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(54) Title: HETEROCYCLIC COMPOUNDS AND THEIR USE IN THE TREATMENT OF MYCOBACTERIAL INFECTIONS

(57) Abstract: The invention relates to compounds or pharmaceutically acceptable salts thereof, compositions containing them, including combinations with at least one additional therapeutic agent, and their use in therapy, for example in the treatment of mycobacterial infections or in the treatment of diseases caused by a mycobacterium, such as tuberculosis.



HETEROCYCLIC COMPOUNDS AND THEIR USE IN THE TREATMENT OF MYCOBACTERIAL INFECTIONS

Field of the invention

The invention relates to a compound or a pharmaceutically acceptable salt thereof, compositions containing them, including combinations with at least one additional therapeutic agent and their use in therapy, for example in the treatment of mycobacterial infections or in the treatment of diseases caused by mycobacterium, such as tuberculosis.

Background to the invention

Nearly ten million people are infected with tuberculosis (TB) each year, causing an estimated 1.6 million deaths each year, according to a report published by The World Health Organisation in 2022. If untreated the death rate is approximately 50% (from WHO). Despite available treatments for tuberculosis, the global disease burden remains a major problem owing to *Mycobacterium tuberculosis*, the causative bacterial agent for TB, becoming resistant to many of the treatments.

In an attempt to prevent resistance to currently available drugs and future approved drugs increasing, TB is treated using combination therapies of three or more drugs. In addition, the treatment of TB often requires therapy using multiple drugs. The standard treatment currently used for drug-susceptible TB is a combination of isoniazid, rifampicin, pyrazinamide and ethambutol, which patients are required to take for two months, followed by isoniazid and rifampicin, only, for a further four months.

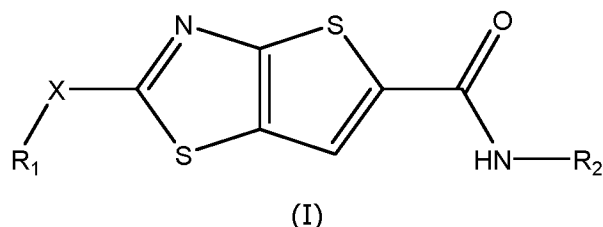
Multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampicin, the two most powerful first-line anti-TB medicines, and extensively drug-resistant TB (XDR-TB) is a form of MDR-TB that is also resistant to at least one fluoroquinolone and any of the second-line anti-TB injectable agents (i.e. amikacin, kanamycin or capreomycin), the two most important classes of medicines in the MDR-TB regimen. For the treatment of M(X)DR TB, it is necessary to administer a regimen of four or more second-line drugs.

The prevalence of TB infection throughout history, is largely due to the ability of *Mycobacterium tuberculosis* to persist in the host for long periods of time and cause disease even in the face of a highly orchestrated host immune response (Flynn, J. L. & Chan, J. (2001) Annu. Rev. Immunol. 19, 93–129.). This unusual ability suggests that mycobacteria may use unique pathogenic mechanisms.

Owing to the ever-growing emergence of multi-drug resistant strains of *Mycobacterium tuberculosis* and continued high incidence of TB, there exists an urgent need to provide further drug compounds for the treatment of TB.

Summary of the invention

At its broadest, the invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



wherein:

R₁ is cyclopropyl which may be halo-substituted;

or R₁ is 4-7 membered heterocyclyl, optionally substituted with one or more of

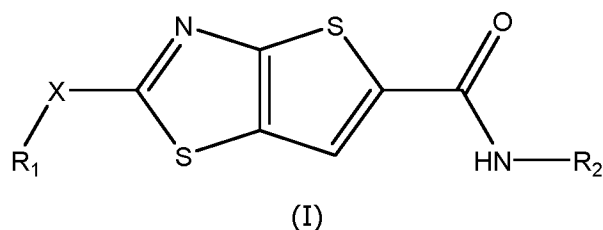
- (i) C₁₋₃ alkyl or C₁₋₃haloalkyl;
- (ii) C₄₋₇heterocyclyl, which may be halo-substituted;
- (iii) -C(=O)-cyclopropyl which cyclopropyl may be halo-substituted;
- (iv) -C(=O)OR₃; wherein R₃ is C₁₋₃ alkyl;

X is a bond, -Y(CH₂)_n*, or -Y-cyclobutyl-* wherein Y is -O- or -S- and * represents the point of attachment to R₁;

n is 0 or 1 or 2;

R₂ is C₃₋₆cycloalkyl, C₅₋₆heteroaryl, or C₅₋₆aryl, each optionally substituted with C₁₋₆alkyl, or C₁₋₆haloalkyl.

In a first aspect of the invention, there is provided a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



wherein:

R₁ is cyclopropyl which may be halo-substituted;

or R₁ is 4-7 membered heterocyclyl, optionally substituted with one or more of

- (i) C₁₋₃ alkyl or C₁₋₃haloalkyl;
- (ii) C₄₋₇heterocyclyl, which may be halo-substituted;

- (iii) $-\text{C}(=\text{O})\text{-cyclopropyl}$ which cyclopropyl may be halo-substituted;
- (iv) $-\text{C}(=\text{O})\text{OR}_3$; wherein R_3 is C_{1-3} alkyl;

X is a bond, $-\text{Y}(\text{CH}_2)_n^*$, or $-\text{Y-cyclobutyl}^*$ wherein Y is $-\text{O}-$ or $-\text{S}-$ and * represents the point of attachment to R_1 ;

n is 0 or 1 or 2;

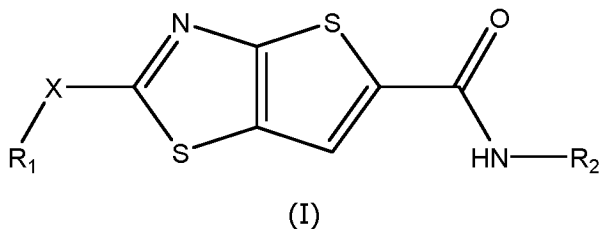
R_2 is $\text{C}_3\text{-6cycloalkyl}$, optionally substituted with $\text{C}_{1-6}\text{alkyl}$, or $\text{C}_{1-6}\text{haloalkyl}$.

Further aspects of the invention include:

- 2) A pharmaceutical composition comprising (a) the compound of Formula (I) or pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable excipient.
- 3) A kit comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition the second aspect, and instructions for administering to a human in need thereof.
- 4) A method of treating a mycobacterial infection (or a disease caused by infection with a mycobacterium) in a human in need thereof, the method comprising administering to said human a therapeutically effective amount of a compound of Formula (I) or pharmaceutically acceptable salt thereof.
- 5) A compound of Formula (I) or pharmaceutically acceptable salt thereof, for use in therapy. In some embodiments, it is for use in the treatment of a mycobacterial infection (or a disease caused by infection with a mycobacterium).
- 6) Use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a mycobacterial infection or a disease caused by infection with a mycobacterium.
- 7) A combination of (a) a compound of Formula (I) or pharmaceutically acceptable salt thereof; and (b) at least one other anti-mycobacterial agent.

Detailed description of the invention

As described above, in one aspect of the invention, there is provided a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



wherein R_1 , R_2 and X are as defined above.

In some embodiments, X is $-Y(CH_2)_n^*$ or $-Y\text{-cyclobutyl}^*$, wherein * represents the point of attachment of R_1 . In such embodiments, Y is attached to the thienodiazole. In some embodiments, X is $-Y(CH_2)_n^*$. In some embodiments, X is $-Y(CH_2)_n^*$, Y is $-O-$ and n is 0 or 1.

In some embodiments, R_1 is selected from the group consisting of cyclopropyl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, 6-oxa-3-azabicyclo[3.1.1]heptan-3-yl, 2-methyl-morpholin-4-yl, 2,2-dimethyl-morpholin-4-yl, 3-methyl-4-(oxetan-3-yl)piperazin-1-yl, 4-(morpholin-4-yl)piperidin-1-yl, 2-oxaspiro[3.3]heptan-6-yl, tetrahydrofuran-3-yl morpholin-4-yl, methyl 2-methyl-piperazin-4-yl-1-carboxylate, and methyl pyrrolidin-3-yl-1-carboxylate

In some embodiments, $-XR_1$ is selected from the group consisting of cyclopropyl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, 6-oxa-3-azabicyclo[3.1.1]heptan-3-yl, 2-methyl-morpholin-4-yl, 2,2-dimethyl-morpholin-4-yl, 3-methyl-4-(oxetan-3-yl)piperazin-1-yl, 4-(morpholin-4-yl)piperidin-1-yl, (2-oxaspiro[3.3]heptan-6-yl)oxy, (tetrahydrofuran-3-yl)methoxy, oxetan-3-yloxy, 4-cyclopropanecarbonyl-3-methyl-piperazin-1-yl, 3-(morpholin-4-yl)cyclobutoxy, methyl 2-methyl-piperazin-4-yl-1-carboxylate, and (methyl pyrrolidin-3-yl-1-carboxylate)oxy.

In some embodiments, R_2 is C_{3-6} cycloalkyl optionally substituted with C_{1-6} alkyl, or C_{1-6} haloalkyl.

In some embodiments, R_2 is selected from the group consisting of 2-methylcyclopropyl, 3-methylcyclobutyl, 3-difluoromethyl-cyclobutyl, cyclobutyl, spiro[2.3]hexanyl, and 5-methylpyridin-2-yl. In some embodiments, R_2 is selected from the group consisting of 2-methylcyclopropyl, 3-methylcyclobutyl, cyclobutyl, spiro[2.3]hexanyl, and 5-methylpyridin-2-yl. In some embodiments, R_2 is selected from the group consisting of 2-methylcyclopropyl, 3-methylcyclobutyl, 3-difluoromethyl-cyclobutyl, cyclobutyl, spiro[2.3]hexanyl. In some embodiments, R_2 is selected from the group consisting of 2-methylcyclopropyl, 3-methylcyclobutyl, cyclobutyl, spiro[2.3]hexanyl. In some embodiments, R_2 is C_{3-4} cycloalkyl, optionally substituted with methyl. In some embodiments, R_2 is selected from 2-methylcyclopropyl, 3-methylcyclobutyl and cyclobutyl. In some embodiments, R_2 is selected from 2-methylcyclopropyl and cyclobutyl. In some embodiments, R_2 is 2-methylcyclopropyl.

It will be appreciated that a compound of Formula (I) may exist in different tautomeric forms. All possible tautomers, and pharmaceutically acceptable salts thereof, are contemplated to be within the scope of the present invention.

The compound of Formula (I) or pharmaceutically acceptable salt thereof may be in crystalline or amorphous forms. Furthermore, some of the crystalline forms may exist as polymorphs, all of which are included within the scope of the present invention. The most thermodynamically stable

polymorphic form or forms of a compound of Formula (I) or a pharmaceutically acceptable salt thereof are of particular interest.

Polymorphic forms of a compound of Formula (I) or a pharmaceutically acceptable salt thereof may be characterised and differentiated using a number of conventional analytical techniques, including, but not limited to, X-ray powder diffraction (XRPD), infrared spectroscopy (IR), Raman spectroscopy, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and solid-state nuclear magnetic resonance (ssNMR).

Terms and Definitions

"Alkyl" refers to a saturated hydrocarbon chain having the specified number of carbon atoms. For example, the term "C₁₋₃alkyl" and "C₁₋₄alkyl" as used herein refers to a straight or branched alkyl group having from 1 to 3 or 1 to 4 carbon atoms respectively. "Alkyl" includes, but is not limited to, methyl, ethyl, *n*-propyl, iso-propyl, *n*-butyl, iso-butyl, *t*-butyl, pentyl and hexyl.

"Cycloalkyl" refers to a saturated hydrocarbon mono or bicyclic ring or a saturated spiro-linked bicyclic hydrocarbon ring, having 3, 4, 5, 6, 7, 8, 9 or 10 member atoms in the ring. Suitable examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclohexyl, spiro[2.3]hexyl.

"Halo" refers to a halogen radical, for example, fluoro, chloro, bromo, or iodo. "haloalkyl" refers to an alkyl group in which one or more hydrogens are replaced by a halogen atom. "halo-substituted" in relation to a cycloalkyl or heterocyclyl refers to a cycloalkyl or heterocyclyl group in which one or more hydrogens are replaced by a halogen atom.

"C₅₋₆heteroaryl" refers to a monocyclic aromatic group having 5 or 6 member atoms, including 1, 2, 3 or 4 heteroatoms independently selected from nitrogen, sulphur and oxygen. The point of attachment to the rest of the molecule may be by any suitable carbon or nitrogen atom. Examples of "C₅₋₆heteroaryl" groups include, but are not limited to, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl and triazinyl.

"Heteroatom" refers to a nitrogen, sulfur, or oxygen atom.

"Heterocyclyl" refers to a non-aromatic heterocyclic monocyclic or bicyclic ring system or a non-aromatic spiro-linked bicyclic ring system, containing 4, 5, 6, 7, 8, 9 or 10 ring member atoms, including one heteroatom and optionally containing a further heteroatom selected from nitrogen, oxygen or sulphur. Examples of "heterocyclyl" groups include, but are not limited to, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, pyrazolidinyl, pyrazolinyl, imidazolidinyl, imidazolinyl, oxazolinyl, thiazolinyl, tetrahydrofuranyl, dihydrofuranyl, 1,3-dioxolanyl, piperidinyl, piperazinyl, homopiperazinyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, 1,4-oxathiolanyl, 1,4-oxathianyl, 1,4-dithianyl, morpholinyl, thiomorpholinyl, hexahydro-1*H*-1,4-diazepinyl, azabicyclo[3.2.1]octyl, azabicyclo[3.3.1]nonyl, azabicyclo[4.3.0]nonyl, oxabicyclo[2.2.1]heptyl, 1,1-dioxidotetrahydro-2*H*-thiopyranyl, 1,5,9-triazacyclododecyl, 3-oxabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.0]hexanyl, (1*r*,5*s*)-3-oxabicyclo[3.1.0]hexanyl, (1*r*,5*s*)-3-azabicyclo[3.1.0]hexanyl. Further examples of "heterocyclyl" groups include 2-oxa-5-azabicyclo[2.2.1]heptanyl, 6-oxa-3-azabicyclo[3.1.1]heptanyl, morpholinyl, piperazinyl, oxetanyl, piperidinyl, 2-oxaspiro[3.3]heptanyl, and tetrahydrofuranyl.

"4-7-membered heterocyclyl" refers to a non-aromatic heterocyclic ring system containing 4, 5, 6 or 7 ring member atoms, including one heteroatom and optionally containing a further heteroatom selected from nitrogen, oxygen or sulphur. Examples of "4-7-membered heterocyclyl" groups include, but are not limited to pyrrolidinyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 6-oxa-3-azabicyclo[3.1.1]heptanyl, morpholinyl, piperazinyl, piperidinyl, 2-oxaspiro[3.3]heptanyl, and tetrahydrofuranyl. "6-7-membered heterocyclyl" refers to a non-aromatic heterocyclic ring system containing 6 or 7 ring member atoms, including one heteroatom and optionally containing a further heteroatom selected from nitrogen, oxygen or sulphur. Examples of "6-7-membered heterocyclyl" groups include, but are not limited to 2-oxa-5-azabicyclo[2.2.1]heptanyl, 6-oxa-3-azabicyclo[3.1.1]heptanyl, morpholinyl, piperazinyl, piperidinyl, and 2-oxaspiro[3.3]heptanyl.

"Substituted" in reference to a group indicates that a hydrogen atom attached to a member atom within a group is replaced. It should be understood that the term "substituted" includes the implicit provision that such substitution be in accordance with the permitted valence of the substituted atom and the substituent and that the substitution results in a stable compound (i.e. one that does not spontaneously undergo transformation such as rearrangement, cyclisation, or elimination). In certain embodiments, a single atom may be substituted with more than one substituent as long as such substitution is in accordance with the permitted valence of the atom. Suitable substituents are defined herein for each substituted or optionally substituted group.

It will be understood that a phrase such as "a compound of Formula (I) or a pharmaceutically acceptable salt thereof" is intended to encompass the compound of Formula (I), a pharmaceutically acceptable salt or solvate of the compound of Formula (I), or any pharmaceutically acceptable combination of these. Thus, by way of non-limiting example used here for illustrative purpose, "a compound of Formula (I) or a pharmaceutically acceptable salt thereof" encompasses a pharmaceutically acceptable salt of a compound of Formula (I) which is present as a solvate, and this phrase also encompasses a mixture of a compound of Formula (I) and a pharmaceutically acceptable salt of a compound of Formula (I).

It is to be further understood that references herein to a compound of Formula (I) or a pharmaceutically acceptable salt thereof includes a compound of Formula (I) as a free base or as a pharmaceutically acceptable salt thereof.

The term "pharmaceutically acceptable" refers to those compounds (including salts), materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

Pharmaceutically acceptable salts include, amongst others, those described in Berge, J. Pharm. Sci., 1977, 66, 1-19, or those listed in P H Stahl and C G Wermuth, editors, *Handbook of Pharmaceutical Salts; Properties, Selection and Use, Second Edition* Stahl/Wermuth: Wiley-VCH/VHCA, 2011 (see <http://www.wiley.com/WileyCDA/WileyTitle/productCd-3906390519.html>).

Where the compound functionality allows, suitable pharmaceutically acceptable salts of the compound of Formula (I) can be formed, which include acid or base addition salts. Acid addition salts may be formed by reaction with the appropriate acid, optionally in a suitable solvent such as an organic solvent, to give the salt which can be isolated by crystallisation and filtration. Base addition salts may be formed by reaction with the appropriate base, optionally in a suitable solvent such as an organic solvent, to give the salt which can be isolated by crystallisation and filtration.

Representative pharmaceutically acceptable acid addition salts include, but are not limited to, 4-acetamidobenzoate, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate (besylate), benzoate, bisulfate, bitartrate, butyrate, calcium edetate, camphorate, camphorsulfonate (camsylate), caprate (decanoate), caproate (hexanoate), caprylate (octanoate), cinnamate, citrate, cyclamate, digluconate, 2,5-dihydroxybenzoate, disuccinate, dodecylsulfate (estolate), edetate (ethylenediaminetetraacetate), estolate (lauryl sulfate), ethane-1,2-disulfonate (edisylate), ethanesulfonate (esylate), formate, fumarate, galactarate (mucate), gentisate (2,5-dihydroxybenzoate), glucoheptonate (gluceptate), gluconate, glucuronate, glutamate, glutarate,

glycerophosphate, glycolate, hexylresorcinate, hippurate, hydrabamine (*N,N'*-di(dehydroabietyl)-ethylenediamine), hydrobromide, hydrochloride, hydroiodide, hydroxynaphthoate, isobutyrate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, methanesulfonate (mesylate), methylsulfate, mucate, naphthalene-1,5-disulfonate (napadisylate), naphthalene-2-sulfonate (napsylate), nicotinate, nitrate, oleate, palmitate, *p*-aminobenzenesulfonate, *p*-aminosalicylate, pamoate (embonate), pantothenate, pectinate, persulfate, phenylacetate, phenylethylbarbiturate, phosphate, polygalacturonate, propionate, *p*-toluenesulfonate (tosylate), pyroglutamate, pyruvate, salicylate, sebacate, stearate, subacetate, succinate, sulfamate, sulfate, tannate, tartrate, teoclate (8-chlorotheophyllinate), thiocyanate, triethiodide, undecanoate, undecylenate, and valerate.

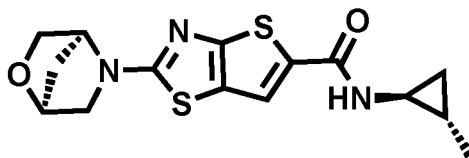
Representative pharmaceutically acceptable base addition salts include, but are not limited to, aluminium, 2-amino-2-(hydroxymethyl)-1,3-propanediol (TRIS, tromethamine), arginine, benethamine (*N*-benzylphenethylamine), benzathine (*N,N'*-dibenzylethylenediamine), *bis*-(2-hydroxyethyl)amine, bismuth, calcium, chlorprocaine, choline, clemizole (1-*p* chlorobenzyl-2-pyrrolidine-1'-ylmethylbenzimidazole), cyclohexylamine, dibenzylethylenediamine, diethylamine, diethyltriamine, dimethylamine, dimethylethanolamine, dopamine, ethanolamine, ethylenediamine, L-histidine, iron, isoquinoline, lepidine, lithium, lysine, magnesium, meglumine (*N*-methylglucamine), piperazine, piperidine, potassium, procaine, quinine, quinoline, sodium, strontium, *t*-butylamine, and zinc.

As used herein, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder.

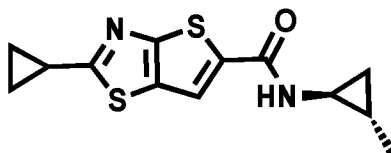
An appropriate "therapeutically effective amount" will depend upon a number of factors including, for example, the age and weight of the subject, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician.

The compound of Formula (I) may contain at least one asymmetric centres (also referred to as a chiral centres) and may, therefore, exist as individual enantiomers, diastereoisomers, or other stereoisomeric forms, or as mixtures thereof.

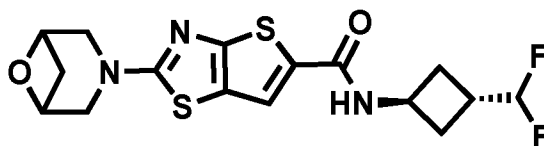
Particular compounds of Formula (I) are:

Example 1

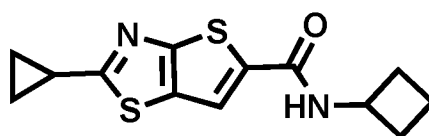
2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-((1S,2S)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide

Example 11

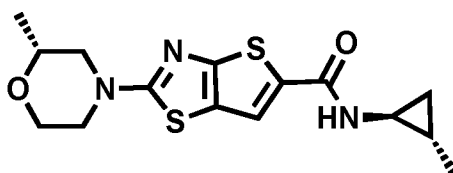
2-cyclopropyl-N-((1S,2S)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide

Example 2

2-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-N-((1*r*,3*r*)-3-(difluoromethyl)cyclobutyl)thieno[2,3-*d*]thiazole-5-carboxamide

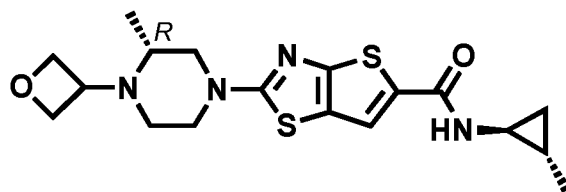
Example 12

N-cyclobutyl-2-cyclopropylthieno[2,3-*d*]thiazole-5-carboxamide

Example 5

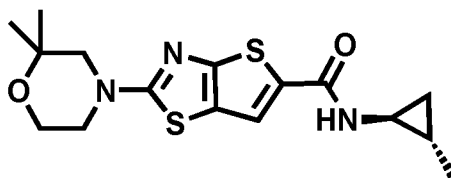
N-((1S,2S)-2-methylcyclopropyl)-2-((*R*)-2-methylmorpholino)thieno[2,3-*d*]thiazole-5-carboxamide

Example 6



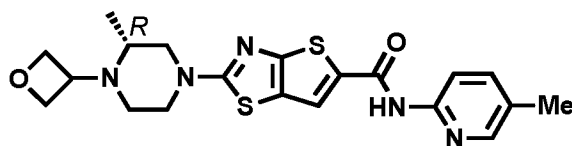
2-((*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide

Example 3



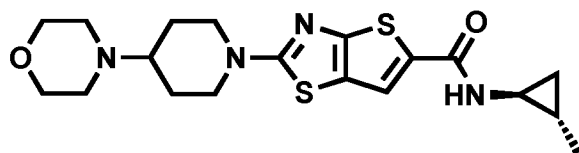
2-(2,2-dimethylmorpholino)-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide

Example 9



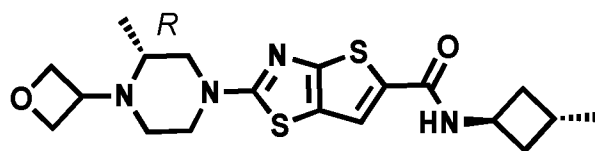
(*R*)-2-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-*N*-(5-methylpyridin-2-yl)thieno[2,3-*d*]thiazole-5-carboxamide

Example 4

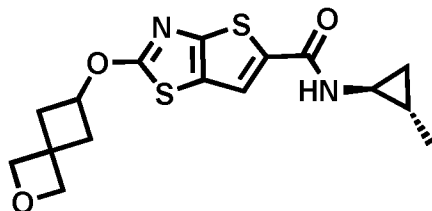


***N*-((1*S*,2*S*)-2-methylcyclopropyl)-2-(4-morpholinopiperidin-1-yl)thieno[2,3-*d*]thiazole-5-carboxamide**

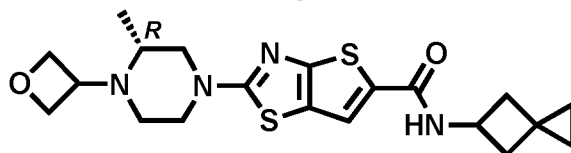
Example 7



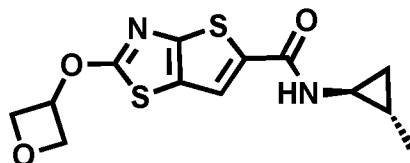
2-((*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-*N*-((1*r*,3*R*)-3-methylcyclobutyl)thieno[2,3-*d*]thiazole-5-carboxamide

Example 14

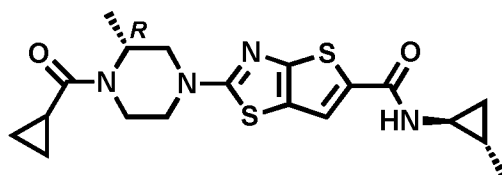
2-((2-oxaspiro[3.3]heptan-6-yl)oxy)-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide

Example 8

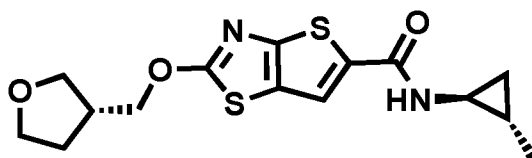
(*R*)-2-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-*N*-(spiro[2.3]hexan-5-yl)thieno[2,3-*d*]thiazole-5-carboxamide

Example 13

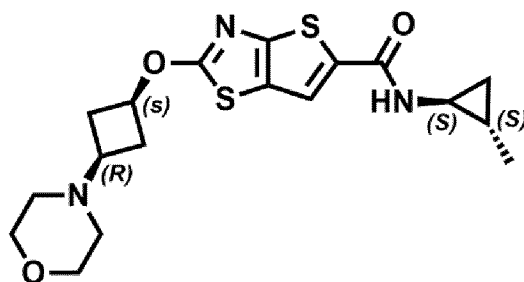
N-((1*S*,2*S*)-2-methylcyclopropyl)-2-(oxetan-3-yloxy)thieno[2,3-*d*]thiazole-5-carboxamide

Example 10

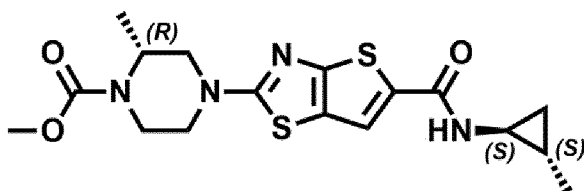
2-((*R*)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide

Example 15

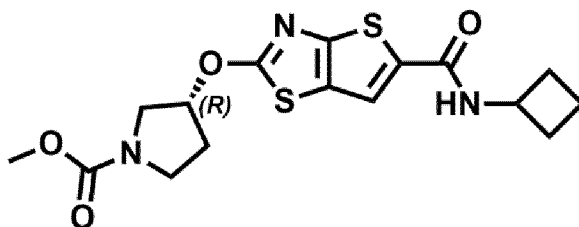
N-((1*S*,2*S*)-2-methylcyclopropyl)-2-(((*R*)-tetrahydrofuran-3-yl)methoxy)thieno[2,3-*d*]thiazole-5-carboxamide

Example 16

N-((1S,2S)-2-methylcyclopropyl)-2-(((1S,3R)-3-morpholinocyclobutoxy)thieno[2,3-d]thiazole-5-carboxamide

Example 17

methyl (R)-2-methyl-4-(5-(((1S,2S)-2-methylcyclopropyl)carbamoyl)thieno[2,3-d]thiazol-2-yl)piperazine-1-carboxylate

Example 18

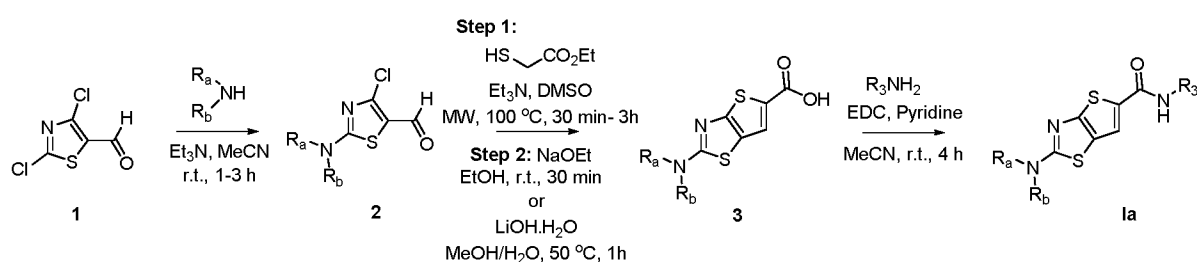
methyl (R)-3-((5-(cyclobutylcarbamoyl)thieno[2,3-d]thiazol-2-yl)oxy)pyrrolidine-1-carboxylate

Compound Preparation

The compound of Formula (I) or a pharmaceutically acceptable salt thereof may be made by a variety of methods, including standard chemistry. The general procedures which can be used to synthesise the compound of Formula (I) are described in reaction **Schemes 1 to 6** below and are further illustrated in the Examples.

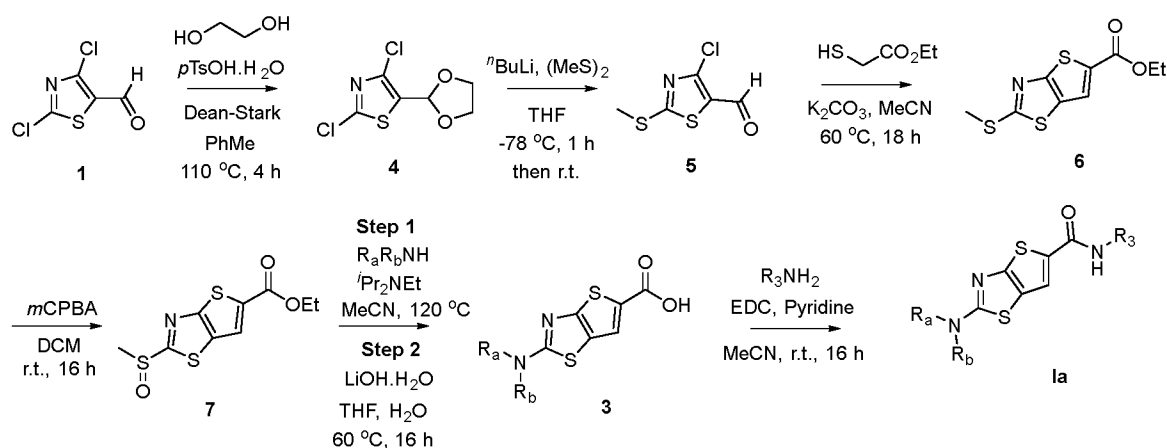
Preparation of the compound of Formula (I)

The compounds of Formula **(Ia)** may be prepared according to **Scheme 1** by an amine displacement reaction of **1**, dissolved in a suitable solvent, for example acetonitrile with an amine of the formula R_1R_2NH and triethylamine. The reaction is carried out at a suitable temperature, for example ambient to produce compounds of Formula **2**. Bicycle ring formation is achieved by displacement of the 4-chloro of **2** with ethylmercaptoacetate dissolved in a suitable solvent, for example, dimethylsulfoxide and triethylamine. The reaction is carried out in a microwave reactor, at a suitable temperature, for example 100 °C. The resulting product hydrolysed by treatment with a suitable base, for example, sodium ethoxide or lithium hydroxide monohydrate dissolved in a suitable solvent, for example ethanol or methanol. The reaction is carried out at a suitable temperature, for example ambient to 50 °C to produce compounds of Formula **3**. An amidation reaction on the acid of Formula **3** with the appropriate amine and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide is carried out in an suitable solvent, for example pyridine. The reaction is a carried out at a suitable temperature, for example, ambient to afford compounds of the Formula **Ia**.



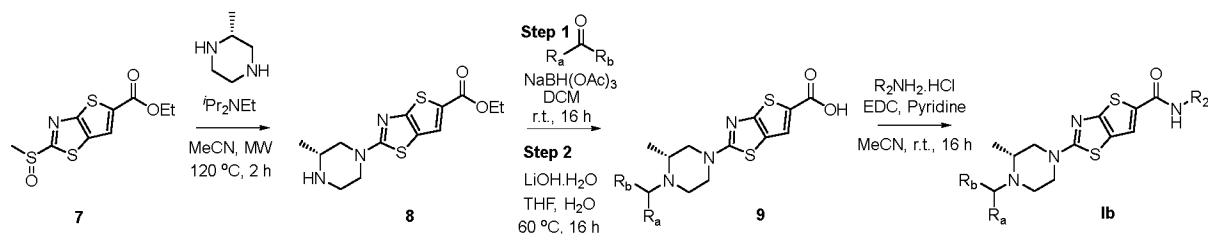
Alternatively, compounds of Formula **Ia** may be prepared according to **Scheme 2**. The aldehyde of **1** is protected as the corresponding acetal by the addition of ethylene glycol and *p*-toluenesulfonic acid monohydrate dissolved in a suitable solvent, for example toluene. The reaction is carried out at a suitable temperature, for example 110 °C to produce compounds of Formula **4**. Displacement of the 2-chloro from of Formula **4** is achieved by treatment with *n*-butyllithium dissolved in a suitable solvent, for example tetrahydrofuran. The reaction is carried out at a suitable temperature, for example -78 °C. Dimethylsulfide added and the reaction allowed to warm to ambient temperature to produce compounds of Formula **5**. Bicycle ring formation is achieved by displacement of the 4-chloro of **5** with ethylmercaptoacetate dissolved in a suitable solvent, for example, acetonitrile with an appropriate base, for example potassium carbonate. The reaction is carried out at a suitable temperature, for example 60 °C to produce compounds of the Formula **6**. An oxidation reaction of the methyl thiol of Formula **6** with meta-chloroperoxybenzoic acid dissolved in a suitable solvent, for example dichloromethane is carried out at a suitable temperature, for example, ambient to produce compounds of the Formula **7**. An amine displacement reaction of the sulfoxide of **7** with the appropriate amine and diisopropylethylamine

dissolved in a suitable solvent, for example acetonitrile is carried out at a suitable temperature, for example 120 °C, hydrolysis of the produce from this reaction is achieved by treatment with the appropriate base, for example lithium hydroxide monohydrate dissolved in a suitable solvent, for example tetrahydrofuran and water. The reaction is carried out at a suitable temperature, for example 60 °C to produce compounds of the Formula **3**. An amidation reaction on the acid of Formula **3** with the appropriate amine and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide is carried out in a suitable solvent, for example pyridine. The reaction is carried out at a suitable temperature, for example, ambient to afford compounds of the Formula **1a**.



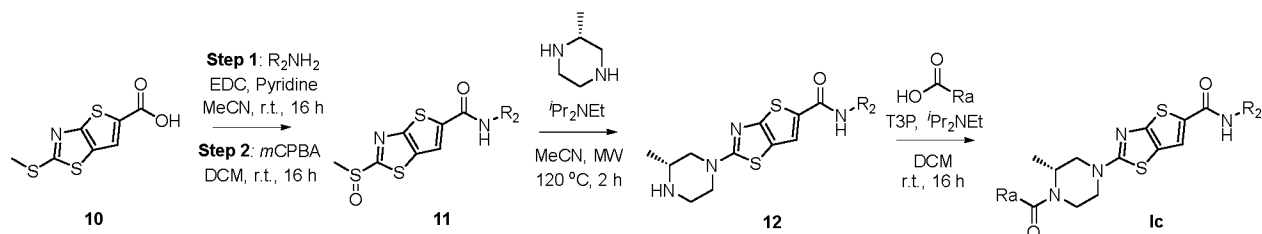
Scheme 2

Compounds of Formula **1b** may be prepared according to **Scheme 3** by an amine displacement reaction on the sulfoxide of **7** with the appropriate amine and diisopropylethylamine dissolved in a suitable solvent, for example, acetonitrile. The reaction is carried out in a microwave reactor, at a suitable temperature, for example 120 °C to produce compounds of the Formula **8**. A reductive amination reaction of **8** dissolved in a suitable solvent, for example dichloromethane and sodium triacetoxyborohydride. The reaction is carried out at suitable temperature, for example, ambient, the resulting product is treated with lithium hydroxide monohydrate, dissolved in a suitable solvent, for example tetrahydrofuran and water. The reaction is carried out a suitable temperature, for example 60 °C to produce compounds of Formula **9**. An amidation reaction on the acid of Formula **9** with the appropriate amine and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide dissolved in a suitable solvent, for example pyridine is a carried out at a suitable temperature, for example, ambient to afford compounds of the Formula **1b**.



Scheme 3

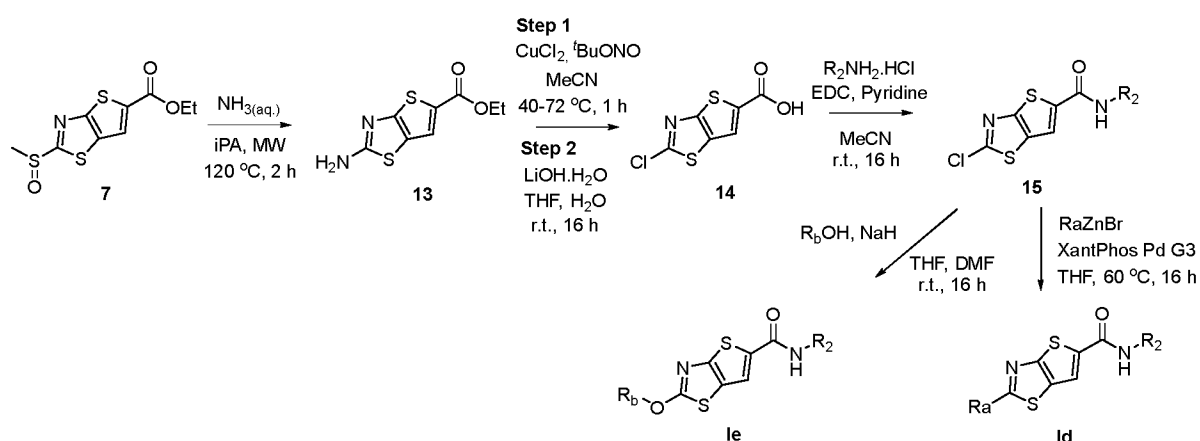
Compounds of Formula **1c** may be prepared according to **Scheme 4**. An amidation reaction out on the acid of Formula **10** with the appropriate amine and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide dissolved in an appropriate solvent, for example pyridine. The reaction is carried out at a suitable temperature, for example, ambient. An oxidation reaction the resulting product with meta-chloroperoxybenzoic acid dissolved in a suitable solvent, for example dichloromethane. The reaction is carried out at a suitable temperature, for example, ambient to produce compounds of the Formula **11**. An amine displacement reaction on the sulfoxide of **11** with the (*R*)-2-methylpiperazine and diisopropylethylamine dissolved in a suitable solvent, for example, acetonitrile. The reaction is carried out in a microwave reactor, at a suitable temperature, for example 120°C to produce compounds of the Formula **12**. An amidation reaction on the amine of **12** with the appropriate acid dissolved in a suitable solvent, for example dichloromethane with diisopropylethylamine and propylphosphonic anhydride solution. The reaction is carried out at a suitable temperature, for example ambient to afford compounds of the Formula **1c**.



Scheme 4

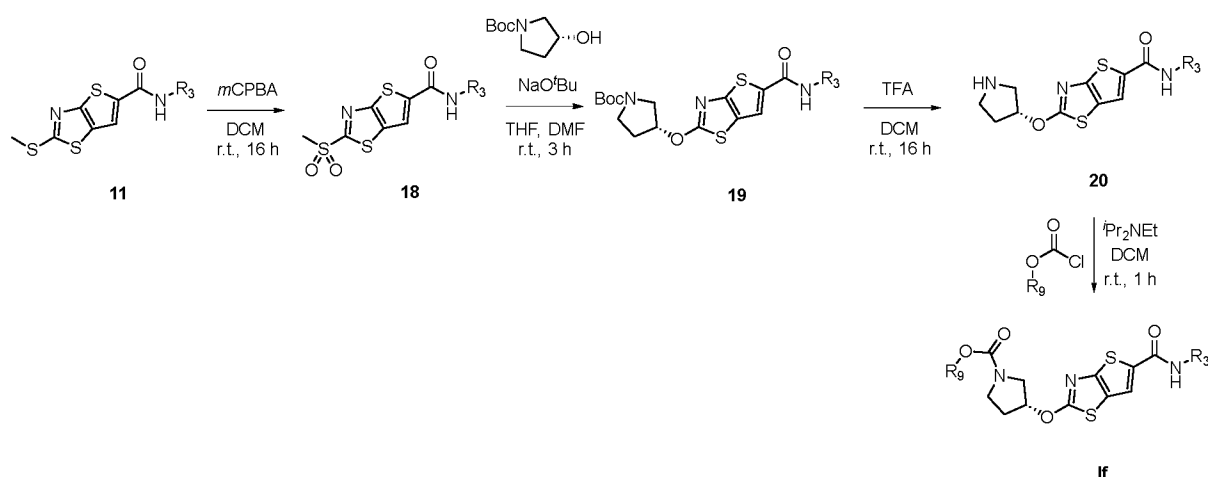
Compounds of Formula **1d** and **1e** may be prepared according to **Scheme 5** by an amidation reaction of **7** dissolved in isopropylalcohol and aqueous ammonia. The reaction is carried out a suitable temperature, for example 120°C to produce compounds of the Formula **13**. A Sandmeyer reaction of **13** with copper (II) chloride and *tert* butylnitrite dissolved in a suitable solvent, for example acetonitrile introduces a chloro substituent. The reaction is carried out at a suitable temperature, for example $40\text{--}72^\circ\text{C}$. The resulting product is treated with lithium hydroxide monohydrate, dissolved in a suitable solvent, for example tetrahydrofuran and water and reacted at a suitable temperature, for example ambient to produce compounds of the Formular **14**. An amidation reaction on the acid of **14** with the appropriate amine and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide in an appropriate solvent, for example pyridine. The reaction is

carried out at a suitable temperature, for example, ambient to produce compounds of the Formula **15**. A Negishi reaction on **15** with the appropriate alkyl zinc bromide, XantPhos Pd G3 dissolved in a suitable solvent, for example tetrahydrofuran introduced an alkyl substituent. The reaction is carried out at a suitable temperature, for example 60 °C to produce compounds of Formula **Id**. Alternatively, an oxygen displacement reaction on **15** with the appropriate alkyl alcohol and sodium hydride dissolved in a suitable solvent, for example *N,N*-dimethylformamide introduced an alkoxy compound. The reaction is carried out at a suitable temperature, for example ambient to produce compounds of the Formula **Ie**.



Scheme 5

Alternatively, compounds of Formula **If** may be prepared according to **Scheme 6**. An oxidation reaction of **11** with meta-chloroperoxybenzoic acid dissolved in a suitable solvent, for example dichloromethane. The reaction is carried out at a suitable temperature, for example, ambient to produce compounds of the Formula **18**. An oxygen displacement reaction on the sulfone of **18** with the appropriate alcohol and sodium tert-butoxide dissolved in a suitable solvent, for example, tetrahydrofuran and *N,N*-dimethylformamide. The reaction is carried out at a suitable temperature, for example ambient to produce compounds of the Formula **19**. A deprotection reaction on the carbamate of **19** with the appropriate acid dissolved in a suitable solvent, for example dichloromethane with trifluoroacetic acid solution. The reaction is carried out at a suitable temperature, for example ambient to afford compounds of the Formula **20**. A carbamate formation reaction on the amine of **20** with the appropriate chloroformate and diisopropylethylamine dissolved in a suitable solvent, for example, dichloromethane. The reaction is carried out at a suitable temperature, for example ambient to afford compounds of the Formula **If**.



Scheme 6

Methods of Use

In one aspect, the invention relates to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

In another aspect, the invention relates to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a mycobacterial infection. A mycobacterial infection is one caused by infection with a mycobacterium.

The mycobacterium may be a member of one of the following groups of mycobacterium: *Mycobacterium tuberculosis complex (MTC)*, *Mycobacterium avium complex (MAC)*, *Mycobacterium gordonae clade*, *Mycobacterium kansasii clade*, *Mycobacterium chelonae clade*, *Mycobacterium fortuitum clade*, *Mycobacterium parafortuitum clade* or *Mycobacterium vaccae clade*. The mycobacterium may also be *Mycobacterium ulcerans* or *Mycobacterium leprae*.

In one embodiment, the mycobacterium is a member of the *Mycobacterium tuberculosis complex (MTC)*.

Members of *Mycobacterium tuberculosis complex (MTC)* include *Mycobacterium tuberculosis*, *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium bovis BCG*, *Mycobacterium canetti*, *Mycobacterium caprae*, *Mycobacterium microti* and *Mycobacterium pinnipedii*. These mycobacteria are causative agents of human and animal tuberculosis. *Mycobacterium tuberculosis* is the major cause of human tuberculosis.

In one embodiment, the infection is a *Mycobacterium tuberculosis* infection. In other words, the mycobacterial infection is caused by infection with *Mycobacterium tuberculosis*.

Members of *Mycobacterium avium complex (MAC)* include *Mycobacterium avium*, *Mycobacterium avium paratuberculosis*, *Mycobacterium avium silaticum*, *Mycobacterium avium hominissuis*, *Mycobacterium colombiense* and *Mycobacterium indicus pranii*.

Members of *Mycobacterium gordonae clade* include *Mycobacterium asiaticum* and *Mycobacterium gordonae*.

Members of *Mycobacterium kansasii clade* include *Mycobacterium gastri* and *Mycobacterium kansasii*.

Members of *Mycobacterium chelonae clade* include *Mycobacterium abscessus*, *Mycobacterium bolletii* and *Mycobacterium chelonae*.

Members of *Mycobacterium fortuitum clade* include *Mycobacterium boenickei*, *Mycobacterium brisbanense*, *Mycobacterium cosmeticum*, *Mycobacterium fortuitum*, *Mycobacterium fortuitum subspecies acetamidolyticum*, *Mycobacterium houstonense*, *Mycobacterium mageritense*, *Mycobacterium neworleansense*, *Mycobacterium peregrinum*, *Mycobacterium porcinum*, *Mycobacterium senegalense* and *Mycobacterium septicum*.

Members of *Mycobacterium parafortuitum clade* include *Mycobacterium austroafricanum*, *Mycobacterium diernhoferi*, *Mycobacterium frederiksbergense*, *Mycobacterium hodleri*, *Mycobacterium neoaurum* and *Mycobacterium parafortuitum*.

Therefore, the mycobacterial infection may be caused by infection with a mycobacterium selected from the following: *Mycobacterium tuberculosis*, *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium bovis BCG*, *Mycobacterium canetti*, *Mycobacterium caprae*, *Mycobacterium microti*, *Mycobacterium pinnipedii*, *Mycobacterium avium*, *Mycobacterium avium paratuberculosis*, *Mycobacterium avium silaticum*, *Mycobacterium avium hominissuis*, *Mycobacterium colombiense*, *Mycobacterium indicus pranii*, *Mycobacterium asiaticum*, *Mycobacterium gordonae*, *Mycobacterium gastri*, *Mycobacterium kansasii*, *Mycobacterium abscessus*, *Mycobacterium bolletii*, *Mycobacterium chelonae*, *Mycobacterium boenickei*, *Mycobacterium brisbanense*, *Mycobacterium cosmeticum*, *Mycobacterium fortuitum*, *Mycobacterium fortuitum subspecies acetamidolyticum*, *Mycobacterium houstonense*, *Mycobacterium mageritense*, *Mycobacterium neworleansense*, *Mycobacterium peregrinum*, *Mycobacterium porcinum*, *Mycobacterium senegalense*, *Mycobacterium septicum*, *Mycobacterium austroafricanum*, *Mycobacterium diernhoferi*, *Mycobacterium frederiksbergense*, *Mycobacterium hodleri*, *Mycobacterium neoaurum*, *Mycobacterium parafortuitum*, *Mycobacterium ulcerans* and *Mycobacterium leprae*.

In another aspect, the invention relates to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease caused by infection with a mycobacterium, where the mycobacterium is selected from those hereinbefore described.

Diseases caused by infection with a mycobacterium include, but are not limited to, tuberculosis (e.g. from *Mycobacterium tuberculosis*), leprosy (e.g. from *Mycobacterium leprae*), Johne's disease (e.g. from *Mycobacterium avium subspecies paratuberculosis*), Buruli or Bairnsdale ulcer (e.g. from *Mycobacterium ulceran*), Crohn's disease (e.g. from *Mycobacterium avium subspecies paratuberculosis*), pulmonary disease or pulmonary infection, pneumonia, bursa, synovial, tendon sheaths, localized abscess, lymphadenitis, skin and soft tissue infections, Lady Windermere syndrome (e.g. from *Mycobacterium avium* complex (MAC)), MAC lung disease, disseminated *Mycobacterium avium* complex (DMAC), disseminated *Mycobacterium avium intracellulare* complex (DMAIC), hot-tub lung (e.g. from *Mycobacterium avium* complex), MAC mastitis, MAC pyomyositis, or granuloma disease.

In one embodiment, the disease is tuberculosis. Thus, one aspect of the invention relates to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of tuberculosis.

In another aspect, the invention relates to a method of treatment of a mycobacterial infection in a mammal in need thereof, said treatment comprising administering to said mammal a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt thereof. As described herein, a mycobacterial infection is one caused by infection with a mycobacterium. The mycobacterium is as hereinbefore described.

In one embodiment, the invention relates to a method of treatment of a *Mycobacterium tuberculosis* infection.

In another aspect, the invention relates to a method of treatment of a disease caused by infection with a mycobacterium in a mammal in need thereof, said treatment comprising administering to said mammal a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In one embodiment, the disease is tuberculosis. Therefore, also described herein is a method of treatment of tuberculosis in a mammal in need thereof, said treatment comprising administering to said mammal a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In one embodiment, the mammal is a human.

In another aspect, the invention relates to use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a mycobacterial infection or a disease caused by infection with a mycobacterium.

Also described herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of tuberculosis.

Formulations

The compound of Formula (I) or pharmaceutically acceptable salt thereof will normally, but not necessarily, be formulated into pharmaceutical formulations prior to administration to a patient. Accordingly, in another aspect there is provided a pharmaceutical formulation comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Pharmaceutical compositions may be administered by any appropriate route, for example by the oral (including buccal or sublingual), inhaled, intranasal, topical (including buccal, sublingual or transdermal), parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. In particular, pharmaceutical compositions are administered via an oral route of administration.

Suitable pharmaceutically acceptable excipients include the following types of excipients: carriers, diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavouring agents, flavour-masking agents, colouring agents, anti-caking agents, humectants, chelating agents, plasticisers, viscosity increasing agents, antioxidants, preservatives, stabilisers, surfactants and buffering agents.

Suitable methods for formulating a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be familiar to those skilled in the art, which are described in Remington: The Science and Practice of Pharmacy, 21st Edition 2006.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage compositions are those containing a daily dose or sub-dose, or an appropriate fraction thereof, of an active ingredient. Such unit doses may therefore be administered more than once a day. Preferred unit dosage compositions are those containing a daily dose or sub-dose (for administration more than once a day), as herein above recited, or an appropriate fraction thereof, of an active ingredient.

When a compound of Formula (I) or pharmaceutically acceptable salt thereof is used in the treatment of tuberculosis, they may be employed alone or in combination with a further therapeutic agent, such as a further anti-mycobacterial agent, in particular a further anti-tuberculosis agent and/or antiviral agent, including antiretroviral agents.

For example, the present invention relates to a combination of (a) a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and (b) a further anti-tuberculosis agent. In an embodiment, the combination comprises two, three, four, five, six or seven additional anti-tuberculosis agents. For example, in the treatment of multidrug-resistant tuberculosis, it is common that combinations of four or more drugs are administered to patients. For example, in the treatment of drug-sensitive tuberculosis, it is common that combinations of three or four drugs are administered to patients.

The further anti-tuberculosis agent is an agent in development, approved or recommended for the treatment of tuberculosis and may be selected from isoniazid, rifampin, pyrazinamide, ethambutol, moxifloxacin, rifapentine, clofazimine, ethionamide, prothionamide, isoxyl, thiacetazone, a diarylquinoline such as bedaquiline (TMC207) or TBAJ-587, nitroimidazo-oxazine PA-824, delamanid (OPC-67683), an oxazolidinone such as linezolid, tedizolid, radezolid, sutezolid (PNU-100480), posizolid (AZD-5847) or TBI-223, EMB analogue SQ109, OPC-167832, GSK3036656 (also known as GSK070), GSK2556286, GSK3211830, a benzothiazinone such as BTZ043 or PBTZ169, an azaindole such as TBA-7371, a dinitrobenzamide, or a beta-lactam such as meropenem, faropenem, ertapenem, tebipenem or beta-lactam combinations such as AUGMENTIN (amoxicillin-clavulanate).

A combination according to the present invention may further comprise an antiviral agent, including an antiretroviral agents. In an aspect of the invention, the composition further comprises a therapeutically effective amount at least one other agent used for treatment of AIDS or HIV infection selected from nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV protease inhibitors, HIV fusion inhibitors, HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, HIV budding or maturation inhibitors, and HIV integrase inhibitors, and a pharmaceutically acceptable carrier.

Such antiretroviral agents may be selected from abacavir, atazanavir, bictegravir, cabotegravir, darunavir, delavirdine, didanosine, dideoxyinosine, dolutegravir, doravirine, efavirenz, elvitegravir, emtricitabine, etavirine, fosamprenavir, fostemsavir, indinavir, slatravir, lamivudine, lopinavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpiverine, ritonavir, saquinavir, stavudine, tipranavir, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, zalcitabine, and zidovudine.

The combinations may conveniently be presented for use in the form of a pharmaceutical composition or formulation. Therefore, also contemplated herein is a pharmaceutical composition comprising (a) a compound of Formula (I) or a pharmaceutically acceptable salt thereof, as herein described, together with (b) a further anti-tuberculosis agent and (c) optionally an antiviral agent including antiretroviral agents, and (d) one or more pharmaceutically acceptable excipients, as herein described.

A compound of Formula (I) or a pharmaceutically acceptable salt thereof and further therapeutic agent may be administered together in a unitary pharmaceutical composition including both compounds or separately in separate pharmaceutical compositions, each including one of the compounds in a sequential manner. Such sequential administration may be close in time (e.g. simultaneously) or remote in time. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and the other compound may be administered orally. The amount of a compound of Formula (I) or pharmaceutically acceptable salt thereof and the further therapeutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

When combined in the same composition it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the composition and may be formulated for administration. When formulated separately they may be provided in any convenient composition, conveniently, in such a manner as known for such compounds in the art.

The combinations may be presented as a combination kit. By the term "combination kit" "or kit of parts" as used herein is meant the pharmaceutical composition or compositions that are used to administer the combination according to the invention. When both compounds are administered simultaneously, the combination kit can contain both compounds in a single pharmaceutical composition, such as a tablet, or in separate pharmaceutical compositions. When the compounds are not administered simultaneously, the combination kit will contain each compound in separate pharmaceutical compositions either in a single package in separate pharmaceutical compositions in separate packages.

The combination kit can also be provided by instruction, such as dosage and administration instructions. Such dosage and administration instructions can be of the kind that are provided to a doctor, for example by a drug product label, or they can be of the kind that are provided by a doctor, such as instructions to a patient.

During a treatment regime, it will be appreciated that administration of each compound may be repeated one or more times.

When the combination is administered separately in a sequential manner wherein one is administered first and the other second or vice versa, such sequential administration may be close in time or remote in time. For example, administration of the other agent several minutes to several dozen minutes after the administration of the first agent, and administration of the other agent several hours to several days after the administration of the first agent are included, wherein the lapse of time is not limited. For example, one agent may be administered once a day, and the other agent may be administered 2 or 3 times a day, or one agent may be administered once a week, and the other agent may be administered once a day and the like.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredients(s) may be used in the form of salts, for example as alkali metal or amine salts or as acid addition salts, or prodrugs, or as esters, for example lower alkyl esters, or as solvates, for example hydrates, to optimise the activity and/or stability and/or physical characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that, where appropriate, the therapeutic ingredients may be used in optically pure form.

When combined in the same composition it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the composition and may be formulated for administration. When formulated separately they may be provided in any convenient composition, conveniently, in such a manner as known for such compounds in the art.

Examples

The invention will now be illustrated by way of the following non-limiting examples. While particular embodiments of the invention are described below a skilled person will appreciate that various changes and modifications can be made. References to preparations carried out in a similar manner to, or by the general method of, other preparations, may encompass variations in routine parameters such as time, temperature, workup conditions, minor changes in reagents amounts, etc.

In certain of the following Intermediates and Examples, starting materials are identified by reference to other Intermediate or Example numbers. This does not signify that the actual material (or "batch") obtained from any particular Intermediate or Example was necessarily used in a subsequent step exemplified herein, but is used as a short-hand means of denoting the relevant compound name.

Abbreviations

The following list provides definitions of certain abbreviations and symbols as used herein. It will be appreciated that the list is not exhaustive, but the meaning of those abbreviations and symbols not herein below defined will be readily apparent to those skilled in the art. In describing the invention, chemical elements are identified in accordance with the Periodic Table of the Elements.

CFU	Colony Forming Unit
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMF	Dimethylformamide
DMSO- <i>d</i> ₆	Deuterated Dimethylsulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ES+ MS	Positive electrospray ionisation mass spectrometry
EtOAc	Ethyl acetate
EtOH	Ethanol
g	grams
HPLC	High Performance Liquid Chromatography
Hz	Hertz
iPA	isopropylalcohol
LCMS	Liquid Chromatography/Mass Spectrometry
M	Molar concentration
MeCN	Acetonitrile
MeOH	Methanol
Min	minutes
mL	Millilitre
μL	Microlitre
μM	Micromolar
μm	Micrometre
mmol	Millimole
MW	Microwave
N	Normal concentration
nm	nanometre
NMI	1-methylimidazole
NMR	Nuclear Magnetic Resonance spectroscopy
R _t	Retention time
r.t.	room temperature

STAB	Sodiumtriacetoxymborohydride
SFC	Supercritical fluid chromatography
TBME	tert-Butylmethylether
TCFH	Chloro- <i>N,N,N',N'</i> -tetramethylformamidium hexafluorophosphate
THF	Tetrahydrofuran
T3P	Propylphosphonic anhydride solution
vs	versus

Analytical Equipment

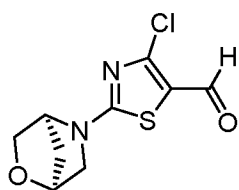
¹H NMR spectra were recorded on a Bruker Avance DPX 500 spectrometer, or a Bruker Avance DPX 400. Chemical shifts (δ) are expressed in ppm recorded using the residual solvent as the internal reference in all cases. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or a combination thereof. Coupling constants (J) are quoted to the nearest 0.1 Hz.

All temperatures reported are in degrees centigrade.

Low resolution electrospray (ES) mass spectra were recorded on either an Advion Compact Mass Spectrometer (CMS; model ExpressIon CMS), connected to Dionex Ultimate 3000 UPLC system with diode array detector; or a Shimadzu LCMS 2020 Mass Spectrometer, connected to Shimadzu Nexera HPLC system with diode array detector. High resolution electrospray (ES) mass spectra were recorded on either a Bruker MicroToF Mass Spectrometer, connected to Dionex U3000 HPLC system with diode array detector; or a Waters Mass Spectrometer (Waters Xevo QToF MS), connected to Aquity UPLC system with diode array detector. HPLC chromatographic separations were conducted using a Waters XBridge C18 column, 2.1 x 50mm, 3.5 μ m particle size; Waters XSelect 2.1 x 30mm, 2.5 μ m particle size; or a Thermo Hypersil Gold column, 50 x 2.1 mm, 1.9 μ m particle size. The compounds were eluted with a gradient of 2 to 98% acetonitrile/water with either 0.05% or 0.01% formic acid; or with a gradient of 5 to 95% acetonitrile/water with either 0.1% ammonia or 0.1% formic acid.

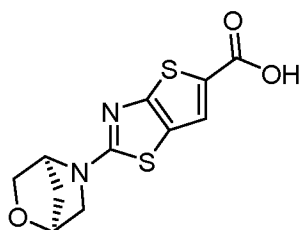
Intermediates

Intermediate 2a: 2-((1*S*,4*S*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-4-chlorothiazole-5-carbaldehyde



To a suspension of 2,4-dichlorothiazole-5-carbaldehyde (2.00 g, 10.99 mmol) and (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (1.79 g, 13.19 mmol) in MeCN (70 mL) at 0 °C was added dropwise triethylamine (9.6 mL, 54.94 mmol). The reaction was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was partitioned between water (30 mL) and EtOAc (30 mL). The mixture was separated and the aqueous was re-extracted with more EtOAc (2 x 30 mL). The combined organics were washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo* to give 2-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-4-chlorothiazole-5-carbaldehyde (2.71 g, 10.67 mmol, 97% yield) as an orange gum. ¹H NMR (500 MHz, DMSO) δ 9.68 (s, 1H), 4.88 - 4.88 (m, 1H), 4.78 (s, 1H), 3.82 - 3.77 (m, 2H), 3.30 (s, 2H), 2.05 (dd, *J* = 2.0, 10.2 Hz, 1H), 1.96 (d, *J* = 10.2 Hz, 1H); MS *m/z* [M + H]⁺ = 245.0.

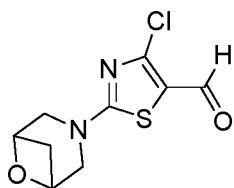
Intermediate 3a: 2-((1*S*,4*S*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)thieno[2,3-*d*]thiazole-5-carboxylic acid



To a solution of 2-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-4-chlorothiazole-5-carbaldehyde (2.71 g, 11.06 mmol, **Example 1 Intermediate 2a**) in DMSO (30 mL) was added ethyl thioglycolate (1.5 mL, 13.27 mmol) followed by triethylamine (3.9 mL, 22.12 mmol) in a round bottomed flask. The reaction was stirred at rt for 16 h. The reaction diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The pale brown solid obtained was dissolved in ethanol (60 mL) and NaOEt (34.8 mL, 17.91 mmol) was added dropwise with stirring and the reaction stirred at room temperature for 4 h. The reaction quenched with a small amount of water (~5 mL) and the solvent concentrated *in vacuo*. The residue was triturated with water but the solid dissolved in the water. The aqueous was re-dissolved in water (30 mL) and washed with EtOAc (30 mL). The aqueous was then acidified with 1 N HCl and the resultant precipitate was filtered to give 2-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)thieno[2,3-*d*]thiazole-5-carboxylic acid (2.31 g, 7.76 mmol, 70% yield) as a dark beige coloured solid. ¹H NMR (500 MHz, DMSO) δ 12.79 (br. s,

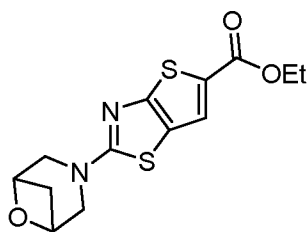
1H), 7.88 (s, 1H), 3.82 - 3.79 (m, 2H), 3.60 - 3.57 (m, 1H), 3.35 - 3.29 (m, 3H), 2.04 (dd, $J = 2.1, 10.1$ Hz, 1H), 1.94 (d, $J = 10.1$ Hz, 1H). MS m/z $[M + H]^+ = 283.0$.

Intermediate 2b: 4-Chloro-2-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)thiazole-5-carbaldehyde



4-Methylbenzenesulfonic acid salt of 6-oxa-3-azabicyclo[3.1.1]heptane (442 mg, 1.63 mmol) and 2,4-dichlorothiazole-5-carbaldehyde (247 mg, 1.36 mmol) were stirred in MeCN (7 mL) and triethylamine (1.18 mL, 6.79 mmol) was added dropwise. The reaction was stirred at rt for 3 h. The solvent was removed *in vacuo* and the residue was triturated with water, filtered, washed with water and air dried to afford the product 4-chloro-2-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)thiazole-5-carbaldehyde (276 mg, 1.13 mmol, 81% yield) as a light grey solid. ^1H NMR (500 MHz, DMSO) δ 9.73 (s, 1H), 4.73 (d, $J = 6.6$ Hz, 2H), 3.95 - 3.53 (m, 4H), 3.24 - 3.17 (m, 1H), 1.93 (d, $J = 9.3$ Hz, 1H). MS m/z $[M + H]^+ = 245.02$.

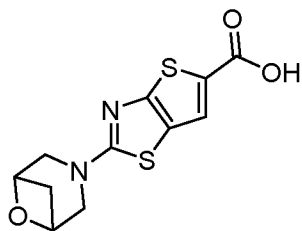
Intermediate 16: Ethyl 2-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)thieno[2,3-*d*]thiazole-5-carboxylate



To a microwave vial, 4-chloro-2-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)thiazole-5-carbaldehyde (276 mg, 1.13 mmol, **Intermediate 2b**) was dissolved in DMSO (4 mL) and ethyl thioglycolate (150 μL , 1.35 mmol) was added followed by triethylamine (390 μL , 2.26 mmol). The reaction was heated to 100 $^{\circ}\text{C}$ in a microwave for 3 h. The reaction was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The organics were combined, washed with brine and dried over MgSO_4 and evaporated *in vacuo*. The pale brown oil obtained was dissolved in ethanol (4 mL) and NaOEt (20% Wt in EtOH, 3.29 mL, 1.69 mmol) added dropwise and the reaction was stirred at rt for 30 min. The reaction was quenched with a small amount of water (~ 1 mL) and the solvent removed *in vacuo*. The residue was triturated with water, filtered and air dried to afford the product ethyl 2-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)thieno[2,3-*d*]thiazole-5-carboxylate (2.51 g, 11.31 mmol,

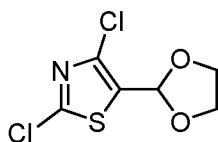
79% yield) as a cream coloured solid. ^1H NMR (500 MHz, DMSO) δ 8.00 (s, 1H), 4.74 (d, J = 6.4 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.74 (s, 4H), 3.22 - 3.17 (m, 1H), 1.96 (d, J = 9.0 Hz, 1H), 1.31 (dd, J = 7.1, 7.1 Hz, 3H). MS m/z $[\text{M} + \text{H}]^+ = 311.05$.

Intermediate 3b: 2-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)thieno[2,3-*d*]thiazole-5-carboxylic acid

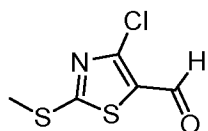


Ethyl 2-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)thieno[2,3-*d*]thiazole-5-carboxylate (227 mg, 0.73 mmol, **Intermediate 16**) was dissolved in methanol (7 mL), water (2.5 mL) was added followed by lithium hydroxide hydrate (88 mg, 3.66 mmol) and the reaction was heated to 50 °C for 1 h. MeOH removed *in vacuo* and the reaction diluted with water and acidified with 1 N HCl. The precipitate formed was filtered off and washed with water and air dried to afford the product 2-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)thieno[2,3-*d*]thiazole-5-carboxylic acid (201 mg, 0.72 mmol, 95% yield) as a cream coloured solid. ^1H NMR (500 MHz, DMSO) δ 12.79 - 12.79 (m, 1H), 7.92 (s, 1H), 4.74 (d, J = 6.6 Hz, 2H), 3.29 (s, 4H), 3.23 - 3.17 (m, 1H), 1.96 (d, J = 9.2 Hz, 1H). MS m/z $[\text{M} + \text{H}]^+ = 283.0$.

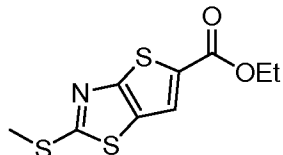
Intermediate 4: 2,4-Dichloro-5-(1,3-dioxolan-2-yl)thiazole



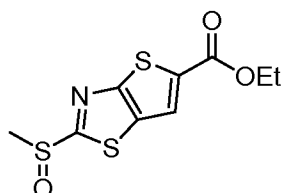
To a solution of 2,4-dichlorothiazole-5-carbaldehyde (2.00 g, 10.99 mmol) and ethylene glycol (2.05 g, 32.96 mmol) in toluene (25 mL) was added 4-methylbenzenesulfonic acid hydrate (152 mg, 0.80 mmol). A Dean-Stark trap was fitted, and the mixture was refluxed for 4 h. It was then cooled to rt and quenched with 10% aqueous Na_2CO_3 (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organics were dried over sodium sulfate and solvent removed *in vacuo*. The residue was purified by flash chromatography (0-20% EtOAc in heptane) to afford the product 2,4-dichloro-5-(1,3-dioxolan-2-yl)thiazole (2.13 g, 9.42 mmol, 81% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.06 (s, 1H), 4.16 - 4.02 (m, 4H). MS m/z $[\text{M} + \text{H}]^+ = 226.0$.

Intermediate 5: 4-Chloro-2-(methylthio)thiazole-5-carbaldehyde

To a solution of 2,4-dichloro-5-(1,3-dioxolan-2-yl)thiazole (1.13 g, 5.00 mmol, **Intermediate 4**) in THF (20 mL) at -78 °C under nitrogen was added *n*BuLi (2.5 M in hexane, 2.0 mL, 5.00 mmol) and the solution stirred for 30 min. 1,2-dimethyldisulfane (495 mg, 5.25 mmol) in THF (2 mL) was added at the same temperature and stirred for 1 h. The mixture warmed to rt and poured into 2N HCl and extracted with diethyl ether (3 x 25 mL). The combined organic extracts were concentrated *in vacuo* and added to a 1:1 mixture of THF/6N HCl (20 mL) and the mixture was stirred at rt for 3 h, neutralised with 10% aqueous Na₂CO₃, extracted with diethyl ether (2 x 20 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was washed with heptane to afford the product 4-chloro-2-(methylthio)thiazole-5-carbaldehyde (712 mg, 3.67 mmol, 70% yield). ¹H NMR (400 MHz, CDCl₃) δ , 9.9 (s, 1H), 2.75 (s, 3H). MS *m/z* [M + H]⁺ = 194.0.

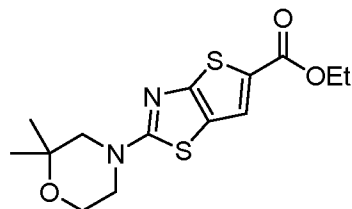
Intermediate 6: Ethyl 2-(methylthio)thieno[2,3-*d*]thiazole-5-carboxylate

To a solution of ethyl thioglycolate (200 μL, 1.81 mmol) and potassium carbonate (1.50 g, 10.84 mmol) in MeCN (5 mL) was added 4-chloro-2-(methylthio)thiazole-5-carbaldehyde (350 mg, 1.81 mmol, **Intermediate 5**) in MeCN (3 mL) and the mixture was heated to 60 °C for 18 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography (0-10% EtOAc in heptane) to afford the product ethyl 2-(methylthio)thieno[2,3-*d*]thiazole-5-carboxylate (250 mg, 0.96 mmol, 51% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.89 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.81 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H). MS *m/z* [M + H]⁺ = 260.0.

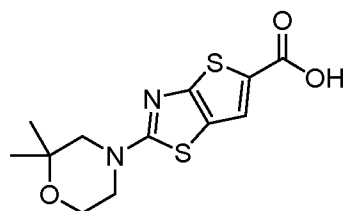
Intermediate 7: Ethyl 2-(methylsulfinyl)thieno[2,3-*d*]thiazole-5-carboxylate

To a 1 L 3-neck rbf fitted with a nitrogen inlet and thermometer was added ethyl 2-(methylthio)thieno[2,3-*d*]thiazole-5-carboxylate (30.00 g, 115.66 mmol, **Intermediate 6**). The solid was dissolved in DCM (450 mL) and the solution cooled in an ice bath (internal temp = 6 °C). 3-Chloroperoxybenzoic acid (27.22 g, 121.45 mmol) was added portionwise at such a rate that the internal temperature remained below 15 °C (approx. 30 min) and the resultant suspension stirred with cooling for a further 30 min and then allowed to warm to rt and stirred for 16 h. The mixture diluted with 1M sodium sulfite (100 mL, 100 mmol) and stirred overnight. The reaction diluted with 1M NaOH (120 mL, 120 mmol) and separated. The organic layer passed through a hydrophobic frit and concentrated *in vacuo* to give crude product. The crude product was suspended in EtOH (400 mL) and heated to reflux and stirred at this temperature for 45 min and then allowed to cool to rt. The resultant suspension was cooled to 0 °C and filtered. The solid washed with more EtOH (20 mL) and dried overnight under vacuum to give ethyl 2-(methylsulfinyl)thieno[2,3-*d*]thiazole-5-carboxylate (27.26 g, 98.99 mmol, 86% yield) as a colourless solid. ¹H NMR (400 MHz, CDCl₃) δ 8.08 (s, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.11 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H). MS *m/z* [M + H]⁺ = 276.5.

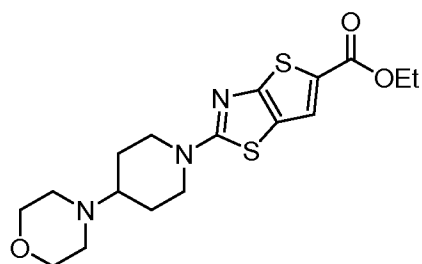
Ester of Intermediate 3c: Ethyl 2-(2,2-dimethylmorpholino)thieno[2,3-*d*]thiazole-5-carboxylate



To a 110 mL ace pressure tube containing ethyl 2-(methylsulfinyl)thieno[2,3-*d*]thiazole-5-carboxylate (1.6 g, 5.81 mmol, **Intermediate 7**) was added 2,2-dimethylmorpholine (1.00 g, 8.72 mmol), followed by MeCN (20 mL) and DIPEA (1.6 mL, 11.62 mmol). The tube sealed and heated to 120 °C in a sand bath whilst stirring for 16 h. The reaction cool to rt and concentrated *in vacuo*. The residue partitioned between EtOAc (75 mL) and water (40 mL), separated and the organic layer passed through a hydrophobic frit and concentrated *in vacuo*, dry-loaded onto silica and purified by flash chromatography (0-100% EtOAc in heptanes) to give ethyl 2-(2,2-dimethylmorpholino)thieno[2,3-*d*]thiazole-5-carboxylate (1.65 g, 5.05 mmol, 87 % yield) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.76 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.87 (apt. t, *J* = 5.0 Hz, 2H), 3.57 (apt. t, *J* = 5.0 Hz, 2H), 3.40 (s, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.31 (s, 6H). MS *m/z* [M + H]⁺ = 327.0.

Intermediate 3c: 2-(2,2-Dimethylmorpholino)thieno[2,3-*d*]thiazole-5-carboxylic acid

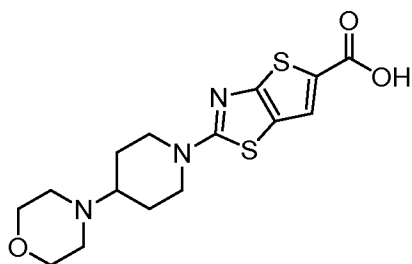
To a mixture of ethyl 2-(2,2-dimethylmorpholino)thieno[2,3-*d*]thiazole-5-carboxylate (1.65 g, 5.05 mmol) in THF (30 mL) and water (15 mL) was added lithium hydroxide hydrate (1.06 g, 25.27 mmol). The reaction was heated to 65 °C and stirred overnight. The reaction was allowed to cool to rt and then concentrated *in vacuo* to remove excess THF. The solution was then transferred to a separating funnel and washed with EtOAc (20 mL). The resultant aqueous phase was acidified to pH 2 with 6 N HCl (4.2 mL) to give a pale yellow precipitate. The solid was filtered and washed with more water (10 mL), and TBME (10 mL) to give the desired product. The solid was dried overnight under vacuum to give 2-(2,2-dimethylmorpholino)thieno[2,3-*d*]thiazole-5-carboxylic acid (1.25 g, 4.19 mmol, 83% yield) as a pale yellow solid. ¹H NMR (500 MHz, DMSO) δ 12.79 (br. s, 1H), 7.89 (s, 1H), 3.77 (apt. t, *J* = 5.1 Hz, 2H), 3.53 (apt. t, *J* = 5.1 Hz, 2H), 3.41 (s, 2H), 1.22 (s, 6H). MS *m/z* [*M* + *H*]⁺ = 289.9.

Ester of Intermediate 3d: Ethyl 2-(4-morpholinopiperidin-1-yl)thieno[2,3-*d*]thiazole-5-carboxylate

To a 110 mL ace pressure tube containing ethyl 2-methylsulfinylthieno[2,3-*d*]thiazole-5-carboxylate (2.00 g, 7.26 mmol, **Intermediate 7**) was added 4-(4-piperidyl)morpholine (2.47 g, 14.53 mmol), followed by MeCN (30 mL) and DIPEA (4.0 mL, 29.05 mmol). The tube was sealed, heated to 120 °C in a sand bath, and then stirred for 16 h. The reaction was concentrated *in vacuo* and partitioned between DCM (50 mL) and water (30 mL). The mixture was passed through a hydrophobic frit and the organic was dry-loaded onto silica and purified by flash chromatography (0-10% MeOH in DCM) to give ethyl 2-(4-morpholinopiperidin-1-yl)thieno[2,3-*d*]thiazole-5-carboxylate (2.47 g, 6.47 mmol, 89% yield) as a pale orange solid. ¹H NMR (400 MHz, DMSO) δ 7.95 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.02 - 3.95 (m, 2H), 3.60 - 3.54 (m, 4H), 3.26 - 3.17 (m,

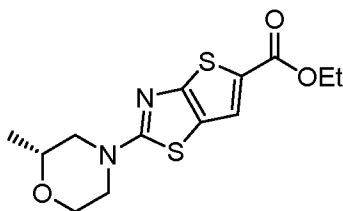
2H), 2.50 - 2.44 (m, 5H), 1.94 - 1.86 (m, 2H), 1.57 - 1.46 (m, 2H), 1.29 (t, $J = 7.1$ Hz, 3H). MS m/z $[M + H]^+ = 382.2$.

Intermediate 3d: 2-(4-Morpholinopiperidin-1-yl)thieno[2,3-*d*]thiazole-5-carboxylic acid



To a solution of ethyl 2-(4-morpholinopiperidin-1-yl)thieno[2,3-*d*]thiazole-5-carboxylate (2.47 g, 6.47 mmol) in THF (40 mL) was added a solution of lithium hydroxide hydrate (543 mg, 12.95 mmol) in water (20 mL). The reaction heated to 65 °C and stirred overnight, cool to rt and concentrated *in vacuo* to remove excess THF. The residue was diluted with more water (30 mL) and then cooled to 0 °C and acidified to ~ pH 6 with 6 N HCl (approx. 2 mL) to give an off-white precipitate. The solid filtered, washed with water (20 mL), EtOH (10 mL), and TBME (10 mL) to give the desired product. Solid was dried overnight under vacuum to give 2-(4-morpholino-1-piperidyl)thieno[2,3-*d*]thiazole-5-carboxylic acid (2.50 g, 7.07 mmol, quantitative yield) as an off-white solid. ^1H NMR (400 MHz, DMSO) δ 7.87 (s, 1H), 3.98 (br. d, $J = 13.1$ Hz, 2H), 3.58 (apt. t, $J = 4.4$ Hz, 4H), 3.26 – 3.10 (m, 2H), 2.55 – 2.41 (m, 5H), 1.91 (br. d, $J = 13.1$ Hz, 2H), 1.65 – 1.42 (m, 2H). MS m/z $[M + H]^+ = 354.2$.

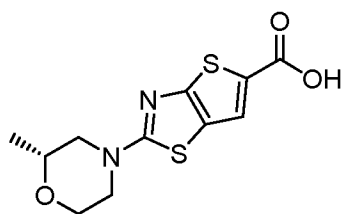
Ester of Intermediate 3e: Ethyl (*R*)-2-(2-methylmorpholino)thieno[2,3-*d*]thiazole-5-carboxylate



To a 110 mL ace pressure tube containing ethyl 2-methylsulfinylthieno[2,3-*d*]thiazole-5-carboxylate (1.00 g, 3.63 mmol, **Intermediate 7**) was added (2*R*)-2-methylmorpholine.hydrochloride (0.85 g, 6.18 mmol), followed by MeCN (20 mL) and DIPEA (2.0 mL, 14.67 mmol). The tube sealed, heated to 120 °C in a sand bath and stirred for 16 h. The reaction concentrated *in vacuo* and partitioned between EtOAc (50 mL) and water (30 mL). The organic layer passed through a hydrophobic frit, dry-loaded onto silica and purified by flash

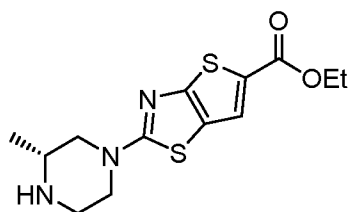
chromatography (0-100% EtOAc in heptanes) to give ethyl 2-[(2*R*)-2-methylmorpholin-4-yl]thieno[2,3-*d*]thiazole-5-carboxylate (0.98 g, 3.14 mmol, 86% yield) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.77 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.01 (dd, *J* = 11.3, 2.9 Hz, 1H), 3.89 (d, *J* = 12.3 Hz, 1H), 3.79 (d, *J* = 13.6 Hz, 1H), 3.75 - 3.70 (m, 2H), 3.29 (dt, *J* = 3.3, 12.0 Hz, 1H), 2.94 (dd, *J* = 12.6, 10.5 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.27 (d, *J* = 6.2 Hz, 3H). MS *m/z* [M + H]⁺ = 313.0.

Intermediate 3e: (*R*)-2-(2-Methylmorpholino)thieno[2,3-*d*]thiazole-5-carboxylic acid



To a mixture of ethyl 2-[(2*R*)-2-methylmorpholin-4-yl]thieno[2,3-*d*]thiazole-5-carboxylate (0.98 g, 3.14 mmol) in THF (20 mL) and water (10 mL) was added lithium hydroxide hydrate (658 mg, 15.69 mmol). The reaction was heated to 65 °C and stirred overnight, cool to rt, concentrated *in vacuo* to remove excess THF and washed with EtOAc (20 mL). The resultant aqueous phase was acidified to pH 2 with 6 N HCl (3 mL) to give a pale yellow precipitate that was filtered and washed with water (10 mL), and TBME (10 mL) to give the desired product. The solid was dried overnight under vacuum to give 2-[(2*R*)-2-methylmorpholin-4-yl]thieno[2,3-*d*]thiazole-5-carboxylic acid (807 mg, 2.84 mmol, 90% yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO) δ 12.81 (s, 1H), 7.90 (s, 1H), 3.93 (dd, *J* = 11.5, 2.3 Hz, 1H), 3.87 (d, *J* = 13.0 Hz, 1H), 3.77 (d, *J* = 13.0 Hz, 1H), 3.69 - 3.57 (m, 2H), 3.23 (td, *J* = 12.3, 3.6 Hz, 1H), 2.91 (dd, *J* = 12.2, 10.8 Hz, 1H), 1.17 (d, *J* = 6.2 Hz, 3H). MS *m/z* [M + H]⁺ = 284.9.

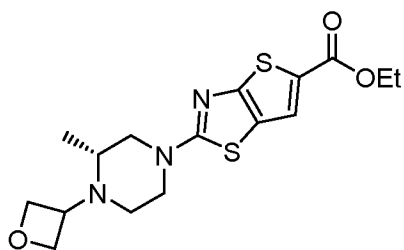
Intermediate 8: Ethyl (*R*)-2-(3-methylpiperazin-1-yl)thieno[2,3-*d*]thiazole-5-carboxylate



Split across 2 x 35mL MW vials to a mixture ethyl 2-methylsulfinylthieno[2,3-*d*]thiazole-5-carboxylate (2.00 g, 7.26 mmol, **Intermediate 7**) in MeCN (20 mL) was added (2*R*)-2-Methylpiperazine (1.45 g, 14.53 mmol) and DIPEA (2.0 mL, 14.53 mmol). The reactions were heated in the MW for 1 h at 120 °C. The reactions were combined, concentrated *in vacuo*, and loaded directly onto silica. The crude product was purified by flash chromatography (0-10% MeOH

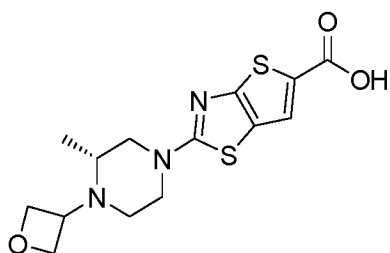
in DCM) to give desired ethyl 2-[(3*R*)-3-methylpiperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxylate (2.07 g, 6.65 mmol, 92 % yield) as yellow/orange solid. ¹H NMR (500 MHz, CDCl₃) δ 7.76 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.97 – 3.85 (m, 2H), 3.17 (td, *J* = 12.1, 3.4 Hz, 1H), 3.11 (ddd, *J* = 12.2, 3.5, 2.0 Hz, 1H), 2.99 (dd, *J* = 11.9, 3.4 Hz, 1H), 2.98 – 2.89 (m, 1H), 2.79 (dd, *J* = 12.4, 10.4 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 6.3 Hz, 3H). MS *m/z* [M + H]⁺ = 312.0.

Ester of Intermediate 9a: Ethyl (*R*)-2-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)thieno[2,3-*d*]thiazole-5-carboxylate



To a solution of ethyl 2-[(3*R*)-3-methylpiperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxylate (800 mg, 2.57 mmol, **Intermediate 8**) in DCM (20 mL) was added 3-oxetanone (330 μL, 5.13 mmol) the reaction stirred at r.t. for 30 min and sodium triacetoxymethylborohydride (871 mg, 4.11 mmol) added, the mixture was stirred at rt for 16 h, 1N NaOH added (10 mL) and the mixture stirred for 30 min and separated. The organic phase was concentrated *in vacuo* to give crude product that was purified by flash chromatography (0-100% EtOAc in heptane) to give desired product ethyl 2-[(3*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxylate (725 mg, 1.97 mmol, 77% yield) as a cream coloured solid. ¹H NMR (500 MHz, CDCl₃) δ 7.79 (s, 1H), 4.75 - 4.62 (m, 4H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.84 - 3.74 (m, 3H), 3.51 (ddd, *J* = 9.5, 3.2, 12.6 Hz, 1H), 3.18 (dd, *J* = 8.6, 12.6 Hz, 1H), 2.76 (td, *J* = 3.9, 11.6 Hz, 1H), 2.57 - 2.51 (m, 1H), 2.32 - 2.26 (m, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H). MS *m/z* [M + H]⁺ = 368.2.

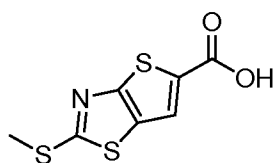
Intermediate 9a: (*R*)-2-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)thieno[2,3-*d*]thiazole-5-carboxylic acid



To a mixture of ethyl 2-[(3*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxylate (725 mg, 1.97 mmol) in THF (12 mL) and water (6 mL) was added lithium hydroxide hydrate (91 mg, 2.17 mmol). The reaction was heated to 65 °C and stirred for 16 h, cooled to rt, concentrated *in vacuo* to remove excess THF. The solution washed with TBME (5 mL) and the

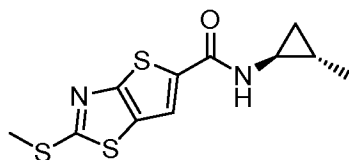
resultant aqueous phase was neutralised with 6 N HCl (320 μ L) and stirred for 1 h. The precipitate filtered, washed with water (3 mL) and TBME (3 mL) to give the desired product. The solid dried overnight under vacuum to give 2-[(3*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxylic acid (488 mg, 1.44 mmol, 73% yield) as a colourless solid. ^1H NMR (500 MHz, DMSO) δ 12.83 (br. s, 1H), 7.88 (d, J = 1.9 Hz, 1H), 4.58 – 4.46 (m, 4H), 3.82 – 3.57 (m, 3H), 3.42 (t, J = 10.7 Hz, 1H), 3.12 (dd, J = 12.8, 8.3 Hz, 1H), 2.71 (d, J = 12.1 Hz, 1H), 2.50 – 2.43 (m, 1H), 2.19 (t, J = 10.0 Hz, 1H), 0.89 (d, J = 6.4 Hz, 3H). MS m/z $[\text{M} + \text{H}]^+ = 340.1$.

Intermediate 10: 2-(Methylthio)thieno[2,3-*d*]thiazole-5-carboxylic acid



To a solution of ethyl 2-methylsulfanythieno[2,3-*d*]thiazole-5-carboxylate (30.0 g, 115.66 mmol, **Intermediate 6**) in THF (300 mL) was added a solution of lithium hydroxide hydrate (7.28 g, 173.38 mmol) in water (150 mL). The reaction heated to 65 $^{\circ}\text{C}$ and stirred for 16 h. TBME (200 mL) added and the mixture partitioned. The resultant aqueous phase acidified to pH 2 with 6 N HCl (approx. 32 mL) to give an off-white precipitate, that was washed with water (100 mL), EtOH (100 mL), and TBME (50 mL) then dried under vacuum at 40 $^{\circ}\text{C}$ for 72 h to give 2-methylsulfanythieno[2,3-*d*]thiazole-5-carboxylic acid (22.28 g, 96.32 mmol, 83% yield) as a colourless solid. ^1H NMR (400 MHz, DMSO) δ 13.35 (br. s, 1H), 8.05 (s, 1H), 2.80 (s, 3H). MS m/z $[\text{M} + \text{H}]^+ = 231.9$.

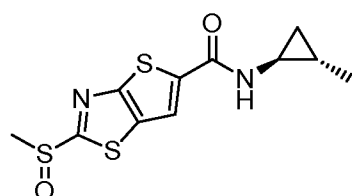
Precursor to Intermediate 11a: *N*-((1*S*,2*S*)-2-methylcyclopropyl)-2-(methylthio)thieno[2,3-*d*]thiazole-5-carboxamide



To a suspension of EDC (995 mg, 5.19 mmol) and 2-(methylthio)thieno[2,3-*d*]thiazole-5-carboxylic acid (1.00 g, 4.32 mmol, **Intermediate 10**) in MeCN (30 mL) was added pyridine (15 mL). The resultant suspension was vigorously stirred for 10 min and (1*S*,2*S*)-2-Methylcyclopropan-1-amine hydrochloride (558 mg, 5.19 mmol) added and the reaction stirred for 16 h at r.t., concentrated *in vacuo* and partitioned between EtOAc (40 mL) and water (20 mL). Sat NaHCO_3 (20 mL) added and the mixture was stirred for 15 min, separated and the aqueous phase washed with EtOAc (10 mL). The combined organics were passed through a hydrophobic frit and

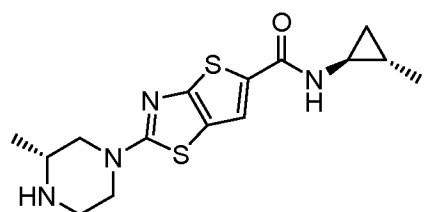
concentrated *in vacuo* to give crude product that was dry-loaded onto silica and purified by flash chromatography (0-100% EtOAc in heptanes) to give *N*[(1*S*,2*S*)-2-methylcyclopropyl]-2-methylsulfanyl-thieno[2,3-*d*]thiazole-5-carboxamide (862 mg, 3.03 mmol, 70% yield) as a cream coloured solid. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (s, 1H), 6.04 (s, 1H), 2.80 (s, 3H), 2.62 - 2.56 (m, 1H), 1.17 (d, *J* = 5.9 Hz, 3H), 1.07 - 0.99 (m, 1H), 0.84 - 0.77 (m, 1H), 0.71 - 0.64 (m, 1H). MS *m/z* [M + H]⁺ = 285.1.

Intermediate 11a: *N*-((1*S*,2*S*)-2-methylcyclopropyl)-2-(methylsulfinyl)thieno[2,3-*d*]thiazole-5-carboxamide



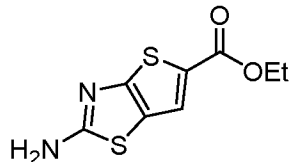
To a solution of *N*[(1*S*,2*S*)-2-methylcyclopropyl]-2-methylsulfanyl-thieno[2,3-*d*]thiazole-5-carboxamide (6.41 g, 21.41 mmol) in DCM (120 mL) was added portionwise over 20 min 3-chloroperoxybenzoic acid (5.17 g, 22.48 mmol). The reaction was stirred at 0 °C for a further 30 min, allowed to warm to rt and stirred at rt for 2 h then quenched with 1 M sodium sulfite (25 mL) and stirred for 16 h. The reaction was diluted with 1 N NaOH (50 mL), stirred for 15 min, partitioned and the organic phase washed with 1M NaOH (50 mL) and passed through a hydrophobic frit, concentrated *in vacuo* to give crude product which was purified by flash chromatography (0-4% MeOH in DCM) to give (5.83 g) as an off-white solid. The solid was heated to reflux in EtOH (50 mL) for 1 h. The resultant mixture was cooled to rt and a thick suspension formed. The solid was then cooled to 0 °C and filtered. The solid was washed with more EtOH (10 mL) and then dried overnight under vacuum to give *N*[(1*S*,2*S*)-2-methylcyclopropyl]-2-methylsulfanyl-thieno[2,3-*d*]thiazole-5-carboxamide (5.05 g, 16.81 mmol, 79% yield) as a colourless solid. ¹H NMR (500 MHz, CDCl₃) δ 7.71 (s, 1H), 6.15 (br. s, 1H), 3.08 (s, 3H), 2.59 (dq, *J* = 7.0, 3.4 Hz, 1H), 1.16 (d, *J* = 6.1 Hz, 3H), 1.08 – 0.97 (m, 1H), 0.81 (ddd, *J* = 9.4, 5.6, 3.8 Hz, 1H), 0.68 (dt, *J* = 7.4, 5.8 Hz, 1H). MS *m/z* [M + H]⁺ = 301.0.

Intermediate 12a: *N*-((1*S*,2*S*)-2-methylcyclopropyl)-2-((*R*)-3-methylpiperazin-1-yl)thieno[2,3-*d*]thiazole-5-carboxamide



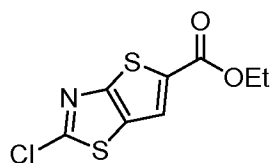
Split across 3 x 35 mL MW vials to a mixture *N*[(1*S*,2*S*)-2-methylcyclopropyl]-2-methylsulfinylthieno[2,3-*d*]thiazole-5-carboxamide (3.00 g, 9.99 mmol, **Intermediate 11a**) in MeCN (20 mL) was added (2*R*)-2-methylpiperazine (2.00 g, 19.98 mmol) and DIPEA (2.7 mL, 19.97 mmol). The reactions were heated in the MW for 2 h at 120 °C. The vials were then combined and concentrated *in vacuo*. The residue partitioned between DCM (100 mL) and water (50 mL) and the organic phase was concentrated *in vacuo*, dry loaded onto silica and purified by flash chromatography (0-20% MeOH in DCM) to give desired product (3.10 g) as an orange/brown solid. The solid was heated to reflux in a mixture of EtOAc (30 mL) and EtOH (7.5 mL) for 1 h and then cooled to 0 °C, filtered and washed with EtOAc (5 mL) to give desired product *N*[(1*S*,2*S*)-2-methylcyclopropyl]-2-[(3*R*)-3-methylpiperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxamide (2.78 g, 8.10 mmol, 81% yield) as a colourless solid. ¹H NMR (500 MHz, CDCl₃) δ 7.51 (s, 1H), 5.88 (s, 1H), 3.95 - 3.87 (m, 2H), 3.18 (td, *J* = 12.0, 3.4 Hz, 1H), 3.17 - 3.11 (m, 1H), 3.01 (dd, *J* = 3.3, 11.9 Hz, 1H), 2.99 - 2.93 (m, 1H), 2.80 (dd, *J* = 10.5, 12.3 Hz, 1H), 2.59 - 2.54 (m, 1H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.16 (d, *J* = 6.1 Hz, 3H), 1.04 - 0.97 (m, 1H), 0.81 - 0.76 (m, 1H), 0.67 - 0.62 (m, 1H). MS *m/z* [M + H]⁺ = 337.1.

Intermediate 13: Ethyl 2-aminothieno[2,3-*d*]thiazole-5-carboxylate



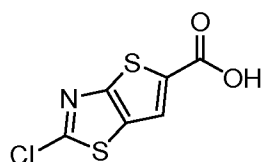
To a series of 5 x 35 mL MW tubes containing ethyl 2-methylsulfinylthieno[2,3-*d*]thiazole-5-carboxylate (500 mg, 1.82 mmol, **Intermediate 7**) was added isopropanol (6 mL) and ammonium hydroxide (33 wt%, 2.1 mL, 18.16 mmol). The reactions were heated in a MW at 120 °C for 2 h. The reactions were combined and concentrated *in vacuo*. The crude product was dry-loaded onto silica and purified by flash chromatography (0-20% MeOH in DCM) to give desired product ethyl 2-aminothieno[2,3-*d*]thiazole-5-carboxylate (1.66 g, 7.27 mmol, 80%) yield as an orange solid. ¹H NMR (400 MHz, DMSO) δ 7.92 (br. s, 2H), 7.85 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). MS *m/z* [M + H]⁺ = 229.0.

Ester of Intermediate 14: Ethyl 2-chlorothieno[2,3-*d*]thiazole-5-carboxylate



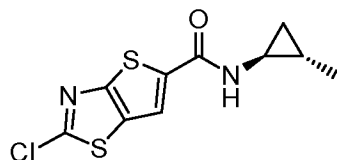
To a suspension of copper (II) chloride (4.42 g, 32.85 mmol) in MeCN (150 mL) was added tert-butyl nitrite (4.7 mL, 39.42 mmol). The mixture was heated to 40 °C and ethyl 2-aminothieno[2,3-*d*]thiazole-5-carboxylate (6.00 g, 26.28 mmol, **Intermediate 13**) added portionwise over 20 min. The reaction heated to 72 °C and stirred for 15 min, cooled to rt and partitioned between EtOAc (100 mL) and sat NH₄Cl (100 mL) and the mixture filtered through celite and washed with DCM (50 mL). The filtrate and washings were combined and partitioned. The organic phase washed with sat. NH₄Cl (50 mL), passed through a hydrophobic frit, and concentrated *in vacuo*. The crude product was dry-loaded onto silica and purified by flash chromatography (0-30% EtOAc in heptanes) to give desired product ethyl 2-chlorothieno[2,3-*d*]thiazole-5-carboxylate (4.10 g, 16.55 mmol, 63% yield) as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.92 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H). MS *m/z* [M + H + MeCN]⁺ = 288.9, 290.9.

Intermediate 14: 2-Chlorothieno[2,3-*d*]thiazole-5-carboxylic acid



To a solution of ethyl 2-chlorothieno[2,3-*d*]thiazole-5-carboxylate (4.12 g, 16.63 mmol, **Intermediate 14**) in THF (40 mL) and water (40 mL) was added lithium hydroxide hydrate (1.40 g, 33.26 mmol). The reaction was stirred at rt overnight and excess THF removed *in vacuo* and the resultant aqueous was washed with EtOAc (40 mL). The aqueous was acidified with 6 N HCl. The desired product precipitated and was stirred for 15 min before filtering. The solid was washed with water (20 mL) and then TBME (20 mL), dried overnight under vacuum at 40 °C to give 2-chlorothieno[2,3-*d*]thiazole-5-carboxylic acid (3.28 g, 14.93 mmol, 90% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO) δ 13.64 (br. s, 1H), 8.09 (d, *J* = 2.0 Hz, 1H).

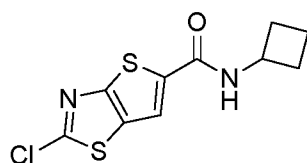
Intermediate 15a: 2-Chloro-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide



To a suspension of 2-chlorothieno[2,3-*d*]thiazole-5-carboxylic acid (2.78 g, 12.66 mmol) and EDC (2.91 g, 15.19 mmol) in MeCN (30 mL) and pyridine (15 mL) was added (1*S*,2*S*)-2-Methylcyclopropan-1-amine hydrochloride (1.77 g, 16.45 mmol, **Intermediate 14**). The reaction stirred for 16 h at rt. The mixture was concentrated *in vacuo* and partitioned between EtOAc (40

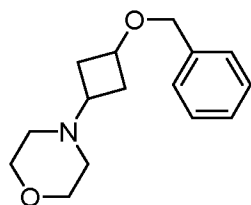
mL) and 1 N HCl (10 mL) the organic phase washed with sat. NaHCO₃ (20 mL), passed through a hydrophobic frit and concentrated *in vacuo* to give crude product as a brown solid. The crude product was purified by flash chromatography (0-20% EtOAc in DCM) to give desired product (2.9 g) as a light brown solid. The solid was suspended in EtOAc (30 mL) and heated to reflux. After stirring at reflux for 1 h the mixture was allowed to cool, filtered and washed with cold EtOAc (5 mL) to give 2-chloro-*N*[(1*S*,2*S*)-2-methylcyclopropyl]thieno[2,3-*d*]thiazole-5-carboxamide (2.51 g, 9.20 mmol, 73% yield) as a colourless solid. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (s, 1H), 6.04 (br. s, 1H), 2.58 (dq, *J* = 6.8, 3.3 Hz, 1H), 1.15 (d, *J* = 6.1 Hz, 3H), 1.08 – 0.94 (m, 1H), 0.79 (ddd, *J* = 9.3, 5.6, 3.8 Hz, 1H), 0.67 (dt, *J* = 7.2, 5.8 Hz, 1H). MS *m/z* [M + H]⁺ = 261.8, 263.7.

Intermediate 15b: 2-Chloro-*N*-cyclobutylthieno[2,3-*d*]thiazole-5-carboxamide



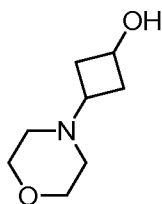
To a suspension of EDC (1.57 g, 8.19 mmol) and 2-chlorothieno[2,3-*d*]thiazole-5-carboxylic acid (1.50 g, 6.83 mmol, **Intermediate 14**) in MeCN (30 mL) was added pyridine (5 mL). The brown suspension was stirred at rt for 10 min. Aminocyclobutane hydrochloride (955 mg, 8.88 mmol) was added portionwise over 5 min and the reaction stirred for 16 h at rt. The reaction was concentrated *in vacuo* and partitioned between DCM (100 mL), sat. NaHCO₃ (30 mL) and sat. brine (5 mL). The phases were separated and the aqueous was re-extracted with EtOAc (20 mL). The combined organics were washed with 1 N HCl (30 mL), passed through a hydrophobic frit, and concentrated *in vacuo* to give crude product as a light brown solid. The crude product was dry-loaded onto silica and purified by flash chromatography (0-5% MeOH in DCM) to give desired product 2-chloro-*N*-cyclobutylthieno[2,3-*d*]thiazole-5-carboxamide (1.53 g, 5.33 mmol, 78% yield) as an off-white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.64 (s, 1H), 6.08 (d, *J* = 5.1 Hz, 1H), 4.64 - 4.55 (m, 1H), 2.51 - 2.43 (m, 2H), 2.04 - 1.96 (m, 2H), 1.85 - 1.78 (m, 2H). MS *m/z* [M + H]⁺ = 273.0, 275.0.

Intermediate 16: 4-(3-Benzoyloxycyclobutyl)morpholine



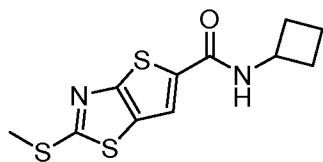
To a solution of 3-(Benzyloxy)cyclobutanone (2.5 mL, 15.47 mmol) in DCM (60 mL) was added morpholine (2.70 mL, 30.93 mmol) and the reaction was stirred for 30 min. The reaction was cooled to 0 °C and sodium triacetoxyborohydride (5.24 g, 24.74 mmol) was added portionwise over 30 min. The resultant suspension was allowed to warm slowly to rt and stirred for 16 h. The reaction was quenched with MeOH (5 mL) and stirred vigorously for 15 min. NaOH (1 M, 40 mL) was added and the mixture was stirred vigorously for a further 30 min. The mixture was then transferred to a separating funnel and left to stand for 3 h. The mixture was passed through a hydrophobic frit (slow separation) and then concentrated *in vacuo*. The crude product was dry-loaded onto silica and purified by flash chromatography (0-10% MeOH in DCM) to give 4-(3-benzyloxycyclobutyl)morpholine (3.31 g, 13.38 mmol, 87% yield, 85:15 cis:trans) as a pale yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.13 (m, 5H), 4.36 (s, 2H), 3.74 (tt, J = 7.8, 6.7 Hz, 1H), 3.68 – 3.59 (m, 4H), 2.42 – 2.31 (m, 2H), 2.31 – 2.20 (m, 5H), 2.10 (dd, J = 6.8, 5.3 Hz, 1H), 1.87 – 1.70 (m, 2H); MS m/z $[\text{M} + \text{H}]^+ = 248.2$.

Intermediate 17: 3-Morpholinocyclobutanol



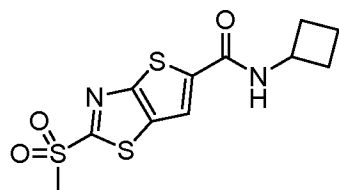
To a solution of 4-(3-benzyloxycyclobutyl)morpholine (3.30 g, 13.34 mmol, **Intermediate 16**) in DCM (40 mL) was added methanesulfonic acid (13.7 mL, 211.48 mmol) and the reaction was stirred at rt for 24 h. The reaction was diluted with more DCM (100 mL) and then sodium carbonate (22.63 g, 213.48 mmol) was added portionwise over 1 h and the resultant suspension was stirred at rt for 24 h. The reaction was filtered, washed with more DCM (50 mL), and concentrated *in vacuo* to give crude product. The crude product was dissolved in mixture of MeOH/DCM (1:1, 20 mL) and then loaded evenly onto 2 x 10 g SCX-2 columns. The columns were each washed with MeOH (80 mL) and then the desired product was eluted with 3.5 N NH_3 in MeOH (80 mL). The product fractions were concentrated *in vacuo* to give clean 3-morpholinocyclobutanol (1.83 g, 11.64 mmol, 87% yield, 85:15 cis:trans) as a brown/orange oil; ^1H NMR (500 MHz, CDCl_3) δ 4.03 (p, J = 7.3 Hz, 1H), 3.71 (t, J = 4.7 Hz, 4H), 3.48 (s, 1H), 2.60 – 2.47 (m, 2H), 2.42 – 2.18 (m, 5H), 1.83 – 1.71 (m, 2H).

Intermediate 11b: *N*-Cyclobutyl-2-(methylthio)thieno[2,3-*d*]thiazole-5-carboxamide



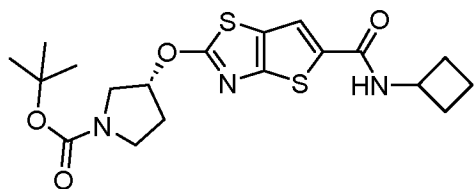
To a suspension of EDC (3.23 g, 16.86 mmol) and 2-(methylthio)thieno[2,3-*d*]thiazole-5-carboxylic acid (3.00 g, 12.97 mmol, **Intermediate 10**) in MeCN (90 mL) was added pyridine (30 mL). The resultant thick off-white suspension was stirred for 10 min and then aminocyclobutane hydrochloride (1.67 g, 15.56 mmol) was added. The thick, partially yellow, suspension was stirred at rt for 72 h. The reaction was then concentrated *in vacuo* and re-suspended in EtOH (40 mL) and stirred at rt for 1 h. The solid was then filtered and washed with more EtOH (5 mL) to give N-cyclobutyl-2-methylsulfanyl-thieno[2,3-*d*]thiazole-5-carboxamide (3.20 g, 11.25 mmol, 87% yield) as an off-white solid; ^1H NMR (500 MHz, DMSO) δ 8.76 (d, J = 7.6 Hz, 1H), 8.04 (s, 1H), 4.45 – 4.28 (m, 1H), 2.78 (s, 3H), 2.29 – 2.14 (m, 2H), 2.14 – 1.99 (m, 2H), 1.78 – 1.55 (m, 2H); MS m/z $[\text{M} + \text{H}]^+ = 285.0$.

Intermediate 18b: *N*-Cyclobutyl-2-methylsulfonyl-thieno[2,3-*d*]thiazole-5-carboxamide



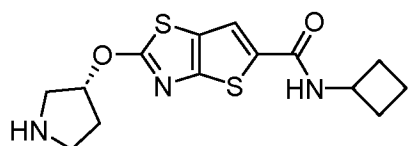
To a suspension of *N*-cyclobutyl-2-(methylthio)thieno[2,3-*d*]thiazole-5-carboxamide (3.20 g, 11.25 mmol, **Intermediate 11b**) in DCM (100 mL) at rt was added portionwise 3-chloroperoxybenzoic acid (5.04 g, 22.50 mmol) over 5 min and then the reaction was stirred at rt for 16 h. The reaction was quenched with NaOH (0.5 M, 250 mL). The mixture was stirred for 15 min and then filtered. The solid was washed with more water (3 x 20 mL), EtOH (20 mL), and EtOAc (20 mL) and dried under vacuum to give desired product *N*-cyclobutyl-2-methylsulfonyl-thieno[2,3-*d*]thiazole-5-carboxamide (3.20 g, 10.11 mmol, 90% yield) as a colourless solid; ^1H NMR (500 MHz, DMSO) δ 9.08 (d, J = 7.5 Hz, 1H), 8.25 (s, 1H), 4.40 (apt. h, J = 8.2 Hz, 1H), 3.55 (s, 3H), 2.31 – 2.17 (m, 2H), 2.17 – 2.01 (m, 2H), 1.80 – 1.59 (m, 2H); MS m/z $[\text{M} + \text{H}]^+ = 317.0$.

Intermediate 19b: *tert*-Butyl (*R*)-3-((5-(cyclobutylcarbamoyl)thieno[2,3-*d*]thiazol-2-yl)oxy)pyrrolidine-1-carboxylate



To a pale orange solution of *tert*-butyl (*R*)-3-hydroxypyrrolidine-1-carboxylate (1.95 g, 10.43 mmol) in THF (30 mL) at 0 °C was added dropwise over 5 min sodium *tert*-butoxide (2 M in THF, 5.20 mL, 10.43 mmol). The reaction was stirred at this temperature for 25 min to give a precipitate. To the orange mixture at 0 °C was added portionwise, over 30 min, a solution of *N*-cyclobutyl-2-methylsulfonyl-thieno[2,3-*d*]thiazole-5-carboxamide (3.00 g, 9.48 mmol, **Intermediate 18b**) in DMF (30 mL). The reaction was allowed to warm to rt and stirred for 3 h. The reaction was concentrated in vacuo and then partitioned between EtOAc (100 mL) and water (100 mL). The mixture was separated, and the organic was washed with more water (2 x 50 mL). The organic was passed through a hydrophobic frit and then dry-loaded onto silica. The crude product was purified by flash chromatography (10-100% EtOAc in heptanes) to give *tert*-butyl (*R*)-3-((5-(cyclobutylcarbamoyl)thieno[2,3-*d*]thiazol-2-yl)oxy)pyrrolidine-1-carboxylate (2.74 g, 6.15 mmol, 65% yield) as a yellow/orange solid; ¹H NMR (500 MHz, CDCl₃) δ 7.52 (s, 1H), 6.00 (d, *J* = 7.7 Hz, 1H), 5.62 (s, 1H), 4.65 – 4.47 (m, 1H), 3.89 – 3.37 (m, 4H), 2.50 – 2.39 (m, 2H), 2.32 (s, 1H), 2.19 (d, *J* = 19.2 Hz, 1H), 2.03 – 1.92 (m, 2H), 1.84 – 1.72 (m, 2H), 1.47 (s, 9H); MS *m/z* [*M* + *H*]⁺ = 423.9.

Intermediate 20b: (*R*)-*N*-Cyclobutyl-2-(pyrrolidin-3-yloxy)thieno[2,3-*d*]thiazole-5-carboxamide

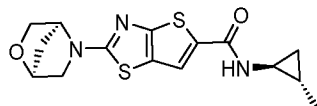


To a pale yellow solution of *tert*-butyl (*R*)-3-((5-(cyclobutylcarbamoyl)thieno[2,3-*d*]thiazol-2-yl)oxy)pyrrolidine-1-carboxylate (2.74 g, 6.47 mmol, **Intermediate 19b**) in DCM (30 mL) was added TFA (5.00 mL, 64.69 mmol) and the reaction was allowed to stir at rt for 16 h. The reaction was concentrated *in vacuo* and then loaded across 4 x 10 g SCX-2 columns. The columns were washed with MeOH (100 mL per column) and then eluted with 3 N NH₃ in MeOH (60 mL per column). The combined ammonia solution was concentrated *in vacuo* to give (*R*)-*N*-cyclobutyl-2-(pyrrolidin-3-yloxy)thieno[2,3-*d*]thiazole-5-carboxamide (2.35 g, 7.27 mmol, quant. Yield) as a yellow/orange solid; ¹H NMR (500 MHz, MeOD) δ 7.79 (s, 1H), 5.59 (ddt, *J* = 6.5, 4.4, 2.2 Hz, 1H), 4.53 – 4.39 (m, 1H), 3.35 (s, 1H), 3.23 – 3.15 (m, 2H), 3.09 (dt, *J* = 11.3, 7.6 Hz, 1H), 3.01 –

2.90 (m, 1H), 2.34 (dtt, $J = 8.9, 7.5, 2.9$ Hz, 2H), 2.26 – 2.05 (m, 4H), 1.84 – 1.72 (m, 2H); MS m/z $[M + H]^+ = 323.9$.

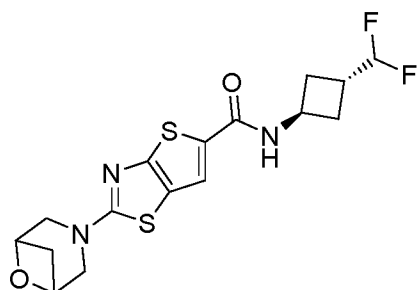
Examples

Example 1: 2-((1*S*,4*S*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide



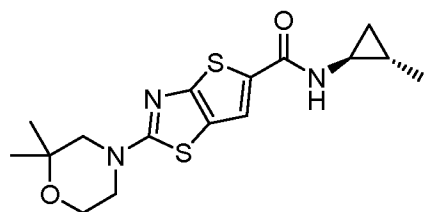
To a series of three flasks containing EDC (1.55 g, 8.08 mmol) and 2-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)thieno[2,3-*d*]thiazole-5-carboxylic acid (**Intermediate 3a**) (1.14 mg, 4.04 mmol), and 2-methylcyclopropanamine (287 mg, 4.04 mmol) in MeCN (8 mL) was added pyridine (2 mL). The reactions stirred at rt for 12 h. The three reaction mixtures were combined, concentrated *in vacuo* and purified by flash chromatography (0-10% MeOH/DCM) to afford the product 2-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide (3.30 g, 9.84 mmol, 81% yield) as an off-white solid. The four diastereoisomers of 2-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide (3.30 g, 9.84 mmol, were separated by SFC (column: DAICEL CHIRALPAK AD (250 mm*30 mm, 10 μ m); mobile phase: [0.1% NH_4OH in EtOH]; B%: 70%-70%, 5 min; 460 min) to give pure 2-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide (1.21 g, 3.61 mmol, 31% yield) as a yellow solid; ^1H NMR (500 MHz, DMSO) δ 8.32 (d, $J = 3.4$ Hz, 1H), 7.80 (s, 1H), 4.72 (d, $J = 16.0$ Hz, 2H), 3.81 (d, $J = 2.9$ Hz, 2H), 3.59 - 3.55 (m, 1H), 3.29 (s, 1H), 2.49 - 2.45 (m, 1H), 2.03 (dd, $J = 2.1, 10.0$ Hz, 1H), 1.93 (d, $J = 10.1$ Hz, 1H), 1.06 (d, $J = 6.1$ Hz, 3H), 0.94 - 0.88 (m, 1H), 0.75 - 0.70 (m, 1H), 0.51 - 0.46 (m, 1H). HRMS $\text{C}_{15}\text{H}_{18}\text{N}_3\text{O}_2\text{S}_2^+$ calcd. 336.0835, found 339.0847.

Example 2: 2-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)-*N*-((1*R*,3*R*)-3-(difluoromethyl)cyclobutyl)thieno[2,3-*d*]thiazole-5-carboxamide



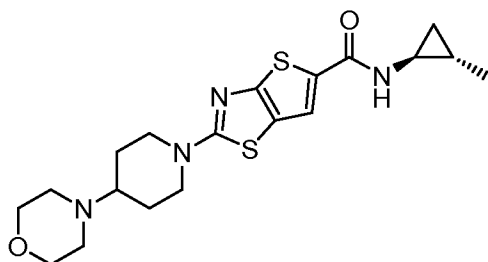
A mixture of compound (1*R*,3*R*)-3-(difluoromethyl)cyclobutan-1-amine hydrochloride (40 mg, 0.25 mmol), 2-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)thieno[2,3-*d*]thiazole-5-carboxylic acid (108 mg, 0.38 mmol, **Intermediate 3b**) and EDC (146 mg, 0.76 mmol) in MeCN (0.6 mL) and pyridine (0.15 mL) was stirred at rt for 12 h. The reaction mixture was concentrated *in vacuo*. The crude product was purified by prep-HPLC to give 2-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-*N*-((1*R*,3*R*)-3-(difluoromethyl)cyclobutyl)thieno[2,3-*d*]thiazole-5-carboxamide (37 mg, 0.09 mmol, 25% yield) as a yellow solid. ¹H NMR (400MHz, DMSO) δ 8.65 (br d, *J* = 7.5 Hz, 1H), 7.92 (s, 1H), 6.42 - 6.06 (m, 1H), 4.72 (br d, *J* = 6.4 Hz, 2H), 4.56 - 4.39 (m, 1H), 3.77 - 3.63 (m, 4H), 3.23 - 3.11 (m, 1H), 2.62 (dtd, *J* = 4.4, 8.8, 17.1 Hz, 1H), 2.37 - 2.22 (m, 4H), 1.94 (d, *J* = 9.0 Hz, 1H). MS *m/z* [M + H]⁺ = 386.1. Prep-HPLC conditions: Column: Phenomenex Synergi C18 150*25*10um, mobile phase: A - water (0.225% formic acid), B- acetonitrile]; B%:35%-65%, 10min.

Example 3: 2-(2,2-Dimethylmorpholino)-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide



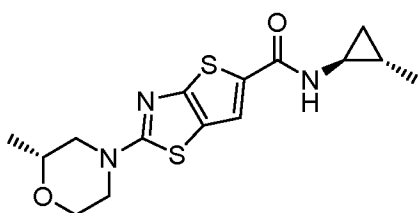
To an rbf containing a suspension of EDC (154 mg, 0.804 mmol) and 2-(2,2-dimethylmorpholino)thieno[2,3-*d*]thiazole-5-carboxylic acid (200 mg, 0.670 mmol) in MeCN (4 mL) and pyridine (2 mL) was added (1*S*,2*S*)-2-Methylcyclopropan-1-amine hydrochloride (79 mg, 0.737 mmol). The reaction was stirred at rt for 16 h. The reaction was concentrated *in vacuo* and partitioned between DCM (20 mL) and sat. NaHCO₃ (10 mL). The mixture was passed through a phase separator and the organic phase was concentrated *in vacuo* to give crude product. The crude product was purified by flash chromatography (0-5% MeOH in DCM) to give desired product (189 mg, 0.54 mmol, 80%) as an orange/brown solid. The solid was further purified by recrystallisation in hot MeOH (3 mL) to give 2-(2,2-dimethylmorpholino)-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide (134 mg, 0.377 mmol, 56%) as a cream coloured solid; ¹H NMR (500 MHz, DMSO) δ 8.33 (d, *J* = 3.6 Hz, 1H), 7.81 (s, 1H), 3.76 (apt. t, *J* = 5.1 Hz, 2H), 3.49 (apt. t, *J* = 5.1 Hz, 2H), 3.38 (s, 2H), 2.50 - 2.46 (m, 1H), 1.22 (s, 6H), 1.06 (d, *J* = 6.1 Hz, 3H), 0.94 - 0.88 (m, 1H), 0.75 - 0.70 (m, 1H), 0.51 - 0.46 (m, 1H); HRMS C₁₆H₂₂N₃O₂S₂⁺ calcd. 352.1148, found 352.1152.

Example 4: *N*-((1*S*,2*S*)-2-Methylcyclopropyl)-2-(4-morpholinopiperidin-1-yl)thieno[2,3-*d*]thiazole-5-carboxamide



To a suspension of EDC (651 mg, 3.40 mmol) and 2-(4-morpholino-1-piperidyl)thieno[2,3-*d*]thiazole-5-carboxylic acid (1.00 g, 2.83 mmol, **Intermediate 3d**) in MeCN (30 mL) and pyridine (15 mL) was added portionwise over 15 min (1*S*,2*S*)-2-Methylcyclopropan-1-amine hydrochloride (457 mg, 4.24 mmol). The reaction was stirred at rt for 16 h. The reaction was concentrated *in vacuo* and partitioned between DCM (50 mL), MeOH (5 mL) and NaOH (0.5 M, 40 mL). The mixture was separated and the organic phase passed through a hydrophobic frit and concentrated *in vacuo*. The crude product was then dry-loaded onto silica and purified by flash chromatography (0-15% MeOH in DCM) to give desired product as a cream coloured solid (1.07 g). The solid was suspended in EtOH (20 mL) and heated to reflux. After 1 h, the suspension was cooled to rt and then to 0 °C and filtered to give *N*-[(1*S*,2*S*)-2-methylcyclopropyl]-2-(4-morpholino-1-piperidyl)thieno[2,3-*d*]thiazole-5-carboxamide (1.00 g, 2.44 mmol, 86%) yield as a colourless solid; ¹H NMR (500 MHz, DMSO) δ 8.35 (d, *J* = 3.9 Hz, 1H), 7.79 (s, 1H), 3.94 (dt, *J* = 13.5, 3.9 Hz, 2H), 3.56 (t, *J* = 4.6 Hz, 4H), 3.22 – 3.05 (m, 2H), 2.48 – 2.42 (m, 6H), 1.87 (dd, *J* = 12.8, 2.7 Hz, 2H), 1.55 – 1.39 (m, 2H), 1.04 (d, *J* = 6.1 Hz, 3H), 0.95 – 0.84 (m, 1H), 0.70 (ddd, *J* = 9.0, 5.0, 3.8 Hz, 1H), 0.47 (dt, *J* = 7.4, 5.4 Hz, 1H); HRMS C₁₉H₂₇N₄O₂S₂⁺ calcd. 407.1570, found 407.1573.

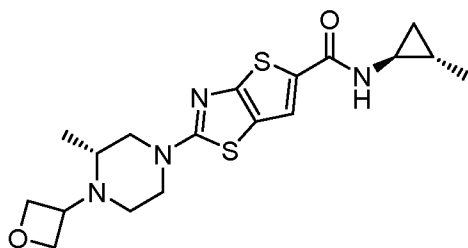
Example 5: *N*-((1*S*,2*S*)-2-Methylcyclopropyl)-2-((*R*)-2-methylmorpholino)thieno[2,3-*d*]thiazole-5-carboxamide



To a suspension of EDC (566 mg, 2.95 mmol) and 2-[(2*R*)-2-methylmorpholin-4-yl]thieno[2,3-*d*]thiazole-5-carboxylic acid (700 mg, 2.46 mmol **Intermediate 2**) in MeCN (20 mL) was added Pyridine (10 mL). The mixture was stirred for 15 min and then (1*S*,2*S*)-2-Methylcyclopropan-1-amine hydrochloride (344 mg, 3.20 mmol) was added. The reaction was

stirred at for 16 h. The reaction was concentrated *in vacuo* and partitioned between DCM (30 mL) and water (20 mL). The mixture was separated and the organic was passed through a hydrophobic frit. The organic was then concentrated *in vacuo* and purified by flash chromatography (20-100% EtOAc in heptanes) to give desired product as a pale yellow solid (656 mg). The solid was recrystallised in hot EtOH (5 mL) to give *N*[(1*S*,2*S*)-2-methylcyclopropyl]-2-[(2*R*)-2-methylmorpholin-4-yl]thieno[2,3-*d*]thiazole-5-carboxamide (492 mg, 1.44 mmol, 59%) yield as a pale yellow coloured solid; ¹H NMR (500 MHz, CDCl₃) δ 7.49 (s, 1H), 5.95 (br. s, 1H), 4.04 – 3.97 (m, 1H), 3.89 – 3.82 (m, 1H), 3.79 – 3.65 (m, 3H), 3.26 (td, *J* = 12.6, 3.7 Hz, 1H), 2.91 (dd, *J* = 12.7, 10.5 Hz, 1H), 2.53 (dq, *J* = 6.8, 3.3 Hz, 1H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.13 (d, *J* = 6.1 Hz, 3H), 1.03 – 0.92 (m, 1H), 0.76 (ddd, *J* = 9.2, 5.5, 3.8 Hz, 1H), 0.62 (dt, *J* = 7.2, 5.7 Hz, 1H); HRMS C₁₅H₂₀N₃O₂S₂⁺ calcd. 338.0997, found 338.0996.

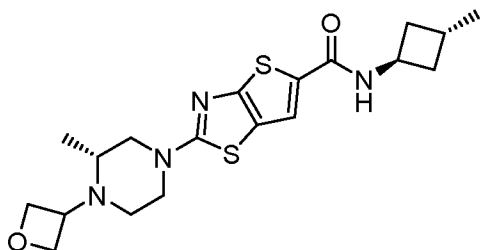
Example 6: 2-((*R*)-3-Methyl-4-(oxetan-3-yl)piperazin-1-yl)-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide



To a suspension of EDC (515 mg, 2.69 mmol) and 2-[(3*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxylic acid (760 mg, 2.24 mmol, **Intermediate 3**) in MeCN (20 mL) was added pyridine (10 mL). The resultant mixture was stirred for 10 min, then (1*S*,2*S*)-2-Methylcyclopropan-1-amine hydrochloride (289 mg, 2.69 mmol) added. The reaction stirred at rt for 16 h, concentrated *in vacuo*, partitioned between DCM (50 mL) and sat. NaHCO₃ (30 mL) and passed through a hydrophobic frit. The organic phase concentrated and purified by flash chromatography (24g column, 0-5% MeOH in DCM) to give *N*[(1*S*,2*S*)-2-methylcyclopropyl]-2-[(3*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxamide (821 mg) as a cream coloured solid. The solid was suspended in isopropanol (8 mL) and heated to reflux to give a solution. The solution was stirred at reflux for 30 min and then cooled to rt. TBME (4 mL) was added as an anti-solvent and the mixture was stirred for 16 h. The suspension was then cooled to 0 °C and filtered. The solid was washed with cold iPA/TBME (2 mL, 1:1) and then cold Et₂O (10 mL) to give *N*[(1*S*,2*S*)-2-methylcyclopropyl]-2-[(3*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxamide (675 mg, 1.70 mmol, 81%) as a colourless solid; ¹H NMR (500 MHz, CDCl₃) δ 7.48 (s, 1H), 5.86 (s, 1H), 4.74 – 4.66 (m, 2H), 4.63 (dt, *J* = 19.0, 6.5 Hz, 2H), 3.84 – 3.77 (m, 1H), 3.77 – 3.68 (m, 2H), 3.47 (ddd, *J* = 12.7, 9.4, 3.3 Hz, 1H), 3.14 (dd, *J* = 12.6, 8.5 Hz, 1H), 2.74 (dt, *J* = 11.6, 3.9 Hz, 1H), 2.58 – 2.48 (m, 2H), 2.27 (ddd, *J* = 11.6,

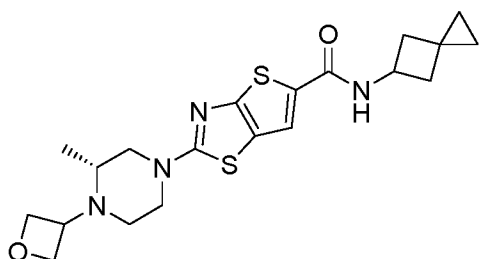
9.4, 3.4 Hz, 1H), 1.14 (d, $J = 6.1$ Hz, 3H), 1.02 – 0.93 (m, 4H), 0.76 (ddd, $J = 9.2, 5.5, 3.8$ Hz, 1H), 0.62 (dt, $J = 7.3, 5.8$ Hz, 1H); HRMS $C_{18}H_{25}N_4O_2S_2^+$ calcd. 393.1413, found 393.1402.

Example 7: 2-((*R*)-3-Methyl-4-(oxetan-3-yl)piperazin-1-yl)-*N*-((1*r*,3*R*)-3-methylcyclobutyl)thieno[2,3-*d*]thiazole-5-carboxamide



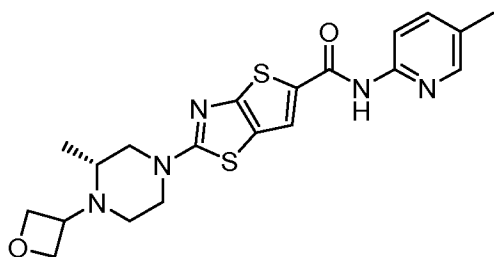
To a suspension of EDC (678 mg, 3.53 mmol) and 2-[(3*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxylic acid (1.00 g, 2.95 mmol, **Intermediate 9a**) in MeCN (30 mL) was added Pyridine (15 mL) and the reaction was stirred at rt for 10 min. To the reaction was added trans-3-Methylcyclobutan-1-amine.HCl (466 mg, 3.83 mmol) and the mixture stirred at rt for 16 h, concentrated *in vacuo* and partitioned between DCM (50 mL) and sat NaHCO₃ (50 mL). then washed with sat. brine (50 mL) the organic phase was passed through a hydrophobic frit. The solution was then dry-loaded onto silica and purified by flash chromatography (0-3% MeOH in DCM) to give *N*-(3-methylcyclobutyl)-2-[(3*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxamide (972 mg, 2.34 mmol, 80% yield) as an off-white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.50 (s, 1H), 5.89 (br. d, $J = 7.5$ Hz, 1H), 4.75 – 4.57 (m, 5H), 3.86 – 3.67 (m, 3H), 3.47 (ddd, $J = 12.7, 9.4, 3.3$ Hz, 1H), 3.14 (dd, $J = 12.6, 8.5$ Hz, 1H), 2.79 – 2.69 (m, 0H), 2.59 – 2.46 (m, 1H), 2.44 – 2.32 (m, 1H), 2.27 (ddd, $J = 11.6, 9.4, 3.4$ Hz, 1H), 2.18 – 2.07 (m, 4H), 1.19 (d, $J = 7.1$ Hz, 3H), 0.98 (d, $J = 6.4$ Hz, 3H); HRMS $C_{19}H_{27}N_4O_2S_2^+$ calcd. 407.1570, found 407.1576.

Example 8: (*R*)-2-(3-Methyl-4-(oxetan-3-yl)piperazin-1-yl)-*N*-(spiro[2.3]hexan-5-yl)thieno[2,3-*d*]thiazole-5-carboxamide



To a suspension of EDC (68 mg, 0.35 mmol) and 2-[(3*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxylic acid (100 mg, 0.29 mmol, **Intermediate 9a**) in MeCN (2 mL) was added pyridine (1 mL). The resultant mixture was stirred for 10 min and then spiro[2.3]hex-5-ylamine hydrochloride (43 mg, 0.32 mmol) added. The reactions stirred for 16 h rt, concentrated *in vacuo* and partitioned between DCM (10 mL) and sat. NaHCO₃ (10 mL) and then passed through a hydrophobic frit. The organic was then concentrated and purified by flash chromatography (0-5% MeOH in DCM) to give 2-[(3*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl]-*N*-spiro[2.3]hexan-5-yl-thieno[2,3-*d*]thiazole-5-carboxamide (111 mg, 0.25 mmol, 86% yield) as a cream coloured solid. ¹H NMR (500 MHz, CDCl₃) δ 7.54 (s, 1H), 6.00 (d, *J* = 7.3 Hz, 1H), 4.80 - 4.62 (m, 5H), 3.85 - 3.72 (m, 3H), 3.53 - 3.47 (m, 1H), 3.17 (dd, *J* = 8.5, 12.6 Hz, 1H), 2.77 (td, *J* = 4.0, 11.6 Hz, 1H), 2.58 - 2.53 (m, 1H), 2.49 - 2.43 (m, 2H), 2.33 - 2.24 (m, 3H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.57 - 0.53 (m, 2H), 0.48 - 0.44 (m, 2H); HRMS C₂₀H₂₇N₄O₂S₂⁺ calcd. 419.1562, found 419.1575.

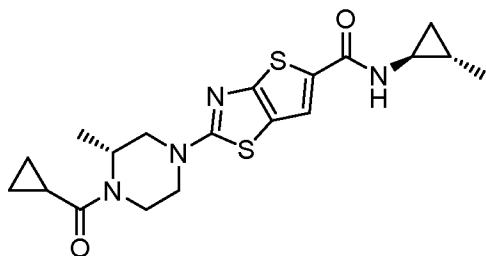
Example 9: (*R*)-2-(3-Methyl-4-(oxetan-3-yl)piperazin-1-yl)-*N*-(5-methylpyridin-2-yl)thieno[2,3-*d*]thiazole-5-carboxamide



To an oven-dried 35 mL MW vial was added 2-[(3*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxylic acid (750 mg, 2.21 mmol, **Intermediate 9a**) and 2-amino-5-methyl pyridine (430 mg, 3.98 mmol). The solids were suspended in DCM (11 mL) and 1-methylimidazole (750 μL, 12.10 mmol) was added. The mixture was stirred for 15 min to give a light brown solution and then TCFH (806 mg, 2.87 mmol) was added. The reaction vial was crimped to seal and heated at 40 °C for 16 h. The reaction was concentrated *in vacuo*, dry-loaded directly onto silica and purified by flash chromatography (0-5% MeOH in DCM) to give an impure yellow solid. The solid was suspended in EtOH (10 mL), heated to reflux, and stirred for 1 h. The resultant suspension was then cooled to rt and filtered. The solid was washed with cold EtOH (2 mL) and then Et₂O (5 mL) and dried under vacuum to give 2-[(3*R*)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl]-*N*-(5-methyl-2-pyridyl)thieno[2,3-*d*]thiazole-5-carboxamide (606 mg, 1.40 mmol, 63% yield) as a cream coloured solid; ¹H NMR (400 MHz, DMSO) δ 10.66 (s, 1H), 8.34 (s, 1H), 8.20 (d, *J* = 2.3 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.63 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.59 - 4.46

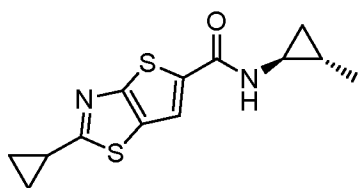
(m, 4H), 3.81 – 3.63 (m, 3H), 3.44 (ddd, $J = 12.4, 8.9, 3.3$ Hz, 1H), 3.14 (dd, $J = 12.7, 8.1$ Hz, 1H), 2.72 (dt, $J = 11.7, 3.9$ Hz, 1H), 2.27 (s, 3H), 2.21 (ddd, $J = 12.0, 9.0, 3.4$ Hz, 1H), 0.90 (d, $J = 6.5$ Hz, 3H); HRMS $C_{20}H_{24}N_5O_2S_2^+$ calcd. 430.1371, found 430.1367.

Example 10: 2-((*R*)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide



To a solution of *N*-[(1*S*,2*S*)-2-methylcyclopropyl]-2-[(3*R*)-3-methylpiperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxamide (100 mg, 0.29 mmol, **Intermediate 4**) in DCM (3 mL) was added cyclopropanecarboxylic acid (30 μ L, 0.36 mmol) followed by DIPEA (81 μ L, 0.59 mmol) and T3P (210 μ L, 0.35 mmol). The reaction was stirred at rt for 16 h, treated with sat. $NaHCO_3$ (20 mL) and passed through a hydrophobic frit, dry-loaded onto silica and purified by flash chromatography (0-4% MeOH in DCM) to give 2-((*R*)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide (70 mg, 0.16 mmol, 55% yield) as an off white solid. 1H NMR (500 MHz, DMSO) δ 8.32 (d, $J = 3.7$ Hz, 1H), 7.8 (s, 1H), 4.66 (br s, 1H), 4.21 (d, $J = 12.3$ Hz, 1H), 3.91 (br s, 1H), 3.78 (br s, 1H), 3.45 (br s, 1H), 3.23 (br s, 1H), 3.17 (d, $J = 5.3$ Hz, 3H), 2.48 – 2.45 (m, 1H), 1.99 – 1.94 (m, 1H), 1.2 (br s, 2H), 0.93 – 0.87 (m, 1H), 0.80 – 0.69 (m, 5H), 0.49 – 0.46 (m, 1H). MS m/z $[M + H]^+ = 405.2$.

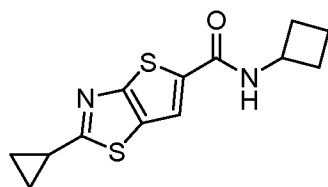
Example 11: 2-Cyclopropyl-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide



A solution of 2-chloro-*N*-[(1*S*,2*S*)-2-methylcyclopropyl]thieno[2,3-*d*]thiazole-5-carboxamide (100 mg, 0.356 mmol, **Intermediate 15a**) and Xantphos Pd G3 (34 mg, 0.036 mmol) in THF (5 mL) at room temperature was degassed with three vacuum/ N_2 cycles, then treated with cyclopropylzinc bromide (0.5 M in THF, 1.4 mL, 0.71 mmol) dropwise to give an orange solution. The reaction was stirred at 60 $^{\circ}C$ for 16 h, cooled to rt, partitioned between water (10

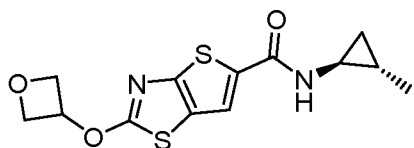
mL) and EtOAc (25 mL). The aqueous phase extracted with EtOAc (25 mL). The combined organic phases were washed with sat. brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-25% EtOAc/DCM) to give product as a mixed white/purple solid (63 mg). The solid was then dissolved in ethanol to give a purple solution, treated with activated charcoal and filtered to give a pale yellow solution. The yellow solution was concentrated *in vacuo* to give 2-cyclopropyl-*N*-[(1*S*,2*S*)-2-methylcyclopropyl]thieno[2,3-*d*]thiazole-5-carboxamide (57 mg, 0.188 mmol, 53% yield) as a brown solid; ¹H NMR (500 MHz, DMSO) δ 8.56 (br. d, *J* = 3.9 Hz, 1H), 7.94 (s, 1H), 2.56 – 2.51 (m, 1H), 1.24 – 1.17 (m, 2H), 1.12 – 1.08 (m, 2H), 1.06 (d, *J* = 6.1 Hz, 3H), 0.96 – 0.90 (m, 1H), 0.74 (ddd, *J* = 9.0, 5.0, 3.8 Hz, 1H), 0.50 (dt, *J* = 7.3, 5.4 Hz, 1H). MS *m/z* [M + H]⁺ = 278.8.

Example 12: *N*-Cyclobutyl-2-cyclopropylthieno[2,3-*d*]thiazole-5-carboxamide



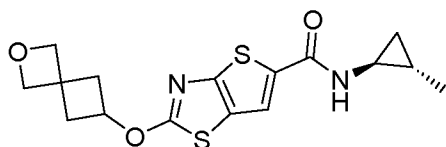
A solution of 2-chloro-*N*-cyclobutylthieno[2,3-*d*]thiazole-5-carboxamide (101 mg, 0.356 mmol, **Intermediate 15b**) and Xantphos Pd G3 (35 mg, 0.036 mmol) in THF (5 mL) at room temperature was degassed with three vacuum/N₂ cycles, then treated with cyclopropylzinc bromide (0.5 M in THF, 1.5 mL, 0.75 mmol) dropwise to give an orange solution. The reaction was stirred at 60 °C for 16 h, cooled to rt, partitioned between water (10 mL) and EtOAc (2 x 25 mL). The combined organic phases were washed with sat. brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-30% EtOAc in DCM) to give product as a purple solid. The solid was then dissolved in ethanol to give a purple solution, treated with activated charcoal and filtered to give a pale yellow solution. The yellow solution was concentrated *in vacuo* to give *N*-Cyclobutyl-2-cyclopropylthieno[2,3-*d*]thiazole-5-carboxamide (75 mg, 0.25 mmol, 69% yield) as a yellow solid; ¹H NMR (400 MHz, DMSO) δ 8.73 (d, *J* = 7.5 Hz, 1H), 8.03 (s, 1H), 4.44 – 4.30 (m, 1H), 2.57 – 2.51 (m, 1H), 2.28 – 2.16 (m, 2H), 2.14 – 1.99 (m, 2H), 1.72 – 1.62 (m, 2H), 1.26 – 1.19 (m, 2H), 1.11 (dt, *J* = 4.7, 3.1 Hz, 2H). MS *m/z* [M + H]⁺ = 279.0.

Example 13: *N*-((1*S*,2*S*)-2-methylcyclopropyl)-2-(oxetan-3-yloxy)thieno[2,3-*d*]thiazole-5-carboxamide



A suspension of sodium hydride (73 mg, 1.83 mmol) in THF (3 mL) at room temperature was added with 3-hydroxyoxetane (140 μ L, 2.20 mmol) and the mixture was stirred at room temperature for 20 minutes to give a precipitate. A solution of 2-chloro-*N*-[(1*S*,2*S*)-2-methylcyclopropyl]thieno[2,3-*d*]thiazole-5-carboxamide (200 mg, 0.73 mmol, **Intermediate 15a**) in THF (2 mL) was added and the mixture was stirred at room temperature. DMF (5 mL) added and the suspension stirred at rt for 5 hours. The reaction was treated with water (25 mL), and EtOAc (25 mL). The phases were partitioned and the aqueous phase was re-extracted with more EtOAc (2 x 25 mL). The combined organic extracts were washed with water (3 x 20 mL) and brine (20 mL), filtered through a plug of Na₂SO₄ in a phase separator and concentrated to give a yellow solid. The crude product was purified by flash chromatography (0-100% EtOAc-heptane) to give desired 2-(oxetan-3-yloxy)-*N*-[(1*S*,2*S*)-2-methylcyclopropyl]thieno[2,3-*d*]thiazole-5-carboxamide (69 mg, 0.218 mmol, 30% yield) as a colourless solid; ¹H NMR (400 MHz, DMSO) δ 8.55 (d, *J* = 3.9 Hz, 1H), 7.89 (s, 1H), 5.82 – 5.72 (m, 1H), 4.93 (ddd, *J* = 7.4, 6.1, 1.1 Hz, 2H), 4.67 (ddd, *J* = 7.9, 4.7, 1.1 Hz, 2H), 2.49 (s, 1H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.93 (ddt, *J* = 12.2, 6.1, 3.2 Hz, 1H), 0.73 (ddd, *J* = 9.0, 5.0, 3.9 Hz, 1H), 0.50 (dt, *J* = 7.4, 5.4 Hz, 1H); HRMS C₁₃H₁₅N₂O₃S₂⁺ calcd. 311.0524, found 311.0522.

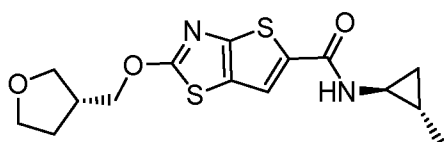
Example 14: 2-((2-Oxaspiro[3.3]heptan-6-yl)oxy)-*N*-((1*S*,2*S*)-2-methylcyclopropyl)thieno[2,3-*d*]thiazole-5-carboxamide



A suspension of sodium hydride (73 mg, 1.83 mmol) in THF (3 mL) at room temperature was treated with 2-oxaspiro[3.3]heptan-6-ol (250 μ L, 2.20 mmol) and the mixture was stirred at room temperature for 20 minutes to give a milky suspension. A solution of 2-chloro-*N*-[(1*S*,2*S*)-2-methylcyclopropyl]thieno[2,3-*d*]thiazole-5-carboxamide (200 mg, 0.73 mmol, **Intermediate 15a**) in THF (3 mL) was added and the mixture was stirred at room temperature for 16 h. The reaction was treated with water (25 mL), and EtOAc (25 mL). The phases were separated, and the aqueous phase was re-extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with water (2 x 20 mL) and brine (20 mL), filtered through a plug of Na₂SO₄ in a phase separator and concentrated *in vacuo* to give a yellow solid. The crude product was purified by

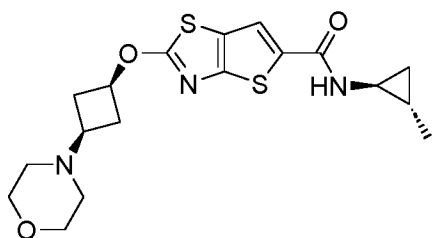
flash chromatography (0-100% EtOAc-heptane) to give desired 2-(2-oxaspiro[3.3]heptan-6-yloxy)-*N*[(1*S*,2*S*)-2-methylcyclopropyl]thieno[2,3-*d*]thiazole-5-carboxamide (141 mg, 0.39 mmol, 54% yield) as an off-white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.51 (s, 1H), 5.96 (br. s, 1H), 5.22 - 5.14 (p, *J* = 7.0 Hz, 1H), 4.77 (s, 2H), 4.72 (s, 2H), 2.95 - 2.88 (m, 2H), 2.60 - 2.55 (m, 1H), 2.51 - 2.44 (m, 2H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.05 - 0.98 (m, 1H), 0.83 - 0.77 (m, 1H), 0.66 (q, *J* = 6.3 Hz, 1H); HRMS C₁₆H₁₉N₂O₃S₂⁺ calcd. 351.0837, found 351.0840.

Example 15: *N*-((1*S*,2*S*)-2-methylcyclopropyl)-2-(((*R*)-tetrahydrofuran-3-yl)methoxy)thieno[2,3-*d*]thiazole-5-carboxamide



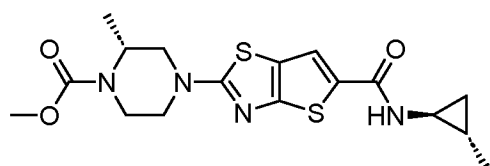
To vial containing sodium hydride (37 mg, 0.92 mmol) in a suspension of DMF (0.5 mL) was added [(3*S*)-tetrahydrofuran-3-yl]methanol (106 μL, 1.10 mmol). The mixture was stirred for 15 min at rt and then a solution of 2-chloro-*N*[(1*S*,2*S*)-2-methylcyclopropyl]thieno[2,3-*d*]thiazole-5-carboxamide (100 mg, 0.37 mmol, **Intermediate 15a**) in DMF (1 mL) was added dropwise. The reaction was stirred for 16 h at rt. The reaction was partitioned between water (10 mL), sat. brine (1 mL), and EtOAc (10 mL). The mixture was shaken and left to settle for 1 h. The organic was then separated and dry-loaded onto silica. The crude product was purified by flash chromatography (30-100% EtOAc in heptanes) to give *N*[(1*S*,2*S*)-2-methylcyclopropyl]-2-[(3*R*)-tetrahydrofuran-3-yl]methoxythieno[2,3-*d*]thiazole-5-carboxamide (35 mg, 0.10 mmol, 27% yield) as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (s, 1H), 5.96 (s, 1H), 4.55 (dd, *J* = 6.6, 10.2 Hz, 1H), 4.47 (dd, *J* = 8.1, 10.2 Hz, 1H), 3.96 - 3.90 (m, 2H), 3.81 (dd, *J* = 15.4, 7.8 Hz, 1H), 3.72 (dd, *J* = 5.2, 9.0 Hz, 1H), 2.88 - 2.81 (m, 1H), 2.61 - 2.55 (m, 1H), 2.20 - 2.10 (m, 1H), 1.80 - 1.71 (m, 1H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.07 - 0.97 (m, 1H), 0.83 - 0.77 (m, 1H), 0.67 (q, *J* = 6.2 Hz, 1H); HRMS C₁₅H₁₉N₂O₃S₂⁺ calcd. 339.0837, found 339.0835.

Example 16: 2-(3-Morpholinocyclobutoxy)-*N*[(1*S*,2*S*)-2-methylcyclopropyl]thieno[2,3-*d*]thiazole-5-carboxamide



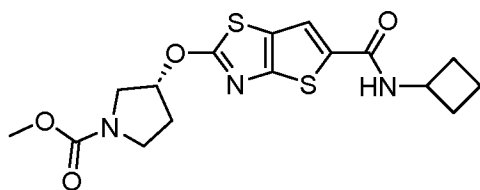
To an oven-dried flask containing a suspension of sodium hydride (94 mg, 2.35 mmol) in THF (2.5 mL) was added a solution of 3-morpholinocyclobutanol (277 mg, 1.76 mmol, **Intermediate 17**) in THF (2.5 mL). The mixture was stirred at rt for 15 min and then a solution of 2-chloro-*N*[(1*S*,2*S*)-2-methylcyclopropyl]thieno[2,3-*d*]thiazole-5-carboxamide (400 mg, 1.47 mmol, **Intermediate 15a**) in THF (5 mL) was added in one portion. The cloudy fine white suspension was stirred for 16 h at rt. The reaction was quenched with sat. NH₄Cl (2 mL) and then concentrated *in vacuo*. The residue was partitioned between 10% MeOH in DCM (40 mL) and water (20 mL). The mixture was separated, and the organic was passed through a hydrophobic frit, dry-loaded onto silica, and purified by flash chromatography (0-10% MeOH in DCM) to elute majority *cis* diastereoisomer (268 mg) and majority trans isomer (60 mg). The majority *cis* diastereoisomer was recrystallised in hot EtOH (12.5 mL) to give 2-(3-morpholinocyclobutoxy)-*N*[(1*S*,2*S*)-2-methylcyclopropyl]thieno[2,3-*d*]thiazole-5-carboxamide (230 mg, 0.58 mmol, 39% yield) as cream coloured crystalline flakes; ¹H NMR (500 MHz, CDCl₃) δ 7.47 (s, 1H), 5.95 (br. s, 1H), 5.09 (p, *J* = 7.5 Hz, 1H), 3.72 (t, *J* = 4.7 Hz, 4H), 2.77 (dt, *J* = 9.1, 7.0, 2.6 Hz, 2H), 2.55 (dq, *J* = 6.8, 3.3 Hz, 1H), 2.50 (tt, *J* = 8.5, 6.7 Hz, 1H), 2.37 (br. s, 4H), 2.19 – 2.09 (m, 2H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.99 (ddt, *J* = 12.3, 6.1, 3.2 Hz, 1H), 0.77 (ddd, *J* = 9.2, 5.5, 3.8 Hz, 1H), 0.64 (dt, *J* = 7.2, 5.8 Hz, 1H); HRMS C₁₈H₂₄N₃O₃S₂⁺ calcd. 394.1259, found 394.1250.

Example 17: Methyl (*R*)-2-methyl-4-(5-(((1*S*,2*S*)-2-methylcyclopropyl)carbamoyl)thieno[2,3-*d*]thiazol-2-yl)piperazine-1-carboxylate



To a fine suspension of *N*[(1*S*,2*S*)-2-methylcyclopropyl]-2-[(3*R*)-3-methylpiperazin-1-yl]thieno[2,3-*d*]thiazole-5-carboxamide (180 mg, 0.54 mmol, **Intermediate 12a**) in DCM (5 mL) at 0 °C was added DIPEA (145 μL, 1.07 mmol) followed by methyl chloroformate (45 μL, 0.58 mmol). The reaction was stirred for 1 h and then quenched with 1 M HCl (3 mL) and passed through a hydrophobic frit. The organic phase was concentrated *in vacuo* and dry-loaded onto silica. The crude product was purified by flash chromatography (0-100% EtOAc in heptanes) to give methyl (*R*)-2-methyl-4-(5-(((1*S*,2*S*)-2-methylcyclopropyl)carbamoyl)thieno[2,3-*d*]thiazol-2-yl)piperazine-1-carboxylate (159 mg, 0.38 mmol, 72% yield) as an off-white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.48 (s, 1H), 5.87 (s, 1H), 4.46 (s, 1H), 4.11 – 3.94 (m, 2H), 3.75 (s, 4H), 3.41 (dd, *J* = 13.0, 4.1 Hz, 1H), 3.36 – 3.26 (m, 1H), 3.19 (td, *J* = 12.1, 3.6 Hz, 1H), 2.54 (dq, *J* = 6.8, 3.3 Hz, 1H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.98 (ddt, *J* = 12.3, 6.2, 3.2 Hz, 1H), 0.76 (ddd, *J* = 9.2, 5.5, 3.8 Hz, 1H), 0.62 (dt, *J* = 7.2, 5.8 Hz, 1H); MS *m/z* [M + H]⁺ = 395.2.

Example 18: Methyl (*R*)-3-((5-(Cyclobutylcarbamoyl)thieno[2,3-*d*]thiazol-2-yl)oxy)pyrrolidine-1-carboxylate



To a suspension of (*R*)-*N*-cyclobutyl-2-(pyrrolidin-3-yloxy)thieno[2,3-*d*]thiazole-5-carboxamide (113 mg, 0.35 mmol, **Intermediate 20b**) and diisopropylethylamine (120 μ L, 0.69 mmol) in DCM (2.5 mL) was added dropwise a solution of methyl chloroformate (0.78 M in DCM, 500 μ L, 0.39 mmol). The reaction was stirred for 1 h and then quenched with 1 M HCl (2 mL) and diluted with more DCM (2.5 mL). The reaction was passed through a phase separator and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-100% EtOAc in heptanes) to give methyl (*R*)-3-((5-(cyclobutylcarbamoyl)thieno[2,3-*d*]thiazol-2-yl)oxy)pyrrolidine-1-carboxylate (41 mg, 0.102 mmol, 29% yield) as an off-white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.51 (s, 1H), 5.97 (d, *J* = 7.8 Hz, 1H), 5.64 (s, 1H), 4.67 – 4.43 (m, 1H), 3.97 – 3.53 (m, 7H), 2.54 – 2.30 (m, 3H), 2.22 (s, 1H), 2.06 – 1.89 (m, 2H), 1.86 – 1.67 (m, 2H); HRMS C₁₆H₂₀N₃O₄S₂⁺ calcd. 382.0890, found 382.0895.

Biological Activity

Assay 1 *Mycobacterium tuberculosis in vitro* H37Rv extracellular inhibition assay (OD readout) (X)

Mtb strain was cultured in Middlebrook 7H9 medium supplemented with 10% ADC and 0,025% Tyloxapol, then incubated at 37 °C for approximately 10 days. Following a purity check, subculture was performed in Middlebrook 7H9 medium supplied with 10% ADC and 0,025% Tyloxapol up to OD (600nm) = 0,01 and incubated at 37°C 4-6 days. By measuring the OD, the inoculum was adjusted to OD (600nm) = 0,00125 that is equivalent to 1x10⁵ cfu/mL.

50ul of the inoculum was dispensed in the 384-well plates. Plates were placed in a sealed box to prevent evaporation and incubated at 37 °C for 8 days. Then the lids were removed, and the plates were covered a seal. Plates were then read by Abs 590 nm in Envision. If the window between negative control with Rifampicin (column 18) and positive control (column 6) was not greater than or equal to 3 times, plates were incubated at 37 °C for one or two additional days and read again.

The results of Assay 1 are provided in Table 1.

Assay 2 *Mycobacterium tuberculosis* in vitro H37Rv in human macrophages THP-1 Inhibition Assay (Intracellular Assay) (1)

Intracellular screening is a valuable tool for identifying new antituberculosis compounds that are active in human macrophages. This *ex-vivo* assay may represent physiological conditions that mimic disease and take into consideration the favorable contribution of host cells.

Procedure was carried out as described in Sorrentino, F. et al. (2016) Antimicrob. Agents Chemother. 60 (1), 640-645 (supplemental material), except that before THP-1 infected cells were seeded in 384 well plates, infected macrophages were filtered in the last step of wash steps with a 40µm cell strainer to remove cell clumps and obtain single cell suspension and the bacteria strain was H37Rv-nanoLuc.

Results of Assay 2 are provided in Table 1.

Assay 3 HepG2 *in vitro* cytotoxicity assay (2, 3)

Actively growing HepG2 cells were removed from a T-175 TC flask using 5 mL Eagle's MEM (containing 10 % FBS, 1 % NEAA, 1 % penicillin/ streptomycin) and dispersed in the medium by >than 50 % confluent at the time of harvesting. Cell suspension was added to 500 µL of the same medium at a final density of 1.2×10^5 cells/mL. This cell suspension was dispensed (25 µL, 3000 cells per well) into 384-well clear-bottom plates using a Multidrop Combi dispenser. Prior to addition of the cell suspension, the screening compounds (250 nL) were pre-dispensed into the plates with an EchoH liquid handler. Plates were incubated for 48 h at 37°C, 5% CO₂. After incubation, plates equilibrated at room temperature for 30 min before proceeding to develop the luminescent signal. The signal developer, CellTiter-GloH Reagent, was allowed to equilibrate at room temperature for 30 min and added to the plates (25 µL per well) using a Multidrop Combi dispenser. Plates were left for 10 min at room temperature for stabilization and then read using a ViewLux.

Results of Assay 3 are provided in Table 1.

Assay 4 Acute *Mycobacterium tuberculosis* in vivo assay (4)

Specific pathogen-free, 8-10 week-old female C57BL/6 mice were purchased from Envigo Laboratories and were allowed to acclimate for one week.

Mice were intratracheally infected with approximately 100,000 CFU/mouse (*Mycobacterium tuberculosis* H37Rv). Moxifloxacin was used as an interassay control. Example 1 and Moxifloxacin were administered once a day via oral from day 1 to day 8 after infection, both included. Moxifloxacin was administered at 30 mg/kg in Captisol 20% and Examples 1 and 3-6 were administered in 1% Methylcellulose at doses from 1 to 300 mg/kg. The volume of administration

was 20 ml/kg. Mice could eat and drink *ad libitum*. Lungs were harvested on day 9 after infection. All lung lobes were aseptically removed, homogenized and frozen. Homogenates were unfrozen and plated in 10% OADC-Middlebrook7H11 medium + 0.4% activated charcoal for 18 days at 37°C.

Blood samples were obtained at different time points from infected mice to measure the blood levels of the tested compounds. Animals were euthanized by CO₂.

All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EU and the GSK Policy on the Care, Welfare and Treatment of Animals.

Results of Assay 4 are provided in Table 2.

Assay 5 Chronic *Mycobacterium tuberculosis* in vivo assay (5)

Example 1 was evaluated in a chronic murine model of infection at 150 and 300 mg/kg as described in Lenaerts, A. J., Gruppo, V., Marietta, K. S., Johnson, C. M., Driscoll, D. K., Tompkins, N. M., Rose, J. D., Reynolds, R. C. & I. M. Orme. 2005. Preclinical testing of the nitroimidazopyran PA-824 for activity against *Mycobacterium tuberculosis* in a series of in vitro and in vivo models. AAC. 49(6):2294-301. Treatment lasted for 4 weeks (dosed 5 days/week) and Example 1 gave a >4 log₁₀ reduction in colony forming units in lung compared to an untreated control.

Results of Assay 5 are provided in Table 2.

Biological Activity conclusion

In light of the results of the above-described extracellular assay 1, intracellular assay 2, cytotoxicity assay 3, acute *in vivo* assay 4 and chronic *in vivo* assay 5, it is concluded that Examples 1-15 exhibit good activity against *Mycobacterium tuberculosis*.

REFERENCES

- 1.- Sorrentino, F. et al. (2016) Antimicrob. Agents Chemother. 60 (1), 640-645.
- 2.- Lilian HJ Richter et al. Toxicol Letters (2019) Vol 301:79-89
- 3.- The use of ATP bioluminescence as a measure of cell proliferation and cytotoxicity. Crouch, S.P. et al. J Immunol Methods. 1993 Mar 15; 160(1):81-8
4. - Rullas, J et al. AAC. 2010 May; 54(5):2262-4.
- 5.- Lenaerts, A. J., Gruppo, V., Marietta, K. S., Johnson, C. M., Driscoll, D. K., Tompkins, N. M., Rose, J. D., Reynolds, R. C. & I. M. Orme.. AAC 2005. 49(6):2294-301

TABLES

Table 1. In vitro activity and cytotoxicity.

	Extracellular Assay			Intramacrophage Assay			Cytotoxicity Assay
Example No.	number of repeats	MIC range (μM)	Mean MIC (μM)	number of repeats	IC90 (μM)	Mean IC90 (μM)	HepG2 Cytotoxicity IC50 (μM)
1	12	1.0-4.0	2.25	6	1.0-2.0	1.4	> 100
2	ND			2	0.6-0.8	0.7	ND
3	6	1.6-7.9	3.44	6	0.5-2.0	0.8	> 100
4	5	1.0-5.0	2.11	4	0.4-0.8	0.6	> 100
5	10	2.0-3.2	2.83	8	0.5-0.8	0.7	> 100
6	6	2.5-5.0	3.40	8	0.8-2.5	1.3	> 100
7	4	1.0-3.2	1.41	4	0.2-0.3	0.3	> 100
8	4	1.0-1.6	1.32	4	0.4-0.6	0.6	> 100
9	2	2.5-3.2	2.75	2	0.5-0.7	0.6	> 100
10	2	2.5-3.2	2.85	2	0.8-0.9	0.8	> 100
11	2	1.3-2.5	1.88	2	0.6-0.6	0.6	> 100
12	2	2.5-3.2	2.72	4	0.3-0.6	0.5	> 100
13	2	1.0-2.0	1.35	2	0.2-0.3	0.3	> 100
14	6	0.5-1.0	0.77	6	0.5-0.7	0.6	> 100
15	6	0.4-1.0	0.63	6	0.3-0.8	0.5	> 100
16	4	0.8-1.0	0.98	4	0.3-0.4	0.3	> 100
17	ND			2	0.5-0.7	0.6	> 100
18	4	0.3-0.8	0.48	6	0.4-0.8	0.5	>100

ND: Not Determined

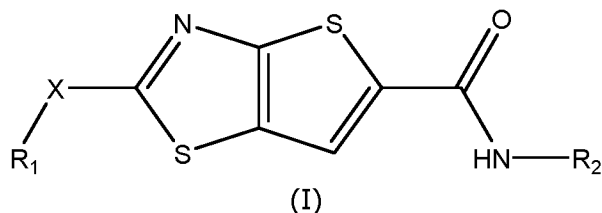
Table 2 In vivo efficacy

Example No.	Acute efficacy study (C57BL/6j mouse)				Chronic efficacy study (Balb/c mouse)
	ED99 (mg/Kg)	AUC _{inf obs} (h*µg/mL) @ ED99	EDmax (mg/kg)	AUC _{inf obs} (h*µg/mL) @ EDmax	
1	33	105.6	88	234.3	> 4 log unit log CFU reduction in lung at 150 and 300 mg/kg
3	26	65.5	61	202.7	ND
4	21	57.1	59	179.8	ND
5	44	55.9	58	73.4	ND
6	25	159.4	62	395.5	ND

ND: Not Determined

Claims

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

R_1 is cyclopropyl which may be halo-substituted;

or R_1 is 4-7-membered heterocyclyl, optionally substituted with one or more of

- (i) C_{1-3} alkyl or C_{1-3} haloalkyl;
- (ii) C_{4-7} heterocyclyl, which may be halo-substituted;
- (iii) $-C(=O)$ -cyclopropyl which cyclopropyl may be halo-substituted;
- (iv) $-C(=O)OR_3$; wherein R_3 is C_{1-3} alkyl;

X is a bond, $-Y(CH_2)_n^*$, or $-Y$ -cyclobutyl-*, wherein Y is $-O-$ or $-S-$ and $*$ represents the point of attachment to R_1 ;

n is 0 or 1 or 2;

R_2 is C_3 -6cycloalkyl, optionally substituted with C_{1-6} alkyl, or C_{1-6} haloalkyl.

2. The compound or pharmaceutically acceptable salt according to claim 1, wherein X is $-Y(CH_2)_n-$ or $-Y$ -cyclobutyl-*.

3. The compound or pharmaceutically acceptable salt according to claim 1 or claim 2, wherein X is $-Y(CH_2)_n-$, Y is $-O-$ and n is 0 or 1.

4. The compound or pharmaceutically acceptable salt according to any of claims 1-3, wherein R_1 is selected from the group consisting of cyclopropyl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, 6-oxa-3-azabicyclo[3.1.1]heptan-3-yl, 2-methyl-morpholin-4-yl, 2,2-dimethyl-morpholin-4-yl, 3-methyl-4-(oxetan-3-yl)piperazin-1-yl, 4-(morpholin-4-yl)piperidin-1-yl, 2-oxaspiro[3.3]heptan-6-yl, tetrahydrofuran-3-yl, morpholin-4-yl, methyl 2-methyl-piperazin-4-yl-1-carboxylate, and methyl pyrrolidin-3-yl-1-carboxylate.

5. The compound or pharmaceutically acceptable salt according to claim 4, wherein $-XR_1$ is selected from the group consisting of cyclopropyl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, 6-oxa-3-azabicyclo[3.1.1]heptan-3-yl, 2-methyl-morpholin-4-yl, 2,2-dimethyl-morpholin-4-yl, 3-methyl-4-

(oxetan-3-yl)piperazin-1-yl, 4-(morpholin-4-yl)piperidin-1-yl, (2-oxaspiro[3.3]heptan-6-yl)oxy, (tetrahydrofuran-3-yl)methoxy, oxetan-3-yloxy, and 4-cyclopropanecarbonyl-3-methyl-piperazin-1-yl, 3-(morpholin-4-yl)cyclobutoxy, methyl 2-methyl-piperazin-4-yl-1-carboxylate, and (methyl pyrrolidin-3-yl-1-carboxylate)oxy.

6. The compound or pharmaceutically acceptable salt according to any of claims 1-5, wherein R₂ is C₃₋₆cycloalkyl optionally substituted with C₁₋₆alkyl, or C₁₋₆haloalkyl.

7. The compound or pharmaceutically acceptable salt according to any of claims 1-5, wherein R₂ is selected from the group consisting of 2-methylcyclopropyl, 3-methylcyclobutyl, 3-difluoromethyl-cyclobutyl cyclobutyl, and spiro[2.3]hexanyl.

8. The compound or pharmaceutically acceptable salt according to claim 6 wherein R₂ is C₃₋₄ cycloalkyl, optionally substituted with methyl.

9. The compound or pharmaceutically acceptable salt according to claim 8 wherein R₂ is selected from the group consisting of 2-methylcyclopropyl, 3-methylcyclobutyl and cyclobutyl.

10. The compound or pharmaceutically acceptable salt according to claim 1, wherein the compound is selected from the group consisting of:

2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-((1S,2S)-2-methylcyclopropyl)thieno[2,3-d]thiazole-5-carboxamide;

2-cyclopropyl-N-((1S,2S)-2-methylcyclopropyl)thieno[2,3-d]thiazole-5-carboxamide;

2-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-N-((1R,3R)-3-(difluoromethyl)cyclobutyl)thieno[2,3-d]thiazole-5-carboxamide;

N-cyclobutyl-2-cyclopropylthieno[2,3-d]thiazole-5-carboxamide;

N-((1S,2S)-2-methylcyclopropyl)-2-((R)-2-methylmorpholino)thieno[2,3-d]thiazole-5-carboxamide;

2-((R)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-N-((1S,2S)-2-methylcyclopropyl)thieno[2,3-d]thiazole-5-carboxamide;

2-(2,2-dimethylmorpholino)-N-((1S,2S)-2-methylcyclopropyl)thieno[2,3-d]thiazole-5-carboxamide;

N-((1S,2S)-2-methylcyclopropyl)-2-(4-morpholinopiperidin-1-yl)thieno[2,3-d]thiazole-5-carboxamide;

2-((R)-3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-N-((1R,3R)-3-methylcyclobutyl)thieno[2,3-d]thiazole-5-carboxamide;

2-((2-oxaspiro[3.3]heptan-6-yl)oxy)-N-((1S,2S)-2-methylcyclopropyl)thieno[2,3-d]thiazole-5-carboxamide;

(R)-2-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-N-(spiro[2.3]hexan-5-yl)thieno[2,3-d]thiazole-5-carboxamide;

N-((1S,2S)-2-methylcyclopropyl)-2-(oxetan-3-yloxy)thieno[2,3-d]thiazole-5-carboxamide;

2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-N-((1S,2S)-2-methylcyclopropyl)thieno[2,3-d]thiazole-5-carboxamide;

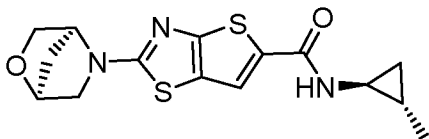
N-((1S,2S)-2-methylcyclopropyl)-2-(((R)-tetrahydrofuran-3-yl)methoxy)thieno[2,3-d]thiazole-5-carboxamide;

N-((1S,2S)-2-methylcyclopropyl)-2-((1S,3R)-3-morpholinocyclobutoxy)thieno[2,3-d]thiazole-5-carboxamide;

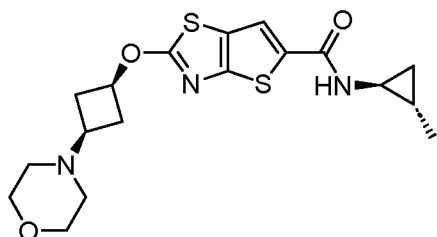
methyl (R)-2-methyl-4-(5-(((1S,2S)-2-methylcyclopropyl)carbonyl)thieno[2,3-d]thiazol-2-yl)piperazine-1-carboxylate; and

methyl (R)-3-((5-(cyclobutylcarbonyl)thieno[2,3-d]thiazol-2-yl)oxy)pyrrolidine-1-carboxylate.

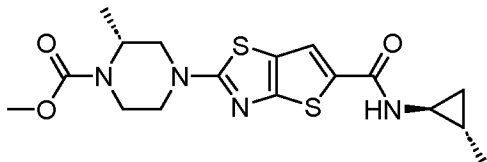
11. The compound or pharmaceutically acceptable salt according to claim 1, wherein the compound is:



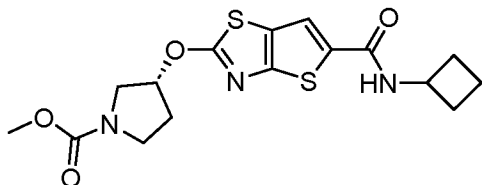
12. The compound or pharmaceutically acceptable salt according to claim 1, wherein the compound is:



13. The compound or pharmaceutically acceptable salt according to claim 1, wherein the compound is:



14. The compound or pharmaceutically acceptable salt according to claim 1, wherein the compound is:



15. A pharmaceutical composition comprising (a) the compound or pharmaceutically acceptable salt thereof according to any of claims 1-14, and (b) a pharmaceutically acceptable excipient.

16. A kit comprising the compound or a pharmaceutically acceptable salt thereof according to any of claims 1-14, or the pharmaceutical composition of claim 15, and instructions for administering to a human in need thereof.

17. A method of treating a mycobacterial infection in a human in need thereof, the method comprising administering to said human a therapeutically effective amount of a compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1-14.

18. A method of treating a disease caused by infection with a mycobacterium in a human in need thereof, the method comprising administering to said human a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1-14.

19. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-14, for use in therapy.

20. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-14, for use in the treatment of a mycobacterial infection.

21. A compound or pharmaceutically acceptable salt thereof for use according to claim 20, wherein the mycobacterial infection is a *Mycobacterium tuberculosis* infection.

22. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-14, for use in the treatment of a disease caused by infection with a mycobacterium.

23. A compound or pharmaceutically acceptable salt thereof for use according to claim 22, wherein the disease is tuberculosis.

24. Use of a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-14, in the manufacture of a medicament for use in the treatment of a mycobacterial infection or a disease caused by infection with a mycobacterium.

25. A combination comprising (a) a compound or pharmaceutically acceptable according to any one of claims 1-14; and (b) at least one other anti-mycobacterial agent.

26. The combination according to claim 25, wherein the at least one other anti-mycobacterial agent is an anti-tuberculosis agent.

27. The combination according to claim 26, wherein the anti-tuberculosis agent is selected from the group consisting of: isoniazid, rifampin, pyrazinamide, ethambutol, rifapentine, clofazimine, ethionamide, prothionamide, isoxyl, thiacetazone, rifabutin, 4-aminosalicylic acid, cycloserine, spectinamide 1810, a fluoroquinolone such as moxifloxacin, gatifloxacin or levofloxacin; a diarylquinoline such as bedaquiline or TBAJ-587 or TBAJ-876; nitroimidazo-oxazine PA-824, delamanid, an oxazolidinone such as linezolid, tedizolid, radezolid, sutezolid (PNU-100480), posizolid, Delpazolid or TBI-223; SPR720, EMB analogue SQ109, OPC-167832, telacebec, spectinamide 1810, GSK3036656, GSK2556286, GSK3211830, GSK3778839, GSK3729098, GSK3653038, a benzothiazinone such as BTZ043 or macozinone; an azaindole such as TBA-7371, a dihyrdocarbostyryl derivative such as OPC-167832; a dinitrobenzamide, a beta-lactam such as meropenem, faropenem, ertapenem, tebipenem, sanfetrinem; a beta-lactam combination such as amoxicillin-clavulanate, or an aminoglycoside such as kanamycin, amikacin, capreomycin or streptomycin.

28. The combination according to claim 27, wherein the anti-tuberculosis agent is selected from the group consisting of: isoniazid, rifampin, pyrazinamide, ethambutol, moxifloxacin, rifapentine, clofazimine, ethionamide, prothionamide, isoxyl, thiacetazone, bedaquiline, TBAJ-587, nitroimidazo-oxazine PA-824, delamanid, linezolid, tedizolid, radezolid, sutezolid, posizolid, TBI-223, EMB analogue SQ109, OPC-167832, GSK3036656, GSK2556286, GSK3211830, BTZ043, PBTZ169, TBA-7371, a dinitrobenzamide, a beta-lactam, meropenem, faropenem, ertapenem, tebipenem, beta-lactam combinations, and amoxicillin-clavulanate.

29. The combination according to any one of claims 25-28, further comprising an antiviral agent.

30. The combination according to claim 29, wherein the antiviral agent is an antiretroviral agent selected from the group consisting of: abacavir, atazanavir, bictegravir, cabotegravir, darunavir, delavirdine, didanosine, dideoxyinosine, dolutegravir, doravirine, efavirenz, elvitegravir, emtricitabine, etavirine, fosamprenavir, fostemsavir, indinavir, slatravir, lamivudine, lopinavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpiverine, ritonavir, saquinavir, stavudine, tipranavir, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, zalcitabine, and zidovudine.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2024/066402

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D513/04 A61K31/381 A61P31/06 C07D519/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 3 157 904 B1 (PASTEUR INSTITUT KOREA [KR]) 18 November 2020 (2020-11-18) claims 1-11; examples 1-360 -----	1 - 30
A	JIN GUANGHAI ET AL: "Discovery of thienothiazolocarboxamide analogues as novel anti-tubercular agent", BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 28, no. 23, 3 October 2020 (2020-10-03), XP086403207, ISSN: 0968-0896, DOI: 10.1016/J.BMC.2020.115797 [retrieved on 2020-10-03] examples 18-23 -----	1 - 30



Further documents are listed in the continuation of Box C.



See patent family annex.

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"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 September 2024

Date of mailing of the international search report

30/09/2024

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/066402

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 3157904	B1	18-11-2020	CN	107027307 A		08-08-2017
			EP	3157904 A1		26-04-2017
			JP	2017518339 A		06-07-2017
			KR	20170030535 A		17-03-2017
			PH	12016502436 A1		06-03-2017
			US	2017121349 A1		04-05-2017
			US	2022153756 A1		19-05-2022
			WO	2015193506 A1		23-12-2015
