434] 15 mg, 28%, tan solid; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.39 (s, 1 H), 9.05 (s, 1 H), 8.05 - 7.95 (m, 2 H), 7.90 (s, 1 H), 7.83 (d, *J* = 7.9 Hz, 1 H), 7.78 (d, *J* = 7.3 Hz, 1 H), 7.70 (s, 1 H), 7.53 (app t, *J* = 7.4 Hz, 1 H), 7.36 (d, *J* = 7.4 Hz, 1 H), 3.08 (s, 3 H) ppm; ^{13}C NMR (125 MHz, d$_6$-DMSO): δ = 180.4, 179.7, 156.0, 151.9, 139.5, 139.0, 138.5, 133.6, 129.9, 126.0, 125.9, 122.6, 120.7, 120.2, 118.2 ppm, SO_2Me resonance obscured by solvent signal; *m/z* LRMS (ESI$^+$): 803 (50%) [2M + Na]$^+$; HRMS (ESI$^+$): calc. for $C_{16}H_{15}N_4O_3S_2^+$ [M + H]$^+$ 375.0580, found 375.0581.

<u>Example 75 – Biological Activity</u>

[00435] The biological activity of the compounds of the invention can be assessed using a kinetic enzyme assay as described further below.

Reagents:

- Doubly-distilled Water (dd. H_2O)
- 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic Acid (HEPES; Fisher Scientific, cat. no. BPE410)
- Sodium Chloride (NaCl; Fisher Scientific, cat. no. BPE358)
- Magnesium Chloride Hexahydrate ($MgCl_2.6H_2O$, BDH, cat. no. 290964Y)
- Phospho(enol)pyruvic Acid (PEP; Sigma Aldrich, cat. no. P0564)
- L-Lactic Dehydrogenase Solution (Type III: from bovine heart; Sigma Aldrich, cat. no. L2625)
- Pyruvate Kinase (type VII: from rabbit muscle; Sigma Aldrich, cat. no. P7768)
- P21 (customised peptide; Genscript)
- β-Nicotinamide Adenine Dinucleotide, reduced disodium Hydrate (NADH, Sigma Aldrich, cat. no. N8129)
- PIM1 Protein (purified at The Structural Genomics Consortium, University of Oxford)
- Adenosine 5'-Triphosphate disodium Salt (ATP; Sigma Aldrich; cat. no. A2383)
- Dimethyl Sulfoxide (DMSO, Sigma Aldrich, cat. no. 154938)

- Inhibitors to be tested (stored at 2.5 mg/mL in DMSO)

Equipment:

- Storage Eppendorfs (Fisherbrand, cat. no. FB74031)
- Falcon tubes (various manufacturers)
- 10, 20, 200 and 1000 µL pipettes (Starlab)
- Frosted DMSO-resistant 96-well plates (Thermo Scientific Matrix, cat. no. PMX-096-045Q)
- 384-Well polystyrene microplates (Greiner Bio-one, cat. no. 781101)
- Adhesive Aluminium foil seals (Thermo Scientific, cat. no. 232698)
- BMG Labtech NANOstar (for measuring protein concentration)
- BMG Labtech FLUOStar

Equipment setup

- Plate reader FLUOSTAR Labtech is setup to read absorbance at 340 nm with temperature set at 30 °C.
- Inhibitors are diluted into stocks of 11 different concentrations plus a blank DMSO. (250, 100, 50, 25, 12.5, 5, 3.75, 2.5, 1.25, 0.5, 0.25 µM and a blank). One inhibitor dilution is stored in one row of a 96-well plate.

Procedure

1. Prior to testing, a master mixture and other components of the assay are made following the recipe listed on Table 1 and are stored in eppendorfs.

Reagents	Stock Concentration (mM)	Final Concentration (mM)	Volume (µL)
dd. H_2O	-	-	342.79
HEPES (pH 7.5)	500	50	112.8
NaCl	5000	100	5.64
$MgCl_2$	50	10	56.4
PEP	500	1	4.51
LDH	-	4 µL/mL	2.26
Pyruvate Kinase	-	10 µL/mL	5.68
P21	2	0.06	22.56
Prepare separately:			
PIM1 Protein*	0.00488	0.00340	3.47
NADH	50	0.2	2.26
ATP	1	0.1	5

Table 1: Recipe is good for one run; *PIM1 stock measured using NANOStar spectrophotometer

2. Add 3.47 µL of the PIM1 stock and 2.26 µL of NADH to the master mixture and mix gently.
3. Using one row of a 384-well microplate, pipette 44 µL of the mixture in every other well (either all-odd or all-even wells; 12 wells used overall).
4. Add 1 µL of inhibitor in each well using a 12-multichannel pipette.
5. Add 5 µL of ATP into each of the wells using a 12-multichannel pipette in order to initiate the reaction.
6. Absorbance is then measured at 340 nm using the FLUOStar microplate reader. Allow for at least 32 cycles.

7. Data collected can be analysed using Graphpad Prism software.

[00436] The percentage inhibition of the PIM1 enzyme was measured at a concentration of 1 µM for each compound and the results are shown in the Table 2 below.

[00437] These data illustrate that the compounds of the invention are potent inhibitors of the PIM1 enzyme.

Table 2

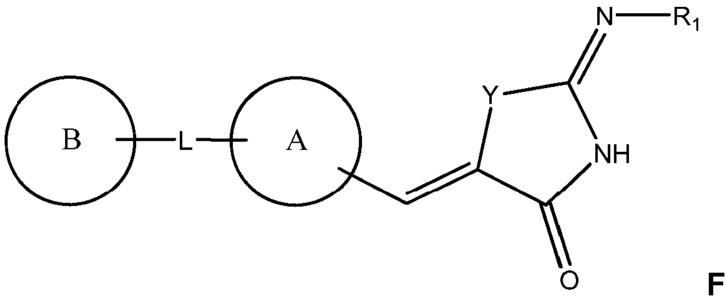
Example Number	Percentage Inhibition of PIM1 kinase at 1 µM	
	Average	SD
1	91	1
2	96	3
3	101	9
4	87	4
5	64	3
6	84	11
7	79	6
8	77	1
9	87	1
10	89	11
11	88	1
12	89	1
13	72	16
14	103	1
15	86	9
16	89	13
17	73	3
18	94	10
19	95	3
20	95	
21	68	
22	85	1
23	60	
24	87	
25	81	8
26	90	12
27	98	6

Example Number	Percentage Inhibition of PIM1 kinase at 1 µM	
	Average	SD
28	87	
29	98	7
30	95	8
31	93	4
32	81	18
33	86	1
34	98	10
35	94	10
36	94	11
37	86	
38	84	
39	74	
40	85	8
41	60	4
42	69	
43	54	3
44	82	0
45	93	6
46	92	7
47	88	1
48	85	
49	95	1
50	74	2
51	86	
52	81	3
53	93	1
54	84	4
55	91	1
56	94	5
57	92	4
58	79	16
59	89	4
60	85	1
61	81	4
62	77	1

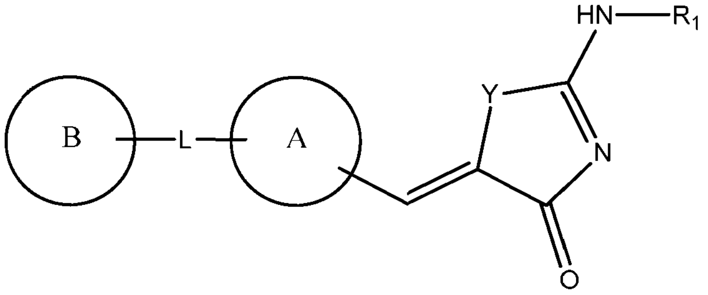
Example Number	Percentage Inhibition of PIM1 kinase at 1 μM	
	Average	SD
63	86	22
64	83	11
65	89	8
66	n/a	
67	63	9
68	76	21
69	83	3
70	78	0
71	82	3
72	77	4
73	58	11
74	83	4

CLAIMS

1. A compound of Formula I or Formula II:



Formula I



Formula II

wherein:

R_1 is selected from hydrogen or a (1-8C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-4C)alkyl, aryl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, heteroaryl, or heteroaryl(1-3C)alkyl group which is optionally substituted with one or more R_a;

R_a is selected from the group consisting of halogeno, trifluoromethyl, trifluoromethoxy, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, ureido, sulfonylamino, (1-6C)alkyl, (1-6C)hydroxyalkyl, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, (1-6C)haloalkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkoxycarbonyl, (1-6C)alkanoyl, (1-6C)alkanoyloxy, (1-6C)alkyl-S(O)$_n$– wherein n is an integer from 0 to 2, *N'*-((1-6C)alkyl)ureido, *N',N'*-((1-6C)alkyl)$_2$ureido, *N'*-((1-6C)alkyl)-*N*-((1-6C)alkyl)ureido, *N',N'*-((1-6C)alkyl)$_2$-*N*-((1-6C)alkyl)ureido, (1-6C)alkanoylamino, *N*-((1-6C)alkyl)-(1-6C)alkanoylamino, *N*-((1-6C)alkyl)carbamoyl, *N,N*-((1-6C)alkyl)$_2$carbamoyl, (1-6C)alkylsulfonylamino, *N*-((1-6C)alkyl)aminosulfonyl, *N,N*-((1-6C)alkyl)$_2$aminosulfonyl, (1-6C)alkoxycarbonylamino, *N*-((1-6C)alkyl)- (1-6C)alkoxycarbonylamino, (1-6C)alkylsulfonylaminocarbonyl, *N*-((1-6C)alkyl)- (1-6C)alkylsulfonylaminocarbonyl, aryl, aryl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, heteroaryl or heteroaryl(1-3C)alkyl;

Y is S or NR_b, where R_b is selected from hydrogen or (1-3C)alkyl;

Ring A is selected from:

(i) a 5-membered heteroaryl ring comprising a nitrogen atom and one or more other heteroatoms selected from the group consisting of N, O or S; or

(ii) a 6-membered heteroaryl ring;

wherein Ring A is optionally substituted by (1-3C)alkyl, halo, trifluoromethyl, trifluoromethoxy, cyano, -CO-O-R_c (wherein R_c is selected from hydrogen, methyl or ethyl) or -CO-NR_dR_e (wherein R_d and R_e are each independently selected from hydrogen or methyl);

L is absent, -O-, -S-, -CH_2-, -C(O)-, -C(O)NR_f-, -NR_fC(O)-, -NR_f-, -N(R_f)CON(R_g)-, -S(O)-, -SO_2-, -$SO_2N(R_f)$-, -N(R_f)SO_2-, -P(O)(OR_h)- wherein R_f and R_g are each independently selected from hydrogen or (1-3C)alkyl; and R_h is selected from (1-3C)alkyl, (4-7C)cycloalkyl or aryl;

Ring B is selected from the group consisting of (4-7C)cycloalkyl, heteroaryl, heterocyclyl or aryl,

wherein

(i) Ring B is optionally substituted on the ring atoms adjacent to the ring atom bonded to L (i.e. in the *ortho* position) by halogeno, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, ureido, methyl, methoxy, ethoxy, (1-3C)alkylthio, (1-3C)alkylsulphinyl, (1-3C)alkylsulphonyl, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, *N*-(1-3C)alkylsulphamoyl, *N*,*N*-di-[(1-3C)alkyl]sulphamoyl, (1-3C)alkanesulphonylamino and *N*-(1-3C)alkyl-(1-3C)alkanesulphonylamino; and

(ii) Ring B may be optionally substituted on any other ring atom by halogeno, trifluoromethyl, trifluoromethoxy, SF_5, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, ureido, or a group of the formula:

$$-L^1-Q^1$$

wherein:

L^1 is selected from a direct bond, -CR_iR_j-, -O-, -S-, -SO-, -SO_2-, -N(R_i)-, -C(O)-, -CH(OR_i)-, -C(O)N(R_i)-, -N(R_i)C(O)-, -C(O)O-, -OC(O)-, -P(O)(R_h)O-, -N(R_i)C(O)N(R_j)-, -S(O)$_2$N(R_i)-, -N(R_i)SO_2-, or -N(R_i)-SO_2-N(R_j)-, wherein R_i and R_j are each independently selected from hydrogen or (1-4C)alkyl;

Q^1 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-4C)alkyl, aryl, aryl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, heteroaryl or heteroaryl(1-3C)alkyl, each of which is optionally substituted with one or more substituents

independently selected from halo, cyano, nitro, hydroxy, amino, trifluoromethyl, trifluoromethoxy, (1-4C)alkyl or (1-4C)alkoxy;
or a pharmaceutically acceptable salt, hydrate or solvate thereof.

2. A compound according to claim 1, wherein Y is S or NH.

3. A compound according to claim 1 or claim 2, wherein Y is S.

4. A compound according to any one of the preceding claims, wherein R_1 is selected from hydrogen or a (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-2C)alkyl, aryl(1-2C)alkyl, heterocyclyl, heterocyclyl(1-2C)alkyl, heteroaryl, or heteroaryl(1-2C)alkyl group which is optionally substituted with one or more R_a, wherein R_a is selected from the group consisting of halogeno, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, mercapto, amino, carboxy, carbamoyl, sulfonylamino, (1-3C)alkyl, (1-3C)hydroxyalkyl, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, (1-3C)haloalkyl, (2-3C)alkenyl, (2-3C)alkynyl, (1-3C)alkoxy, (1-3C)alkoxycarbonyl, (1-3C)alkanoyl, or (1-3C)alkanoyloxy.

5. A compound according to claim4, wherein R_1 is selected from hydrogen or a (1-8C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-4C)alkyl, aryl(1-3C)alkyl, or heterocyclyl(1-3C)alkyl group which is optionally substituted with one or more R_a, wherein R_a is selected from the group consisting of halogeno, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, mercapto, amino, carboxy, carbamoyl, sulfonylamino, (1-3C)alkyl, (1-3C)hydroxyalkyl, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, (1-3C)haloalkyl, (1-3C)alkoxy, (1-3C)alkoxycarbonyl, (1-3C)alkanoyl, (1-3C)alkanoyloxy.

6. A compound according to any one of the preceding claims, wherein Ring A is:
(i) a 5-membered heteroaryl ring comprising a nitrogen atom and one other heteroatom selected from the group consisting of O and S; or
(ii) a 6-membered heteroaryl ring;

7. A compound according to claim 6, wherein Ring A is a thiazole, oxazole, or pyridyl ring, optionally substituted as described herein.

8. A compound according to any one of the preceding claims, wherein L is absent, -O-, -S-, $-CH_2-$, -C(O)-, $-C(O)NR_f-$, $-NR_fC(O)-$, $-NR_f-$, -S(O)-, $-SO_2-$, and wherein R_f is independently selected from hydrogen or (1-2C)alkyl.

9. A compound according to claim 8, wherein L is absent, $-CH_2-$, $-C(O)NR_f-$ or $-NR_fC(O)-$, and wherein R_f is independently selected from hydrogen or methyl.

10. A compound according to any one of the preceding claims, wherein Ring B is selected from the group consisting of (4-7C)cycloalkyl, 5 or 6-membered heteroaryl and aryl,

wherein

(i) Ring B is optionally substituted on the ring atoms adjacent to the ring atom bonded to L (i.e. in the *ortho* position) by halogeno, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, methyl, methoxy, ethoxy, (1-2C)alkylthio, (1-2C)alkylsulphinyl, (1-2C)alkylsulphonyl, (1-2C)alkylamino, di-[(1-2C)alkyl]amino; and

(ii) Ring B may be optionally substituted on any other ring atom by halogeno, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, mercapto, amino, carboxy, carbamoyl, or a group of the formula:

$$-L^1-Q^1$$

wherein:

L^1 is selected from a direct bond, -O-, -S-, -SO-, $-SO_2-$, $-N(R_i)-$, -C(O)-, $-CH(OR_i)-$, $-C(O)N(R_i)-$, $-N(R_i)C(O)-$, -C(O)O-, -OC(O)-, $-P(O)(R_h)O-$, $-N(R_i)C(O)N(R_j)-$, $-S(O)_2N(R_i)-$, $-N(R_i)SO_2-$, or $-N(R_i)-SO_2-N(R_j)-$, wherein R_i and R_j are each independently selected from hydrogen or (1-4C)alkyl;

Q^1 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-4C)alkyl, aryl, aryl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, heteroaryl or heteroaryl(1-3C)alkyl, each of which is optionally substituted with one or more substituents independently selected from halo, cyano, nitro, hydroxy, amino, trifluoromethyl, trifluoromethoxy, (1-4C)alkyl or (1-4C)alkoxy.

11. A compound according to claim 10, wherein Ring B is selected from the group consisting of (5-6C)cycloalkyl, 5 or 6-membered heteroaryl and phenyl,

wherein

Ring B may be optionally substituted on any ring atom other than those ring atoms in the positions *ortho* to the point of attachment to L by halogeno, trifluoromethyl, trifluoromethoxy, hydroxy, or a group of the formula:

$$-L^1-Q^1$$

wherein:

L^1 is selected from a direct bond, $-SO_2-$, $-N(R_i)SO_2-$, or $-N(R_i)-SO_2-N(R_j)-$, wherein R_i and R_j *are each independently selected from hydrogen or* (1-4C)alkyl;

Q^1 is selected from hydrogen, (1-6C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, each of which is optionally substituted with one or more substituents independently selected from (1-4C)alkyl;

12. A compound according to claim 1, which is selected from any one of the following:

(*Z*)-5-((2-(4-Fluorophenyl)thiazol-4-yl)methylene)-2-iminothiazolidin-4-one;

(*Z*)-5-((2-(4-Fluorophenyl)thiazol-4-yl)methylene)-2-((1-methylpiperidin-4-yl)methylamino)thiazol-4(5*H*)-one;

(*Z*)-5-((2-(2-Hydroxyphenyl)thiazol-4-yl)methylene)-2-iminothiazolidin-4-one;

(*Z*)-5-((2-(2-Hydroxyphenyl)thiazol-4-yl)methylene)-2-(((1-methylpiperidin-4-yl)methyl)amino)thiazol-4(5 H)-one;

(Z)-2-(((1-cyclopropylpiperidin-4-yl)methyl)amino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(*Z*)-2-((3-Hydroxy-2,2-dimethylpropyl)amino)-5-((2-(2-hydroxyphenyl)thiazole-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-(((1-(Hydroxymethyl)cyclopropyl)methyl) amino)-5-((2-(2-hydroxy phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-(((1-(Hydroxymethyl)cyclobutyl)methyl)amino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(Z)-2-((4-hydroxy-1-methylpiperidin-4-yl)methylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1R,2R)-2-(hydroxymethyl)cyclopentylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1R,2R)-2-(hydroxymethyl)cyclopentylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1S,2R,5S)-2-(hydroxymethyl)-5-isopropylcyclopentylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1-(2-hydroxyethyl)piperidin-4-yl)methylamino)-5-((2-(2-hydroxyphenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(*Z*)-5-((2-(4-Hydroxyphenyl)thiazol-4-yl)methylene)-2-iminothiazolidin-4-one;

(*Z*)-5-((2-(4-Hydroxyphenyl)thiazol-4-yl)methylene)-2-(((1-methylpiperidin-4-yl) methyl)amino)thiazol-4(5 H)-one;

(*Z*)-*N*-(3-(4-((2-Imino-4-oxothiazolidin-5-ylidene)methyl)thiazol-2-yl)phenyl)methanesulfonamide;

(*Z*)-*N*-(4-(4-((2-Imino-4-oxothiazolidin-5-ylidene)methyl)thiazol-2-yl) phenyl)methanesulfonamide;

(*Z*)-*N*-(4-(4-((2-(((1-Methylpiperidin-4-yl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl) methanesulfonamide;

(*Z*)-*N*-(3-(4-((2-Imino-5-oxo-1,3-dithiolan-4-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide;

(*Z*)-*N*-Methyl-*N*-(3-(4-((2-(((1-methylpiperidin-4-yl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)methanesulfonamide;

N-(3-(4-((*Z*)-(2-(((1*R*,2*S*)-2-Hydroxycyclopentyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide;

N-(3-(4-((*Z*)-(2-(((1*R*,2*S*)-2-Hydroxycyclopentyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide;

(*Z*)-*N*-(3-(4-((2-(((1-(Hydroxymethyl)cyclopropyl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide;

(*Z*)-*N*-(3-(4-((2-(((1-(Hydroxymethyl)cyclobutyl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide;

(*Z*)-*N*-(3-(4-((2-(((1-(Hydroxymethyl)cyclopentyl)methyl)amino)-4-oxothiazol-5(4*H*)-ylidene)methyl)thiazol-2-yl)phenyl)-*N*-methylmethanesulfonamide;

(Z)-N-(3-(4-((2-((4-hydroxy-1-methylpiperidin-4-yl)methylamino)-4-oxothiazol-5(4H)-

ylidene)methyl)thiazol-2-yl)phenyl)-N-methylmethanesulfonamide;

(*Z*)-2-Imino-5-((2-(3-*N*,*N*-dimethylsulfamoylamino)thiazol-4-yl)methylene)thiazolidin-4-one;

N-(3-(4-((Z)-(2-((3-hydroxy-2,2-dimethylpropyl)amino)-4-oxothiazol-5(4H)-ylidene)methyl)thiazol-2-yl)phenyl)-N,N-dimethylsulfonamide;

(*Z*)-2-Imino-5-((2-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)thiazol-4-yl)methylene)thiazolidin-4-one;

(*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one;

(*Z*)-2-Imino-5-((2-(4-(trifluoromethoxy)phenyl) thiazol-4-yl)methylene)thiazolidin-4-one;

(*Z*)-2-(Cyclopropylmethylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-((1*S*,2*S*)-2-Hydroxycyclopentylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-(3-Hydroxybenzylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-((1*R*,4*R*)-4-Hydroxycyclohexylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-(2-(Dimethylamino)ethylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one

(*Z*)-2-((3-Hydroxy-2,2-dimethylpropyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-(((1-(Hydroxymethyl)cyclopropyl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-2-(((1-(Hydroxymethyl)cyclobutyl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(Z)-2-((4-Hydroxy-1-methylpiperidin-4-yl)methylamino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene) thiazol-4(5H)-one;

(Z)-2-(3-Hydroxy-2,2-dimethylpropylamino)-5-((2-(2-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((3-hydroxy-2,2-dimethylpropyl)amino)-5-((2-(3-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((3-hydroxy-2,2-dimethylpropyl)amino)-5-((2-(2-hydroxy-5-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-imino-5-((2-(3-(methylsulfonyl)phenyl)thiazol-4-yl)methylene) thiazolidin-4-one;

(*Z*)-2-Imino-5-((2-(4-(methylsulfonyl)phenyl)thiazol-4-yl)methylene)-1,3-dithiolan-4-one;

(*Z*)-2-Imino-5-((2-(3-(piperidin-1-yl)phenyl)thiazol-4-yl)methylene)-1,3-dithiolan-4-one;

(Z)-2-Imino-5-((2-(4-(piperidin-1-ylmethyl)phenyl)thiazol-4-yl)methylene)thiazolidin-4-one;

(Z)-2-((3-Hydroxy-2,2-dimethylpropyl)amino)-5-((2-(4-(piperidin-1-ylmethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one;

(Z)-2-imino-5-((2-(3-(morpholinomethyl)phenyl)thiazol-4-yl)methylene)thiazolidin -4-one;

(*Z*)-2-Imino-5-((2-(4-(trifluoromethyl)phenyl) thiazol-4-yl)methylene) thiazolidin-4-one;

(Z)-2-(Cyclopropylmethylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1R,2S)-2-Hydroxycyclopentylamino)-5-((2-(4-(trifluoromethyl)phenyl) thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-(2-(dimethylamino)ethylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1r,4r)-4-hydroxycyclohexylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-((1-methylpiperidin-4-yl)methylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5H)-one;

(Z)-2-(3-hydroxybenzylamino)-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl) methylene) thiazol-4(5H)-one;

(Z)-5-((2-(4-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-(3-hydroxy-2,2-dimethylpropylamino)thiazol-4(5H)-one;

(Z)-5-((2-(5-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-((1S,2S)-2-(hydroxymethyl)cyclopentylamino)thiazol-4(5H)-one;

(Z)-5-((2-(5-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-(3-hydroxy-2,2-dimethylpropylamino)thiazol-4(5H)-one;

(*Z*)-5-((2-(3-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-((3-hydroxy-2,2-dimethylpropyl)amino)thiazol-4(*5H*)-one;

(*Z*)-5-((2-(3-Fluoro-2-hydroxyphenyl)thiazol-4-yl)methylene)-2-((4-hydroxy-1-methylpiperidin-4-yl)methyl)amino)thiazol-4(*5H*)-one;

(*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one acetate;

(*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one methane sulfonate;

(*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((2-(4-(trifluoromethoxy)phenyl)thiazol-4-yl)methylene)thiazolidin-4(*5H*)-one Hydrochloride;

(*Z*)-2-Amino-5-((2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methylene)thiazol-4(5*H*)-one methane sulfonate;

(Z)-2-(4-((2-((3-Acetoxy-2,2-dimethylpropyl)amino)-4-oxothiazol-5(4H)-ylidene)methyl)thiazol-2-yl)phenyl acetate;

N-(4-((*Z*)-((*E*)-2-(3-Hydroxy-2,2-dimethylpropylimino)-4-oxothiazolidin-5-ylidene)methyl)thiazol-2-yl)-*N*-methylbenzamide;

(Z)-N-(4-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)thiazol-2-yl)cyclohexanecarboxamide;

(*Z*)-2-((1-Methylpiperidin-4-yl)methylamino)-5-((2-phenyloxazol-4-yl)methylene)thiazol-4(5H)-one;

(2E,5Z)-2-(3-Hydroxy-2,2-dimethylpropylimino)-5-((6-phenylpyridin-2-yl)methylene)thiazolidin-4-one;

(2E,5Z)-2-((1-(Hydroxymethyl)cyclopropyl)methylimino)-5-((6-phenylpyridin-2-yl)methylene)thiazolidin-4-one;

((2E,5Z)-2-((4-Hydroxy-1-methylpiperidin-4-yl)methylimino)-5-((6-phenylpyridin-2-yl)methylene)thiazolidin-4-one;

((2E,5Z)-2-((4-Hydroxy-1-methylpiperidin-4-yl)methylimino)-5-((6-phenylpyridin-2-yl)methylene)thiazolidin-4-one;

(*Z*)-2-(((1-Methylpiperidin-4-yl)methyl)amino)-5-((6-(4-(trifluoromethoxy) phenyl)pyridin-2-yl)methylene)thiazol-4(5*H*)-one;

(*Z*)-*N*-(3-(6-((2-Imino-4-oxothiazolidin-5-ylidene)methyl)pyridin-2-yl) phenyl)methanesulfonamide;

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in admixture with a pharmaceutically acceptable diluent or carrier.

14. 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 according to any one of claims 1 to 12, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition according to claim 13.

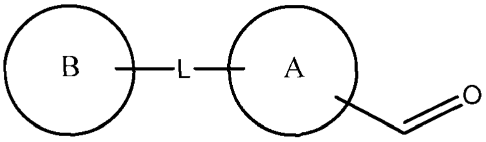
15. A method according to claim 14, wherein said proliferative disorder is cancer.

16. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition according to claim 13, for use in therapy.

17. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition according to claim 13, for use in the treatment of a proliferative condition.

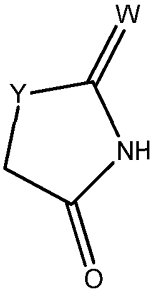
18. A compound according to claim 17, wherein said proliferative condition is cancer.

19. A process for preparing a compound of formula I or II according to claim 1, the process comprising the steps of:
reacting a compound of formula B:



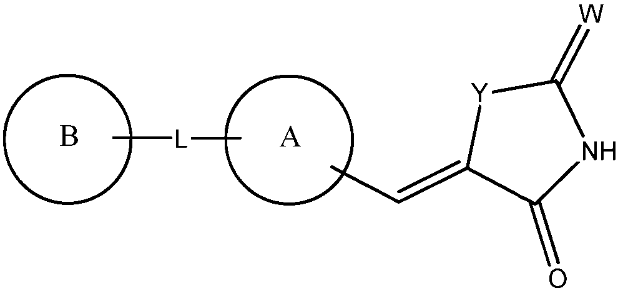
Formula B

with a compound of formula B1:



Formula B1

to form a compound of formula C:



Formula C

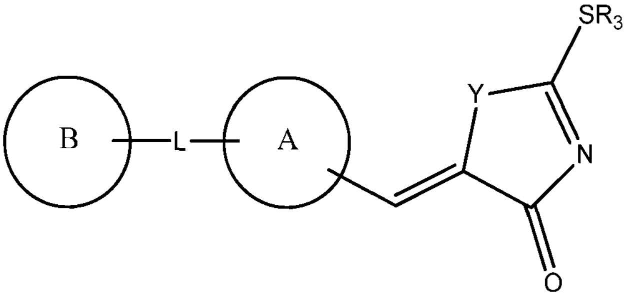
wherein either:

(a) W is NH, and the compound of formula C is a compound of formula I where R_1 is hydrogen;

or

(b) W is S and the compound of formula C is an intermediate compound which is then:

(i) further reacted with a compound of the formula R_3-LG to form an activated intermediate compound of formula D, wherein LG is any suitable leaving group (e.g. halide, tosyl, mesyl, etc.), and R_3 is any group which renders $-SR_3$ a suitable leaving group from compound D:



Formula D

and

compound D is then further reacted with an amine of the formula R_1NH_2;

or

(ii) compound C is reacted with an amine of the formula R_1NH_2;

wherein Y, R_1, Ring A, L, and Ring B each as defined in claim 1;

and optionally thereafter (and if necessary):

(i) removing any protecting groups present into R_1;

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

(iii) forming a pharmaceutically acceptable salt, hydrate or solvate thereof; and/or

(iv) forming a prodrug thereof.

Application No:	GB1222826.8	**Examiner:**	Dr S. David Evans
Claims searched:	1-19	**Date of search:**	17 April 2013

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1, 13, 16-18 at least	WO 2009/123948 A (IRM LLC) see whole document, but especially Example 50 in Table 1 on page 88 and the Markush structure disclosed in claim 1
X	1, 13, 16-18 at least	WO 2006/124874 A (KALYPSYS INC) see entire document, but particularly Example 29 in Table 1 on page 47 and the generic structures disclosed in claims 1 and 16
X	1, 13, 16 at least	WO 2005/075471 A (BIOVITRUM AB) see Chem. Abs. No. 143:211905 and the whole document, especially the Markush structure described in claim 1
X	1, 13, 16-18 at least	Chemistry & Biology (Cambridge, MA, United States), Vol. 18(7), 2011, (Miduturu, Chandrasekhar V. et al), "High-Throughput Kinase Profiling: A More Efficient Approach toward the Discovery of New Kinase Inhibitors", pages 868-879, ISSN: 1074-5521 see Chem. Abs. No. 156:410730
X	1, 13, 16 at least	WO 2007/032028 A (TORRENT PHARMACEUTICALS LTD) see Chem. Abs. No. 146:358833 and the generic structure described in claim 1
X	1 at least	Organic Letters, Vol. 10(3), 2008, (Vergne, Carine et al), "Debromodispacamides B and D: Isolation from the Marine Sponge Agelas mauritiana and Stereoselective Synthesis Using a Biomimetic Proline Route", pages 493-496, ISSN: 1523-7060 see entire article, but especially compounds 17a and 17b in Scheme 3 on page 495
X	1, 13, 16-18 at least	US 2011/190299 A1 (IRIE et al) see whole document, but especially the Markush structure described in claim 1

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

The following online and other databases have been used in the preparation of this search report

CAS ONLINE

International Classification:

Subclass	Subgroup	Valid From
C07D	0417/06	01/01/2006
A61K	0031/427	01/01/2006
A61K	0031/445	01/01/2006
A61P	0035/00	01/01/2006
C07D	0413/14	01/01/2006