THIADIAZOLES AS GLUTAMINASE 1 INHIBITORS

Field of the invention

The present invention relates to compounds and their use in treating or preventing fibrotic and/or inflammatory diseases, particularly those of the lung, and to related compositions, methods and intermediate compounds.

Background of the invention

Glutaminase 1 (GLS1) is a metabolic enzyme which catalyses the conversion of glutamine to glutamate. Glutamate is a central metabolite in many pathways including synthesis of α-ketoglutarate, the TCA cycle, glutathione synthesis and protein synthesis.

Many tumour cells are reliant on glutamine for their growth and survival, and this has led to the discovery of allosteric inhibitors of GLS1 for the treatment of cancer (Zimmermann et. al. 2019). The first reported allosteric inhibitor was bis-2-[5-(phenyl-acetamido)-1,3,4-thiadiazol-2-yl]ethyl sulfide (BPTES) and following its discovery many inhibitors derived from BPTES have been identified including CB-839, which entered clinical trials in 2014. More recently the recognition of the role of GLS1 in fibrosis, in senescent cell survival and in TH17 mediated inflammation has demonstrated a therapeutic potential for a GLS1 inhibitor in the treatment of chronic lung diseases. GLS1 has been shown to regulate the profibrotic activity of myofibroblasts (Ge et al. 2018). In particular, in idiopathic pulmonary fibrosis, the GLS1 inhibitor CB-839 has also shown efficacy in mouse models of pulmonary fibrosis induced by Bleomycin or TGF-β1 (Cui et al. 2019). GLS1 has a role in TH17 cell differentiation and function (Kono et al. 2018) and is elevated in TH17 cells isolated from human and mice. Human senescent cells rely on glutaminase 1 for their survival and inhibition of glutaminase 1 has a senolytic effect (Johmura et al. 2021). A GLS1 inhibitor is a potential therapy for lung diseases where senescent cells and/or TH17 mediated inflammation contribute to the pathology, such as in COPD (Cottage et al. 2019) or asthma (Contreras Healey et al. 2021).

GLS1 inhibitors may be useful for the treatment of other lung diseases such as pulmonary hypertension where increased GLS1 expression is observed in lungs of human pulmonary arterial hypertension (PAH) patients, and the GLS1 inhibitor CB-839 can decrease endothelial growth, vessel thickening and right ventricular pressure in monocrataline induced rat PAH models (Bertero et al. 2016).

A GLS1 inhibitor also has a therapeutic potential in lung cancer, as GLS1 is the rate limiting enzyme for growth in cancer cell lines sensitive to glutamine (Enyu et al. 2022). GLS1 inhibitors could also augment radiation treatments to lung cancer patients by enhancement of radiation-induced cell death (Fujimoto et al. 2022).

GLS1 inhibitors may be useful as antiviral agents as glutamine metabolism has been demonstrated to be increased in virus-infected host cells with glutamine required for viral replication (Hirabara et al. 2021). Glutamine metabolism has been shown to be impacted in infections of respiratory viruses such as SARS-CoV-2 (Bharadwaj et al. 2021), influenza (Janke et al. 2011) and HRSV (Lu et al. 2023) demonstrating a relevance for a GLS1 inhibitor as an antiviral agent in the lung.

A GLS1 inhibitor may also provide a therapy in other diseases where fibrosis, inflammation or accumulation of senescent cells contribute to the pathology such as long covid, radiation induced fibrosis, non-alcoholic steatohepatitis diabetes, non-alcoholic fatty liver disease/Cirrhosis, chronic kidney disease, osteoporosis, osteoarthritis and obesity, asthma, psoriasis, psoriatic arthritis, hidradenitis suppurativa, rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease and retinal vasculopathies such as diabetic macular edema, diabetic retinopathy and dry and neovascular age-related macular degeneration (WO2022/251370, Unity Biotechnology, Inc.).

For diseases of the lung such as interstitial lung diseases including idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), lung cancer, radiation induced fibrosis, pulmonary hypertension, asthma, respiratory viral infection and long covid, an inhaled GLS1 inhibitor may be preferable to administer to the target organ while minimising systemic exposure. An ideal inhaled candidate will have high cellular potency, good retention of the compound in the respiratory tract and low oral bioavailability (Pasqua et al, 2022). Furthermore for nebulised delivery the compound must have high aqueous solubility, and high solution stability.

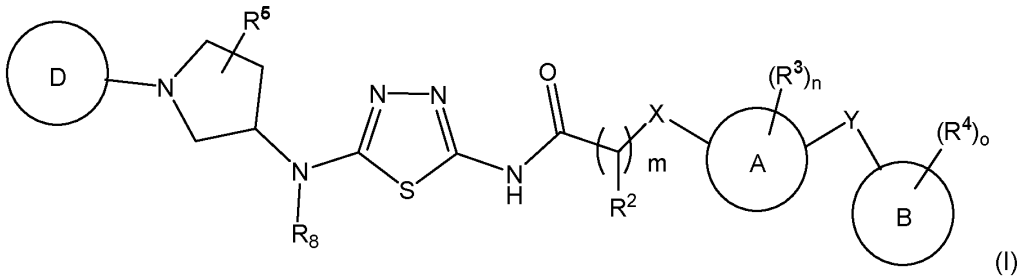
A number of GLS1 inhibitors are disclosed in Zhang et al. (2019), WO2015/181539 and WO2017/093301 (both from AstraZeneca and Cancer Research Technology). In particular, WO2015/181539 and WO2017/093301 disclose compounds which are known to epimerise which is not desirable for drug development. In addition, the compounds disclosed in WO'539 and WO'301 do not exhibit retention in the lung.

Furthermore, WO2024/233839 (Leal Therapeutics, Inc.) discloses compounds which are said to be inhibitors of glutaminase (GLS1).

There remains a need to identify and develop GLS1 inhibitors with acceptable or improved potency compared with known compounds, which do not epimerise, which have an improved duration in the lung and which have improved solubility compared to compounds known in the art.

Summary of the invention

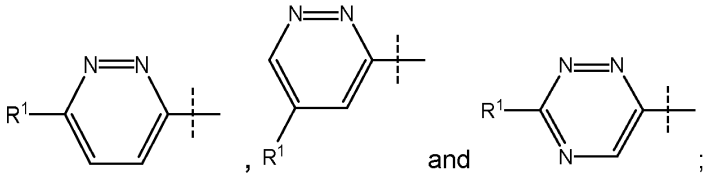
The present invention provides a compound of formula (I):



(I)

wherein:

D is selected from the group consisting of:



;

wherein R^1 is selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl and NH_2;

R^2 is selected from the group consisting of H, C_{1-4} alkyl, C_{1-4} alkoxy, $NR^{2a}R^{2b}$ and C_{0-3}alkyleneC_{3-6}cycloalkyl;

wherein: R^{2a} is independently H or C_{1-3}alkyl;

R^{2b} is independently H or C_{1-3}alkyl;

each R^3 is independently selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and C_{1-4} haloalkoxy;

each R^4 is independently selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CO_2R^{4a}, SC_{1-4}alkyl, OC_{0-3}alkyleneC_{3-6}cycloalkyl and C_{0-3}alkyleneC_{3-6}cycloalkyl wherein the C_{3-6}cycloalkyl is optionally substituted by one or two R^{4b}, or when ring B is phenyl two R^4 groups which are attached to adjacent carbon atoms join to form a C_{4-7}cycloalkyl ring;

wherein: R^{4a} is independently H or C_{1-3}alkyl;

R^{4b} is independently halo or C_{1-3}alkyl;

R^5 is H or halo;

A is selected from the group consisting of 4-10 membered heterocyclyl, 6-11 membered heterospirocycloalkyl and C_{3-6}cycloalkyl;

B is selected from the group consisting of phenyl, C_{5-10}cycloalkyl, 4-7 membered heterocyclyl, 4-10 membered heteroaryl and C_{6-11} spirocycloalkyl;

X is either absent or is selected from the group consisting of O, S and NR^6C_{1-4}alkylene;

wherein R^6 is independently H or C_{1-3}alkyl;

Y is either absent or is selected from the group consisting of O, S, C_{1-4}alkylene and NR^7C_{1-4}alkylene, wherein the C_{1-4}alkylene group is optionally substituted by one or more R^9;

wherein R^7 is independently H or C_{1-3}alkyl;

R^8 is independently H or C_{1-3}alkyl;

R^9 is independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} alkoxy and $NR^{2a}R^{2b}$;

m is 0, 1 or 2;

n is 0, 1 or 2; and

o is 0, 1, 2, 3 or 4;

wherein:

when B is phenyl, o is 1, 2, 3 or 4;

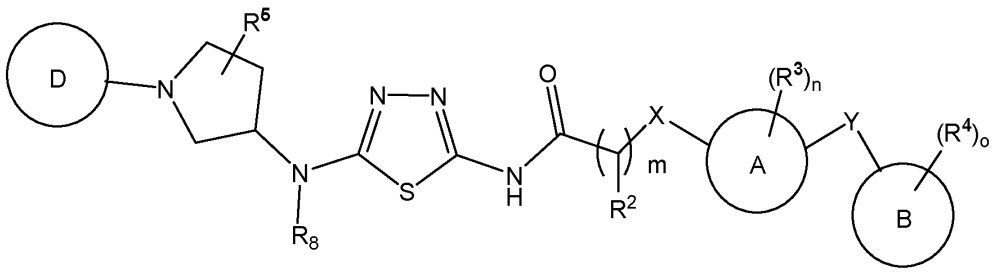
or a salt and/or solvate thereof.

Detailed description of the invention

Compounds of formula (I)

Embodiments and preferences set out herein with respect to the compound of formula (I) apply equally to the pharmaceutical composition, compound or pharmaceutically acceptable salt and/or solvate thereof for use, pharmaceutical composition for use, use and method aspects of the invention, as well as intermediates used in the synthesis of the compounds of formula (I). Embodiments and preferences set out herein with respect to the compound of formula (I) also apply equally to the compounds of formulae (IA), (IB), (IC), (ID), (IE) and (IF).

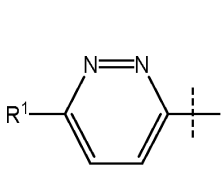
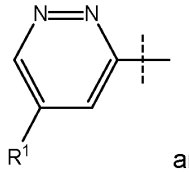
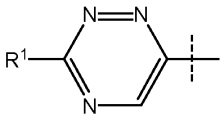
The present invention also provides a compound of formula (IB):



(IB)

wherein:

D is selected from the group consisting of:


, 
and 
;

wherein R^1 is selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl and NH_2;

R^2 is selected from the group consisting of H, C_{1-4} alkyl, C_{1-4} alkoxy, $NR^{2a}R^{2b}$ and C_{0-3}alkyleneC_{3-6}cycloalkyl;

wherein: R^{2a} is independently H or C_{1-3}alkyl;

R^{2b} is independently H or C_{1-3}alkyl;

R^3 is selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and C_{1-4} haloalkoxy;

R^4 is selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CO_2R^{4a}, SC_{1-4}alkyl, OC_{0-3}alkyleneC_{3-6}Cycloalkyl and C_{0-3}alkyleneC_{3-6}Cycloalkyl wherein the C_{3-6}Cycloalkyl is optionally substituted by one or two R^{4b};

wherein: R^{4a} is independently H or C_{1-3}alkyl;

R^{4b} is independently halo or C_{1-3}alkyl;

R^5 is H or halo;

A is selected from the group consisting of 4-10 membered heterocyclyl, 6-11 membered heterospirocycloalkyl and C_{3-6}cycloalkyl;

B is selected from the group consisting of phenyl, C_{5-10}cycloalkyl, 4-7 membered heterocyclyl, 4-10 membered heteroaryl and C_{6-11} spirocycloalkyl;

X is either absent or is selected from the group consisting of O, S and NR^6C_{1-4}alkylene;

wherein R^6 is independently H or C_{1-3}alkyl;

Y is either absent or is selected from the group consisting of O, S, C_{1-4}alkylene and NR^7C_{1-4}alkylene;

wherein R^7 is independently H or C_{1-3}alkyl;

R^8 is independently H or C_{1-3}alkyl;

m is 0, 1 or 2;

n is 0, 1 or 2; and

o is 0, 1, 2, 3 or 4;

or a salt and/or solvate thereof.

The term “alkyl”, such as “C_{1-4} alkyl or “C_{1-3} alkyl” refers to a straight or branched fully saturated

hydrocarbon group having the specified number of carbon atoms. The term encompasses methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. The term "alkyl" also encompasses "alkylene", such as C_{1-4}alkylene or C_{0-3}alkylene which is a bifunctional straight or branched fully saturated hydrocarbon group having a specified number of carbon atoms. Example "alkylene" groups include methylene, ethylene, n-propylene and n-butylene.

The term "alkoxy" refers to an alkyl group, such as "C_{1-4} alkyl" as defined above, singularly bonded via an oxygen atom. Examples of alkoxy groups include OCH_3.

The term "halo" refers to fluoro, chloro, bromo or iodo. Particular examples of halo are fluoro and chloro, especially fluoro.

The term "haloalkyl", such as "C_{1-3} haloalkyl" or "C_{1-2} haloalkyl" as used herein refers to a straight or a branched fully saturated hydrocarbon chain containing the specified number of carbon atoms and at least one halogen atom, such as fluoro or chloro, especially fluoro. An example of haloalkyl is CF_3. Further examples of haloalkyl are CHF_2 and CH_2CF_3.

The term "haloalkoxy" refers to a haloalkyl group, such as "C_{1-4} haloalkyl", as defined above, singularly bonded via an oxygen atom. Examples of haloalkoxy groups include OCF_3, $OCHF_2$ and OCH_2CF_3.

The term "hydroxy" (which may also be referred to as "hydroxyl") refers to an -OH group.

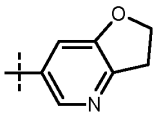
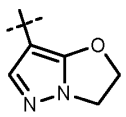
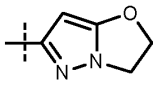
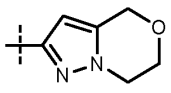
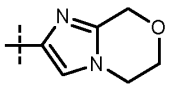
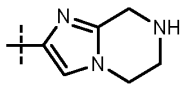
The term "cycloalkyl", such as "C_{5-10} cycloalkyl", "C_{3-6}cycloalkyl", or "C_{4-7}cycloalkyl", refers to a fully saturated cyclic hydrocarbon group having the specified number of carbon atoms. The term encompasses cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl as well as bridged systems such as bicyclo[1.1.1]pentyl, bicyclo[2.2.1]heptyl, bicyclo[4.1.0]heptyl bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl and adamantyl. Particularly preferred groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. In certain circumstances as defined herein, the cycloalkyl ring may be fused to a phenyl ring via two carbon atoms that are shared by the cycloalkyl and phenyl rings.

The term "spirocycloalkyl" such as C_{6-12} spirocycloalkyl, refers to a bicyclic cycloalkyl group wherein the two rings are connected through just one atom. The rings can be different or identical in ring atom number. The term encompasses spiro[3.3]heptyl, spiro[2.5]octyl, spiro[3.5]nonyl, spiro[4.5]decyl, spiro[5.5]undecane.

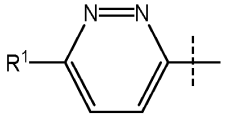
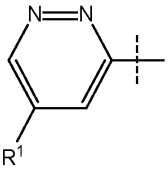
The term “heterocyclyl”, such as “4-7 membered heterocyclyl” or “4-10 membered heterocyclyl”, refers to a non-aromatic cyclic group having the specified number of ring atoms and wherein at least one of the ring atoms is a heteroatom selected from N, O, S and B. The term “heterocyclic ring” is interchangeable with “heterocyclyl”. The term encompasses oxetanyl, thietanyl, azetidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl.

The term "heterospirocycloalkyl" such as 6-11 membered heterospirocycloalkyl, means a bicyclic, saturated heterocycle with 6, 7, 8, 9, 10 or 11 ring atoms in total, in which the two rings share one common ring carbon atom, which "heterospirocycloalkyl" contains one or two identical or different ring heteroatoms from the series: N, O, S; it being possible for said heterospirocycloalkyl group to be attached to the rest of the compound via any one of the carbon atoms, except the spiro carbon atom. Said heterospirocycloalkyl group is, for example 8-azaspiro[4.5]decane or 2,6-diazaspiro[3.4]octane.

The term “heteroaryl” or “heteroaryl ring”, such as “4-10 membered heteroaryl” refers to a cyclic group with aromatic character having the specified number of ring atoms, at least one of which is a heteroatom independently selected from N, O and S. For example, “4-10 membered heteroaryl” has 4-10 ring atoms. The term encompasses pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, dioxazolyl, dithiazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, quinolinyl, isoquinolinyl, naphthyridinyl, quinolizinyl, quinoxalinyl, phthalazinyl, quinazolinyl and cinnolinyl as well as groups having a ring which is not aromatic in character, such as:

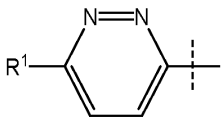

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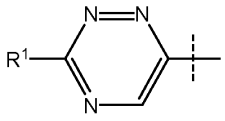
wherein ⊣⊢ indicates the bond via which the heteroaryl is attached to the rest of the molecule.

In some suitable compounds of formula (I), D is

or

wherein

represents the point of connection to the remainder of the compound comprising the D

group.

In other suitable compounds of formula (I), D is  wherein  represents the point of connection to the remainder of the compound comprising the D group.

In other suitable compounds of formula (I) D is  wherein  represents the point of connection to the remainder of the compound comprising the D group.

In some suitable compounds of formula (I), R^1 is H. In other suitable compounds of formula (I), R^1 is halo such as chloro. In other suitable compounds of formula (I), R^1 is C_{1-4} alkyl. In other suitable compounds of formula (I), R^1 is C_{1-4} haloalkyl. In other suitable compounds of formula (I), R^1 is NH_2.

In some suitable compounds of formula (I), R^2 is H. In other suitable compounds of formula (I), R^2 is C_{1-4} alkyl. In other suitable compounds of formula (I), R^2 is methyl or ethyl. In other suitable compounds of formula (I), R^2 is C_{1-4} alkoxy. In other suitable compounds of formula (I), R^2 is OCH_3. In other suitable compounds of formula (I), R^2 is $NR^{2a}R^{2b}$ wherein R^{2a} and R^{2b} are independently C_{1-3} alkyl or H. In other suitable compounds of formula (I), R^2 is $N(CH_3)_2$. In other suitable compounds of formula (I), R^2 is C_{0-3} alkyleneC_{3-6}cycloalkyl. In other suitable compounds of formula (I), R^2 is cyclopropyl or cyclobutyl.

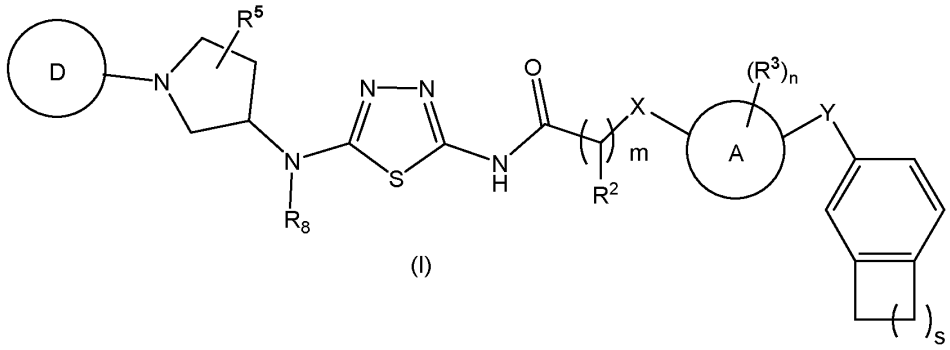
In some suitable compounds of formula (I), R^{2a} is H. In other suitable compounds of formula (I), R^{2a} is C_{1-3}alkyl. In some suitable compounds of formula (I), R^{2b} is H. In other suitable compounds of formula (I), R^{2b} is C_{1-3}alkyl.

In some suitable compounds of formula (I) both R^1 and R^2 are H.

In some suitable compounds of formula (I), R^2 is H or C_{1-4} alkyl e.g. methyl.

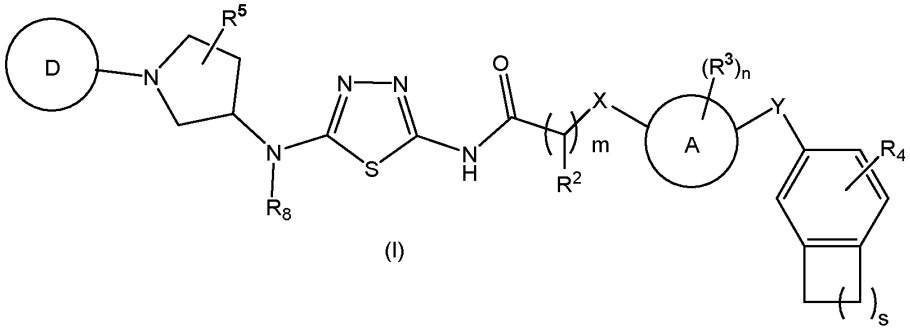
In some suitable compounds of formula (I), R^3 is halo e.g., fluoro. In other suitable compounds of formula (I), R^3 is hydroxy. In other suitable compounds of formula (I), R^3 is C_{1-4} alkyl e.g., methyl, ethyl or isopropyl. In other suitable compounds of formula (I), R^3 is C_{1-4} alkoxy. In other suitable compounds of formula (I), R^3 is C_{1-4} haloalkyl e.g. CF_3. In other suitable compounds of formula (I), R^3 is C_{1-4} haloalkoxy e.g. OCF_3.

In some suitable compounds of formula (I), R^4 is halo e.g. fluoro. In other suitable compounds of formula (I), R^4 is hydroxy. In other suitable compounds of formula (I), R^4 is C_{1-4} alkyl e.g. methyl, ethyl or isopropyl. In other suitable compounds of formula (I), R^4 is C_{1-4} alkoxy e.g. $OCH(CH_3)_2$. In other suitable compounds of formula (I), R^4 is C_{1-4} haloalkyl e.g. CF_3. In other suitable compounds of formula (I), R^4 is C_{1-4} haloalkoxy e.g. OCF_3. In other suitable compounds of formula (I), R^4 is CO_2R^{4a}. In other suitable compounds of formula (I), R^4 is SC_{1-3}alkyl e.g. $SCH(CH_3)_2$. In other suitable compounds of formula (I), R^4 is OC_{0-3}alkyleneC_{3-6}cycloalkyl e.g. Ocyclobutyl or Ocyclopentyl. In other suitable compounds of formula (I), R^4 is C_{0-3}alkyleneC_{3-6}cycloalkyl. In some suitable compounds, such as when ring B is phenyl, two R^4 groups which are attached to adjacent carbon atoms join to form a C_{4-7}cycloalkyl ring, such as a C_5cycloalkyl ring. In such suitable compounds, for example compounds of formula (I) are formed:



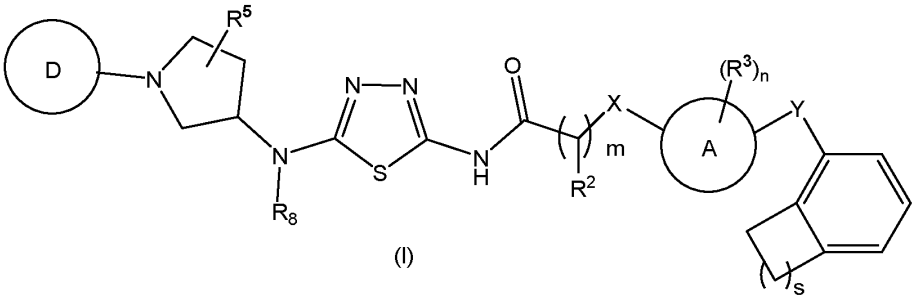
(I)

wherein s is 1, 2, 3 or 4, such that a fused C_4cycloalkyl, C_5cycloalkyl, C_6cycloalkyl or C_7cycloalkyl ring forms respectively. Suitably s is 2. Ring B may be further substituted by other R^4 groups as defined herein e.g. Ring B may be substituted by one further R^4 group:



(I)

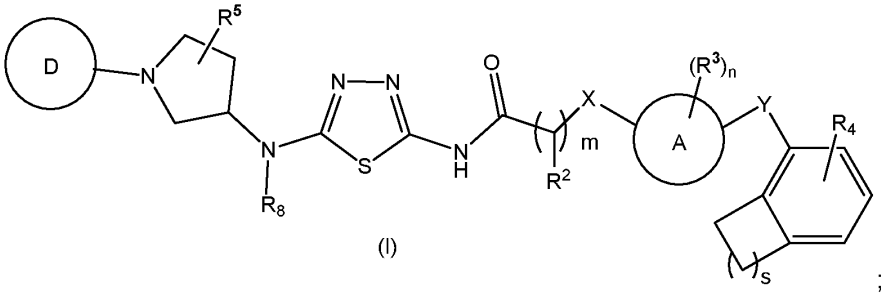
Alternatively, compounds of the formula (I) may form:



(I)

;

such as:



(I)

;

wherein s is defined above.

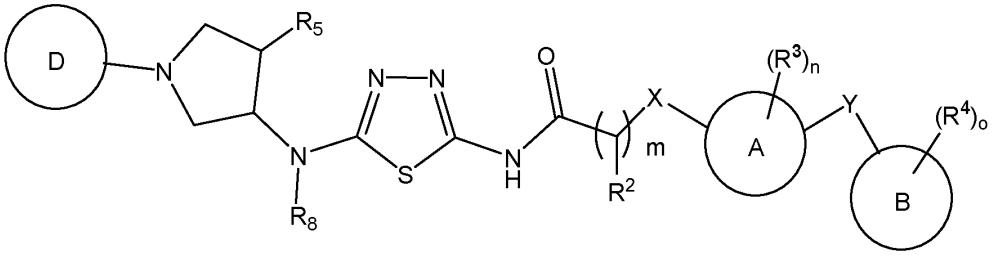
In some suitable compounds of formula (I), R^{4a} is H. In other suitable compounds of formula (I), R^{4a} is C_{1-3}alkyl e.g. methyl.

In some suitable compounds of formula (I), R^{4b} is halo e.g. F. In other suitable compounds of formula (I), R^{4b} is C_{1-3}alkyl e.g. methyl. In some suitable compounds of formula (I), the C_{3-6}cycloalkyl group of R^4 is not substituted. In other suitable compounds of formula (I), the C_{3-6}cycloalkyl group of R^4 is substituted by one or two (e.g. two) R^{4b}.

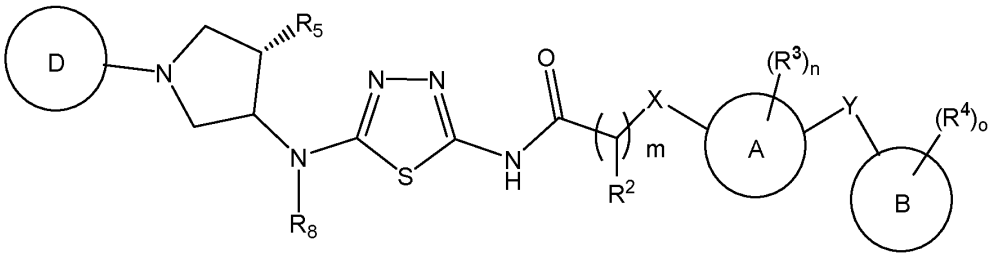
In some suitable compounds of formula (I), R^4 is selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and C_{1-4} haloalkoxy.

In some suitable compounds of formula (I), R^5 is H. In other suitable compounds of formula, R^5 is halo such as fluoro. It will be clear to the skilled person that R^5 may be attached to any carbon atom in the pyrrolidinyl ring.

Suitably, R^5 is attached to the carbon atom as shown below:



More suitably, the stereochemistry of the carbon atom to which R^5 is attached is:



In some suitable compounds of formula (I), both R^1 and R^5 are H.

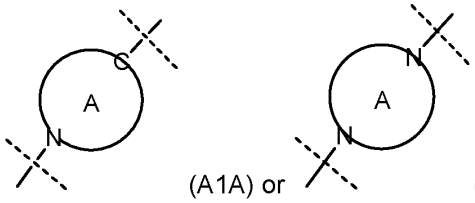
In some suitable compounds of formula (I) R^1, R^2 and R^5 are all H.

In some suitable compounds of formula (I), A is selected from 4-10 membered heterocyclyl, 6-11 membered heterospirocycloalkyl and C_{3-4}cycloalkyl.

In some suitable compounds of formula (I), A is selected from 4-10 membered heterocyclyl and 6-11 membered heterospirocycloalkyl.

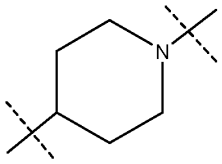
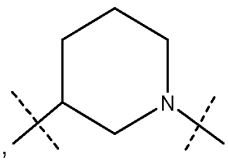
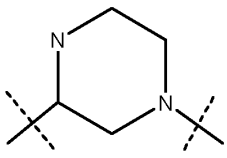
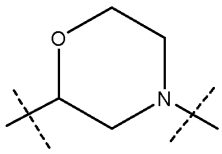
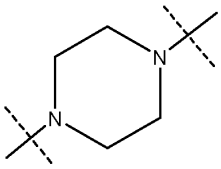
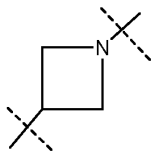
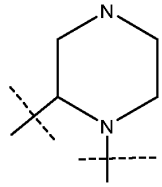
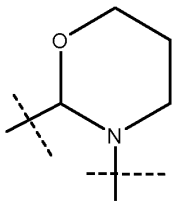
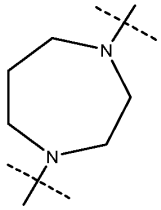
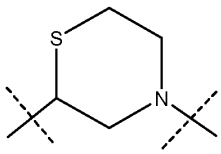
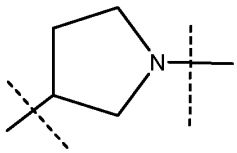
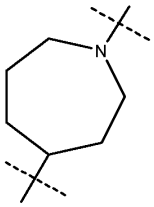
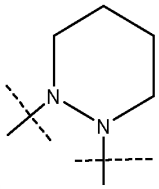
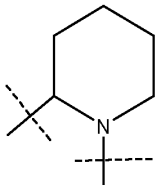
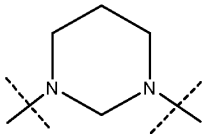
In some suitable compounds of formula (I), A is 4-10 membered heterocyclyl.

In some suitable compounds of formula (I), A is a 4-10 membered heterocyclyl wherein the heterocyclyl ring is C, N linked e.g. as per (A1A) or N, N linked e.g. as per (A1B)

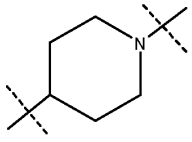
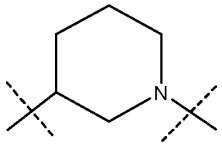
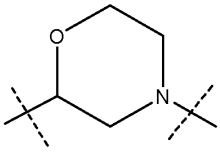


(A1A) or (A1B), wherein  represents the point of connection to the remainder of the compound comprising the heterocyclyl group.

In other suitable compounds of formula (I), A is selected from the group consisting of:

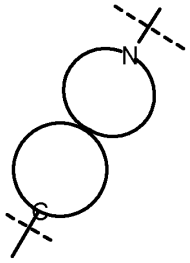
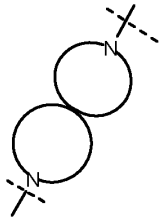

(A1C),

(A1D),

(A1E),

(A1F),

(A1G),

(A1H),

(A1I),

(A1J),

(A1K),

(A1L),

(A1M),

(A1N),

(A1O),

(A1P), or

(A1Q).

wherein  represents the point of connection to the remainder of the compound comprising the heterocyclyl group.

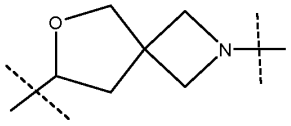
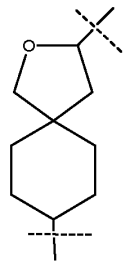
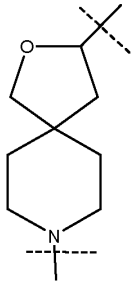
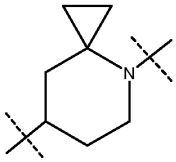
Most suitably (A) is selected from the group consisting of  (AIC),  (A1D) or,  (A1F) wherein  represents the point of connection to the remainder of the compound comprising the heterocyclyl group.

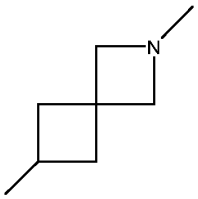
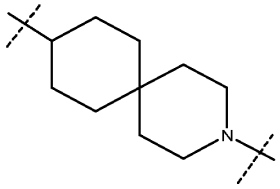
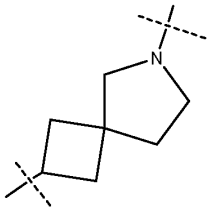
In some suitable compounds of formula (I), A is 6-11 membered heterospirocycloalkyl.

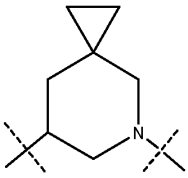
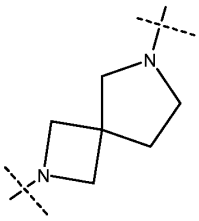
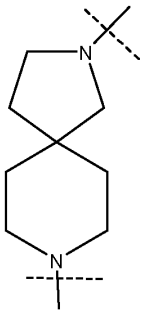
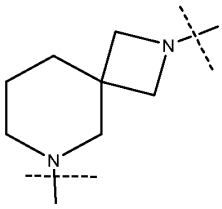
In some suitable compounds of formula (I), A is a 6-11 membered heterospirocycloalkyl wherein both rings are either C, N linked e.g. as per (A2A) or N, N linked e.g. as per (A2B)

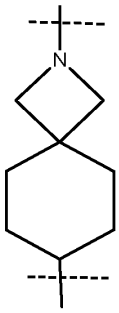
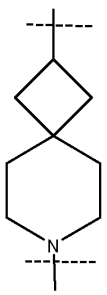
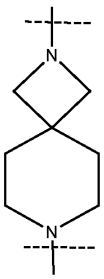

(A2A) 
(A2B) wherein  represents the point of connection to the remainder of the compound comprising the heterospirocycloalkyl group.

In some suitable compounds of formula (I), A is selected from the group consisting of

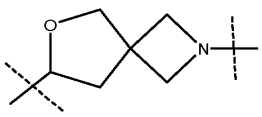
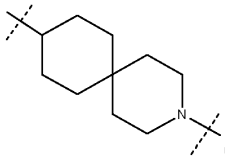
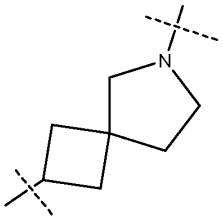

(A2C), 
(A2D), 
(A2E), 
(A2F),


(A2G), 
(A2H), 
(A2I),


(A2J), 
(A2K), 
(A2L), 
(A2M),

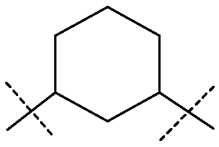

(A2N), 
, 
(A2O) or (A2P) wherein  represents the point of connection to the remainder of the compound comprising the heterospirocycloalkyl group.

In some suitable compounds of formula (I), A is selected from the group consisting of

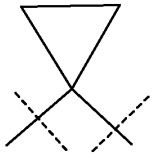
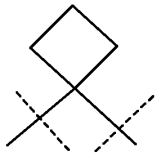

(A2C)

(A2H) or

(A2I).

wherein  represents the point of connection to the remainder of the compound comprising the heterospirocycloalkyl group.

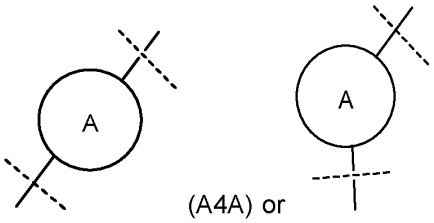
In some suitable compounds of formula (I), A is C_{3-6}cycloalkyl. In other suitable compounds of formula (I), A is cyclohexyl.

In other suitable compounds of formula (I), A is  (A3A) wherein  represents the point of connection to the remainder of the compound comprising the cycloalkyl group.

In other suitable compounds of formula (I), A is C_{3-6}cycloalkyl which is directly bonded to the carbon backbone e.g. where X is absent and m is 1 such as:


(A3B) or

(A3C), wherein  represents the point of connection to the remainder of the compound comprising the cycloalkyl group.

In some suitable compounds of formula (I) in group A, the points of connection to the remainder of the compound comprising A, are either in the meta e.g. as per (A4B) or para position e.g. as per (A4A) relative to each other. In other suitable compounds of formula (I), in group A, the points of connection to the remainder of the compound comprising A, are in the para position e.g. as per (A4A) relative to each other.



(A4A) or (A4B), wherein represents the point of connection to the remainder of the compound comprising the heterocyclyl group.

In some suitable compounds of formula (I), B is selected from the group consisting of phenyl, C_{5-10}cycloalkyl and 4-10 membered heteroaryl. The phenyl is substituted as defined elsewhere herein (i.e. o is 1, 2, 3 or 4) and the C_{5-10}cycloalkyl and 4-10 membered heteroaryl are optionally substituted as defined elsewhere herein (i.e. o is 0, 1, 2, 3 or 4). In other suitable compounds of formula (I), B is phenyl or 4-10 membered heteroaryl. The phenyl is substituted as defined elsewhere herein (i.e. o is 1, 2, 3 or 4) and the 4-10 membered heteroaryl is optionally substituted as defined elsewhere herein (i.e. o is 0, 1, 2, 3 or 4). In other suitable compounds of formula (I), B is selected from the group consisting of phenyl, C_{5-6}cycloalkyl and 5-6 membered heteroaryl. The phenyl is substituted as defined elsewhere herein (i.e. o is 1, 2, 3 or 4) and the C_{5-6}cycloalkyl and 5-6 membered heteroaryl are optionally substituted as defined elsewhere herein (i.e. o is 0, 1, 2, 3 or 4). Most suitably B is selected from the group consisting of phenyl, cyclohexyl and pyridine. The phenyl is substituted as defined elsewhere herein (i.e. o is 1, 2, 3 or 4) and the cyclohexyl and pyridine are optionally substituted as defined elsewhere herein (i.e. o is 0, 1, 2, 3 or 4).

In some suitable compounds of formula (I), B is phenyl. In some suitable compounds of formula (I), B is phenyl which is substituted by one, two, three or four R^4 groups (i.e. o is 1, 2, 3 or 4), such as one or two R^4 groups (i.e. o is 1 or 2). In other suitable compounds of formula (I), phenyl is substituted by one R^4 (i.e. o is 1). In other suitable compounds of formula (I), phenyl is substituted by two R^4 (i.e. o is 2). In other suitable compounds of formula (I), phenyl is substituted by three R^4 (i.e. o is 3). In other suitable compounds of formula (I), phenyl is substituted by four R^4 (i.e. o is 4). When B is phenyl, two R^4 groups which are attached to adjacent carbon atoms may join to form a C_{4-7}cycloalkyl ring, as defined above.

In other suitable compounds of formula (I), B is C_{5-10}cycloalkyl. In other suitable compounds of formula (I), B is C_{3-6}cycloalkyl. In other suitable compounds of formula (I), B is cyclopropyl or cyclohexyl. In other suitable compounds of formula (I), B is cyclohexyl.

In some suitable compounds of formula (I), C_{5-10}cycloalkyl is not substituted (i.e. o is 0). In other suitable compounds of formula (I), C_{5-10}cycloalkyl is substituted by one R^4 (i.e. o is 1). In other

suitable compounds of formula (I), C_{5-10}cycloalkyl is substituted by two R^4 (i.e. o is 2). In other suitable compounds of formula (I), C_{5-10}cycloalkyl is substituted by three R^4 (i.e. o is 3). In other suitable compounds of formula (I), C_{5-10}cycloalkyl is substituted by four R^4 (i.e. o is 4).

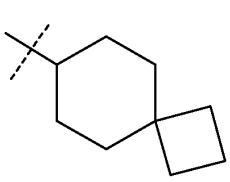
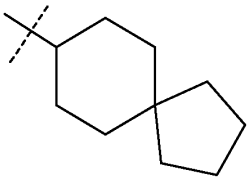
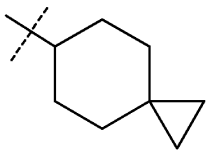
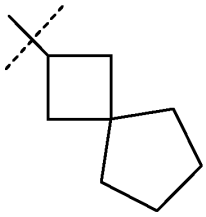
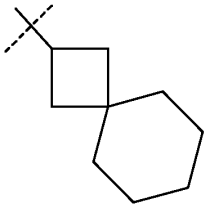
In other suitable compounds of formula (I), B is 4-7 membered heterocyclyl. In other suitable compounds of formula (I), B is a 6 membered heterocyclyl. In other suitable compounds of formula (I), B is piperidine.

In some suitable compounds of formula (I), 4-7 membered heterocyclyl is not substituted (i.e. o is 0). In other suitable compounds of formula (I), 4-7 membered heterocyclyl is substituted by one R^4 (i.e. o is 1). In other suitable compounds of formula (I), 4-7 membered heterocyclyl is substituted by two R^4 (i.e. o is 2). In other suitable compounds of formula (I), 4-7 membered heterocyclyl is substituted by three R^4 (i.e. o is 3). In other suitable compounds of formula (I), 4-7 membered heterocyclyl is substituted by four R^4 (i.e. o is 4).

In other suitable compounds of formula (I), B is 4-10 membered heteroaryl. In other suitable compounds of formula (I), B is a 5-6 membered heteroaryl. In other suitable compounds of formula (I), B is pyridine.

In some suitable compounds of formula (I), 4-10 membered heteroaryl is not substituted (i.e. o is 0). In other suitable compounds of formula (I), 4-10 membered heteroaryl is substituted by one R^4 (i.e. o is 1). In other suitable compounds of formula (I), 4-10 membered heteroaryl is substituted by two R^4 (i.e. o is 2). In other suitable compounds of formula (I), 4-10 membered heteroaryl is substituted by three R^4 (i.e. o is 3). In other suitable compounds of formula (I), 4-10 membered heteroaryl is substituted by four R^4 (i.e. o is 4).

In some suitable compounds of formula (I), B is C_{6-12}spirocycloalkyl. In other suitable compounds of formula (I), B is selected from the group consisting of:


(B1A),

(B1B),

(BIC)

(B1D) or

(B1E) wherein

represents the point of connection to the remainder of the compound comprising the spirocycloalkyl group.

In some suitable compounds of formula (I), C_{6-12}spirocycloalkyl is not substituted (i.e. o is 0). In other suitable compounds of formula (I), C_{6-12}spirocycloalkyl is substituted by one R^4 (i.e. o is 1). In other suitable compounds of formula (I), C_{6-12}spirocycloalkyl is substituted by two R^4 (i.e. o is 2). In other suitable compounds of formula (I), C_{6-12}spirocycloalkyl is substituted by three R^4 (i.e. o is 3). In other suitable compounds of formula (I), C_{6-12}spirocycloalkyl is substituted by four R^4 (i.e. o is 4).

In some suitable compounds of formula (I), X is absent. In other suitable compounds of formula (I), X is O. In other suitable compounds of formula (I), X is S. In other suitable compounds of formula (I), X is NR^6C_{1-4}alkylene e.g. NR^6C_1alkylene.

In some suitable compounds of formula (I), R^6 is H. In other suitable compounds of formula (I), R^6 is C_{1-3}alkyl. In other suitable compounds of formula (I), R^6 is methyl.

In some suitable compounds of formula (I) Y is absent. In some suitable compounds of formula (I), Y is O. In some suitable compounds of formula (I), Y is S. In some suitable compounds of formula (I), Y is C_{1-4}alkylene such as C_1alkylene. In some suitable compounds of formula (I) Y is NR^7C_{1-4}alkylene such as NR^7C_1alkylene.

In any of the above suitable compounds, the C_{1-4}alkylene of Y (such as when Y is C_{1-4}alkylene or NR^7C_{1-4}alkylene) is optionally substituted by one or more such as one, two, three or four e.g. one R^9. In some suitable compounds, the C_{1-4}alkylene group is not substituted by R^9. In other suitable compounds, the C_{1-4}alkylene group is substituted by one or more such as one, two, three or four e.g. one R^9.

In some suitable compounds of formula (I), R^7 is H. In other suitable compounds of formula (I), R^7 is C_{1-3}alkyl. In other suitable compounds of formula (I), R^7 is methyl.

In some suitable compounds of formula (I), X is absent and Y is C_{1-4}alkylene. In other suitable compounds of formula (I), X and Y are both absent.

Most suitably in compounds of formula (I), X is absent and Y is $-CH_2-$.

In some suitable compounds of formula (I), R^8 is H. In other suitable compounds of formula (I), R^8 is C_{1-4} alkyl. In other suitable compounds of formula (I), R^8 is methyl.

In some suitable compounds of formula (I), R^9 is halo. In other suitable compounds of formula (I), R^9 is C_{1-4} alkyl e.g. methyl. In other suitable compounds of formula (I), R^9 is C_{1-4} alkoxy e.g. methoxy. In other suitable compounds of formula (I), R^9 is $NR^{2a}R^{2b}$ wherein R^{2a} and R^{2b} are defined elsewhere herein.

Most suitably in compounds of formula (I), R^1, R^2, R^5 and R^8 are all H.

In some suitable compounds of formula (I), m is 0. In other suitable compounds of formula (I), m is 1. In other suitable compounds of formula (I), m is 2. Most suitably, m is 1.

When m is 0, R^2 is absent.

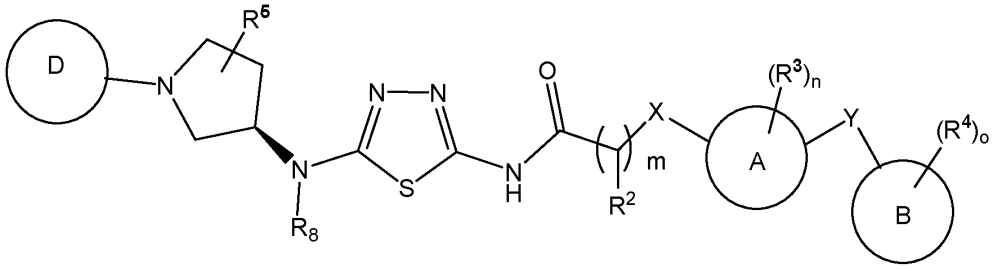
In some suitable compounds of formula (I), n is 0. In other suitable compounds of formula (I), n is 1. In other suitable compounds of formula (I), n is 2. In other suitable compounds of formula (I), n is 0 or 1. Most suitably, n is 0.

In some suitable compounds of formula (I), o is 0. In other suitable compounds of formula (I), o is 1. In other suitable compounds of formula (I), o is 2. In other suitable compounds of formula (I), o is 3. In other suitable compounds of formula (I), o is 4. Most suitably, o is 1 or 2.

In some suitable compounds of formula (I), n is 0 and m is 0. In other suitable compounds of formula (I), n is 0 and m is 1.

Most suitably in compounds of formula (I), n is 0 and o is 1 or 2. Most suitably in compounds of formula (I), n is 0 and B is substituted by 1 or 2 R^4 groups.

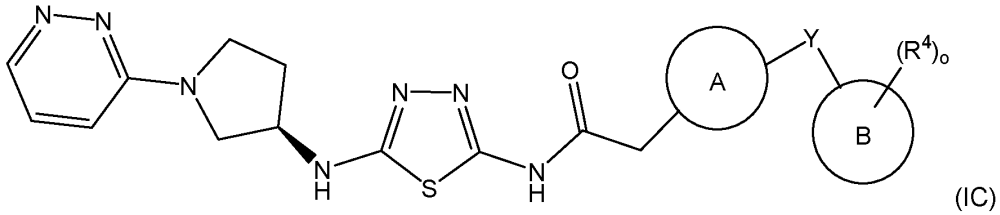
In some suitable compounds, the compound is a compound of formula (IA):



(IA)

wherein R^2, R^3, R^4, R^4, R^5, R^8, m, n, o, X, Y, A, B and D are as defined elsewhere herein; or a salt and/or solvate thereof.

In some suitable compounds there is provided a compound of formula (IC):



(IC)

wherein:

R^4 is selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CO_2R^{4a}, SC_{1-4}alkyl, OC_{0-3}alkyleneC_{3-6}cycloalkyl and C_{0-3}alkyleneC_{3-6}cycloalkyl wherein the C_{3-6}cycloalkyl is optionally substituted by one or two R^{4b};

wherein: R^{4a} is independently H or C_{1-3}alkyl;

R^{4b} is independently halo or C_{1-3}alkyl;

A is selected from the group consisting of 4-10 membered heterocyclyl, 6-11 membered heterospirocycloalkyl and C_{3-6}cycloalkyl;

B is selected from the group consisting of phenyl, C_{5-10}cycloalkyl, 4-7 membered heterocyclyl, 4-10 membered heteroaryl and C_{6-11} spirocycloalkyl;

Y is either absent or is selected from the group consisting of O, S, C_{1-4}alkylene and NR^7C_{1-4}alkylene;

wherein R^7 is independently H or C_{1-3}alkyl; and

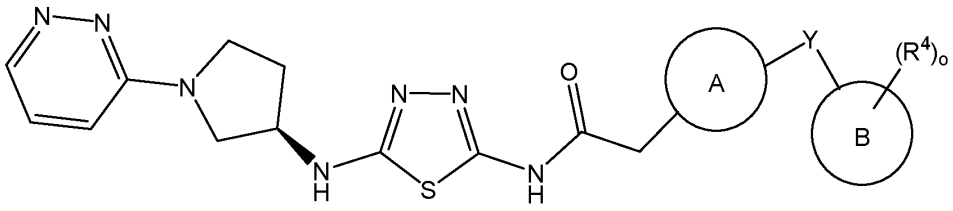
o is 0, 1, 2, 3 or 4;

wherein:

when B is phenyl, o is 1, 2, 3 or 4;

or a salt and/or solvate thereof.

In some suitable compounds there is provided a compound of formula (ID):



(ID)

wherein:

R^4 is selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CO_2R^{4a}, SC_{1-4}alkyl, OC_{0-3}alkyleneC_{3-6}cycloalkyl and C_{0-3}alkyleneC_{3-6}cycloalkyl wherein the C_{3-6}cycloalkyl is optionally substituted by one or two R^{4b};

wherein: R^{4a} is independently H or C_{1-3}alkyl;

R^{4b} is independently halo or C_{1-3}alkyl;

A is 4-10 membered heterocyclyl;

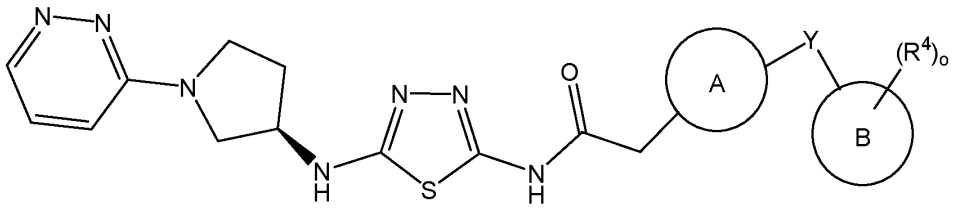
B is phenyl;

Y is C_{1-4}alkylene; and

o is 1, 2, 3 or 4;

or a salt and/or solvate thereof.

In some suitable compounds there is provided a compound of formula (IE):



(IE)

wherein:

R^4 is selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and C_{1-4} haloalkoxy;

A is 4-10 membered heterocyclyl;

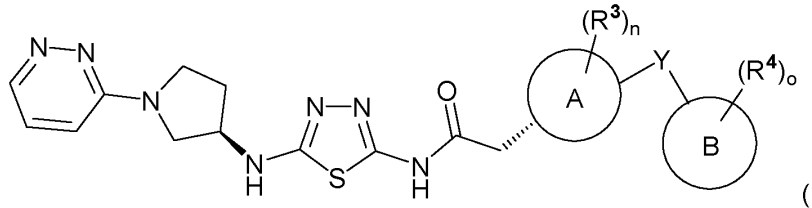
B is phenyl;

Y is C_{1-4}alkylene; and

o is 1 or 2;

or a salt and/or solvate thereof.

In some suitable compounds there is provided a compound of formula (IF):



(IF);

wherein:

A is 4-10 membered heterocyclyl, wherein A is attached via a carbon ring atom to the -C(H)CH_2C(=O)NH- moiety; and

Y, B, R_3, R_4, n and o are as defined herein.

Suitably, in such suitable compounds, A is a 6 membered heterocyclyl.

In one embodiment there is provided a compound of formula (I), which is selected from any one of Examples 1 to 291, or a salt and/or solvate thereof.

In one embodiment there is provided a compound of formula (I), which is selected from the list consisting of:

(*R*)-3-(4-((2-isopropoxyphenyl)thio)piperidin-1-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;

(*R*)-2-(1-(methyl(3-(trifluoromethoxy)benzyl)amino)cyclobutyl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(*R*)-3-(4-((3,5-difluorophenyl)thio)piperidin-1-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;

(*R*)-3-(4-(2-isopropoxyphenyl)piperidin-1-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;

(*R*)-2-(2-(2-(isopropylthio)benzyl)-2,6-diazaspiro[3.4]octan-6-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(4-(2-methylbenzyl)thiomorpholin-2-yl)-*N*-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(*R*)-2-(2-(3,5-dimethylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(*R*)-2-(2-(2-(isopropylthio)benzyl)-2,8-diazaspiro[4.5]decan-8-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamate;

2-{1-[(4-methoxy-3,5-dimethylphenyl)methyl]piperidin-4-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(4-{[4-(trifluoromethoxy)phenyl]methyl}piperazin-1-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetamide;

(3*R*)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-1-{[4-(trifluoromethoxy) phenyl]methyl}piperidine-3-carboxamide;

(3*S*)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-1-{[4-(trifluoromethoxy) phenyl]methyl}piperidine-3-carboxamide;

(3*S*)-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-1-{[3-(trifluoromethoxy) phenyl]methyl}piperidine-3-carboxamide;

(3*R*)-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-1-{[3-(trifluoromethoxy) phenyl]methyl}piperidine-3-carboxamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*S*)-1-{[3-(trifluoromethoxy)phenyl] methyl}piperidin-3-yl]acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)propanamide;

(*R*)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)propanamide;

(*S*)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)propanamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3R)-1-{[4-(trifluoromethoxy)phenyl] methyl}piperidin-3-yl]acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*R*)-1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-3-yl]acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3S)-1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-3-yl]acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[5-(trifluoromethyl)pyridin-3-yl]methyl}piperidin-4-yl)propanamide;

2-(4-methyl-1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(4-{[4-(trifluoromethoxy)phenyl]methyl}-1,4-diazepan-1-yl)acetamide

2-(4-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperazin-1-yl)-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-{3-benzyl-3-azaspiro[5.5]undecan-9-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(1-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(1-{[6-methyl-4-(trifluoromethyl)pyridin-2-yl]methyl}piperidin-4-yl)-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-{1-[(3,5-dimethylphenyl)methyl]piperidin-4-yl}-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-{[3-(difluoromethoxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*R*,5*S*)-3,5-dimethyl-4-{[4-(trifluoromethoxy)phenyl]methyl}piperazin-1-yl]-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

3-[(4-{[(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamoyl]methyl}piperidin-1-yl)methyl]benzoic acid;

4-[(4-{[(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamoyl]methyl}piperidin-1-yl)methyl]benzoic acid;

2-(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(dimethylamino)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetamide;

2-(1-{[4-(difluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*R*)-1-{[3-(trifluoromethoxy)phenyl]methyl}pyrrolidin-3-yl]acetamide;

2-[(3*S*)-1-[(4,4-dimethylcyclohexyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*S*)-1-{[3-(trifluoromethoxy)phenyl]methyl} pyrrolidin-3-yl]acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(5-{[5-(trifluoromethyl)pyridin-3-yl]methyl}-5-azaspiro[2.5]octan-7-yl)acetamide;

2-(5-{[5-methoxy-6-(trifluoromethyl)pyridin-2-yl]methyl}-5-azaspiro[2.5]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)sulfanyl]acetamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)sulfanyl]acetamide;
2-[(3*S*)-1-[(3-chlorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-(6-{[3-(difluoromethoxy)phenyl]methyl}-6-azaspiro[3.4]octan-2-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{3-[(4,6-dimethylpyridin-2-yl)methyl]-3-azaspiro[5.5]undecan-9-yl}-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{4-[(4,4-dimethylcyclohexyl)methyl]piperazin-1-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-{1-[(3,3,5,5-tetramethylcyclohexyl)methyl] piperidin-4-yl}acetamide;
2-(2-{[3-(difluoromethoxy)phenyl]methyl}-2-azaspiro[3.3]heptan-6-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{1-[(4,4-dimethylcyclohexyl)methyl]piperidin-4-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
3-(1-{[3-(difluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)propanamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-8-{[3-(trifluoromethoxy)phenyl]methyl}-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-{4-[(3,3,5,5-tetramethylcyclohexyl)methyl]piperazin-1-yl}acetamide;
2-{1-[methyl({[3-(trifluoromethoxy)phenyl]methyl})amino]cyclopropyl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-(1-{[4-hydroxy-3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{1-[(2-chlorophenyl)methyl]piperidin-4-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-(4-methyl-1-{[3-(trifluoromethoxy)phenyl]methyl}piperazin-2-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-4-methyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*R*)-4-methyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-methoxy-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[4-(trifluoromethoxy)phenyl] methyl}piperidin-4-yl)acetamide;
(*R*)-2-methoxy-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)acetamide;
(*S*)-2-methoxy-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)acetamide;
4-[(4,4-dimethylcyclohexyl)methyl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)thiomorpholine-2-carboxamide;
2-{4-[(4,4-dimethylcyclohexyl)methyl]morpholin-2-yl}-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-((*R*)-4-((4,4-dimethylcyclohexyl)methyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-4-((4,4-dimethylcyclohexyl)methyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-(1-{[3-(propan-2-yloxy)pyridin-2-yl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[3-(trifluoromethoxy)phenyl]methyl}azetidin-3-yl)acetamide;
2-(1-{[2-(difluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-(4-{[3-(propan-2-yloxy)pyridin-2-yl]methyl}-4-azaspiro[2.5]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-({1-[(3,5-dimethylphenyl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(2-{[3-(trifluoromethoxy)phenyl]methyl}-6-oxa-2-azaspiro[3.4]octan-7-yl)acetamide;
N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-2-(3-(trifluoromethoxy)benzyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)acetamide;
N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-2-(3-(trifluoromethoxy)benzyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)acetamide;
2-(2-{[3-(difluoromethoxy)phenyl]methyl}-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-(2,2-dimethyl-1-{[3-(propan-2-yloxy)pyridin-2-yl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-(2-{[2-(cyclopentyloxy)phenyl]methyl}-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-[(2-cyclobutoxyphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-{[2-(cyclopentyloxy)phenyl] methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-({1-[(2-cyclobutoxyphenyl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(4-cyclohexylmorpholin-2-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-{[2-(3,3-difluorocyclobutoxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(4-cyclopentylmorpholin-2-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(2-{[2-(propan-2-ylsulfanyl)phenyl]methyl}-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide

2-(1-{[(4,4-dimethylcyclohexyl)methyl] (methyl)amino}cyclopropyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(4-hydroxy-1-{[2-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-{4-[(4,4-dimethylcyclohexyl)methyl]-1,4-diazepan-1-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-({1-[(3-tert-butyl-1,2-oxazol-5-yl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-{2-[(4,4-dimethylcyclohexyl)methyl]-6-oxa-2-azaspiro[3.4]octan-7-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-((*R*)-2-((4,4-dimethylcyclohexyl)methyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-2-((4,4-dimethylcyclohexyl)methyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[(1-{[2-(propan-2-yloxy)phenyl] methyl}piperidin-3-yl)sulfanyl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(((*R*)-1-(2-isopropoxybenzyl)piperidin-3-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(((*S*)-1-(2-isopropoxybenzyl)piperidin-3-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[(1-{[2-(methylsulfanyl)phenyl]methyl}piperidin-3-yl)oxy]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(((*R*)-1-(2-(methylthio)benzyl)piperidin-3-yl)oxy)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(((*S*)-1-(2-(methylthio)benzyl)piperidin-3-yl)oxy)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[(1-{[2-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-3-yl)oxy]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(((*R*)-1-(2-(isopropylthio)benzyl)piperidin-3-yl)oxy)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(((*S*)-1-(2-(isopropylthio)benzyl)piperidin-3-yl)oxy)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[4-(4,4-dimethylcyclohexyl)morpholin-2-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-4-(4,4-dimethylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*R*)-4-(4,4-dimethylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[(2-{[2-(propan-2-yloxy)phenyl]methyl}-2-azaspiro[3.3]heptan-6-yl)sulfanyl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-[(3,5-dimethylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-4-yl)sulfanyl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)butanamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-{4-[(1s,4s)-4-tert-butylcyclohexyl]morpholin-2-yl}acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-{4-[(1r,4r)-4-tert-butylcyclohexyl]morpholin-2-yl}acetamide;

2-[(3*S*)-1-[(4-ethyl-2-fluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[4-(3,3,4,4-tetramethylcyclopentyl)morpholin-2-yl]acetamide;

2-[(3*R*)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-[(4-fluoro-3,5-dimethylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-[(3-fluoro-5-methylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-[(4-fluoro-3-methoxy-5-methylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(4-ethoxy-3,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-{[3-fluoro-5-(propan-2-yloxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{3-[(5-ethyl-3-methyl-1,2-oxazol-4-yl)methyl]-3-azaspiro[5.5]undecan-9-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-{[3-methyl-5-(propan-2-yloxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{4-[(1*S*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]morpholin-2-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{(*R*)-4-[(1*S*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]morpholin-2-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{(*S*)-4-[(1*S*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]morpholin-2-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(3-ethoxy-4,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(3-fluoro-5-methoxy-4-methylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-{[3-(difluoromethoxy)-5-methylphenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(2-ethyl-1-benzofuran-3-yl)methyl]piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(3-fluoro-4,5-dimethylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(*3R)*-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(2,5-dimethylthiophen-3-yl)methyl]piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-({1-[(2,5-dimethylthiophen-3-yl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{methyl[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[4-(4,4-dimethylcyclohexyl)morpholin-2-yl]-*N*-(5-{methyl[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[4-(4,4-dimethylcyclohexyl)piperazin-1-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-({1-[(1-tert-butyl-1H-pyrrol-3-yl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-({1-[(1-tert-butyl-1H-pyrazol-4-yl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[4-(3,3,5,5-tetramethylcyclohexyl)piperazin-1-yl]acetamide;

N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(4-{spiro[4.5]decan-8-yl}piperazin-1-yl)acetamide;

2-(4,4-difluoro-1-{spiro[2.5]octan-6-yl}piperidin-3-yl)-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(1-cyclohexyl-4,4-difluoropiperidin-3-yl)-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[1-(4,4-dimethylcyclohexyl)-4,4-difluoropiperidin-3-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[4-(4,4-diethylcyclohexyl)morpholin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-((R)-4-(4,4-diethylcyclohexyl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((S)-4-(4,4-diethylcyclohexyl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-(((R)-1-(1,2,4-triazin-6-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(4,4-dimethylcyclohexyl)morpholin-2-yl)acetamide;

N-(5-{[(3R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3S)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]acetamide;

2-[4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(*R*)-4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(*S*)-4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(1-cycloheptyl-4,4-difluoropiperidin-3-yl)-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

isopropyl (R)-4-((4-(2-oxo-2-((5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)piperidin-1-yl)methyl)benzoate;

isopropyl (R)-3-((4-(2-oxo-2-((5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)piperidin-1-yl)methyl)benzoate;

(R)-2-(1-(3-methyl-5-(trifluoromethoxy)benzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(2,4,6-trimethylbenzyl)piperidin-4-yl)acetamide;
(R)-2-(1-(2-methyl-4-(trifluoromethoxy)benzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(1-(3-methyl-4-(trifluoromethyl)benzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-((5-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)acetamide;
(R)-2-(1-((5-methoxy-6-(trifluoromethyl)pyridin-2-yl)methyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((S)-1-(3-methyl-5-(trifluoromethoxy)benzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(1-(3-(difluoromethoxy)-5-methylbenzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
isobutyl (R)-4-((4-(2-oxo-2-((5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)piperidin-1-yl)methyl)picolinate;
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(2-(trifluoromethoxy)benzyl)piperidin-4-yl)acetamide;
(R)-2-(1-(4-fluoro-2-(trifluoromethoxy)benzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(1-(2-(difluoromethoxy)-5-methylbenzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(1-(2-(isopropylthio)benzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-((1-(2-isopropoxybenzyl)piperidin-4-yl)thio)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(1-(3-isopropoxybenzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(1-(2-cyclobutoxybenzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(1-(2-isopropoxy-4-methylbenzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(2-(3-(difluoromethoxy)benzyl)-2-azaspiro[3.5]nonan-7-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(2-(3-(trifluoromethoxy)benzyl)-2-azaspiro[3.3]heptan-6-yl)acetamide;
2-((S)-1-(2-isopropoxybenzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((R)-1-(2-isopropoxybenzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((S)-1-(2-isopropoxyphenethyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((R)-1-(2-isopropoxyphenethyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
8-(3,5-dimethylbenzyl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
8-(2-isopropoxybenzyl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
(R)-2-(3-((6-(difluoromethyl)pyridin-3-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(3-((5-(trifluoromethyl)pyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)acetamide;
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(3-((2,4,6-trimethylpyridin-3-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)acetamide;
(R)-2-(3-((5-chloropyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(3-((5-bromopyridin-3-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(6-(3-(trifluoromethoxy)benzyl)-6-azaspiro[3.4]octan-2-yl)acetamide;
N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((2r,4R)-6-(3-(trifluoromethoxy)benzyl)-6-azaspiro[3.4]octan-2-yl)acetamide;
N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((2s,4S)-6-(3-(trifluoromethoxy)benzyl)-6-azaspiro[3.4]octan-2-yl)acetamide;
(R)-2-(6-(3-(difluoromethoxy)-5-methylbenzyl)-6-azaspiro[3.4]octan-2-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(6-(2-isopropoxy-4-methylbenzyl)-6-azaspiro[3.4]octan-2-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((2r,4R)-6-(2-isopropoxy-4-methylbenzyl)-6-azaspiro[3.4]octan-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((2s,4S)-6-(2-isopropoxy-4-methylbenzyl)-6-azaspiro[3.4]octan-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

8-(3-(difluoromethoxy)benzyl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;

(*R*)-8-(3-(difluoromethoxy)benzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;

(*S*)-8-(3-(difluoromethoxy)benzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;

(R)-2-(3-((3-cyclobutoxypyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(1-(3,5-dimethylbenzyl)piperidin-4-yl)-2-methoxy-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(1-(2-cyclobutoxybenzyl)piperidin-4-yl)-2-methoxy-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(1-(2-(isopropylthio)benzyl)piperidin-4-yl)-2-methoxy-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(3-((5-chloropyridin-3-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(3-((4-bromopyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(3-((5-bromopyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(4-ethyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*R*)-4-ethyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-4-ethyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(1-(2-isopropoxybenzyl)piperidin-4-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide;

(*R*)-2-(1-(2-isopropoxybenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide;

(*S*)-2-(1-(2-isopropoxybenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide;

(R)-3-(1-(2-isopropoxybenzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;

(R)-2-((1-(2-(isopropylthio)benzyl)piperidin-4-yl)oxy)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
8-(2-cyclobutoxybenzyl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
(*R*)-8-(2-cyclobutoxybenzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
(*S*)-8-(2-cyclobutoxybenzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
2-((*R*)-2-(2-(isopropylthio)benzyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-2-(2-(isopropylthio)benzyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-cyclobutyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(*R*)-2-cyclobutyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(*S*)-2-cyclobutyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
3-cyclopropyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;
(*R*)-3-cyclopropyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;
(*S*)-3-cyclopropyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;
3-methyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide;
(*R*)-3-methyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide;
(*S*)-3-methyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide;
2-(4-cyclohexylmorpholin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*R*)-4-cyclohexylmorpholin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-4-cyclohexylmorpholin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[4-(4,4-dimethylcyclohexyl)-1,4-oxazepan-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(1-(4-(difluoromethoxy)benzyl)piperidin-4-yl)-2-ethoxy-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(S)-2-(1-(4-(difluoromethoxy)benzyl)piperidin-4-yl)-2-ethoxy-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((1-(1-(2-isopropoxyphenyl)ethyl)piperidin-4-yl)thio)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((1-((*R*)-1-(2-isopropoxyphenyl)ethyl)piperidin-4-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((1-((*S*)-1-(2-isopropoxyphenyl)ethyl)piperidin-4-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((S)-1-(3,5-difluoro-4-methylbenzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((S)-1-(3,5-difluoro-2-methylbenzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-(1-(3,5-difluorobenzyl)azepan-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(methyl(2-(1-(3-(trifluoromethoxy)benzyl)piperidin-4-yl)propan-2-yl)amino)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-(4-((4,4-dimethylcyclohexyl)methyl)thiomorpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((3S)-1-(1-(3,5-difluorophenyl)ethyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-1-((*S*)-1-(3,5-difluorophenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-1-((*R*)-1-(3,5-difluorophenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-(4-(4-isopropylcyclohexyl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-4-((1*r*,4*S*)-4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*R*)-4-((1*r*,4*R*)-4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-4-((1*s*,4*R*)-4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*R*)-4-((1*s*,4*S*)-4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(2-(3-fluoro-5-methylbenzyl)-2,6-diazaspiro[3.4]octan-6-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*R*)-1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[2.5]octan-6-yl)morpholin-2-yl)acetamide;

N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((S)-4-(spiro[2.5]octan-6-yl)morpholin-2-yl)acetamide;

N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((R)-4-(spiro[2.5]octan-6-yl)morpholin-2-yl)acetamide;

N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[3.5]nonan-2-yl)morpholin-2-yl)acetamide;

N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-4-(spiro[3.5]nonan-2-yl)morpholin-2-yl)acetamide;

N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-4-(spiro[3.5]nonan-2-yl)morpholin-2-yl)acetamide;

(R)-2-(8-(2-(isopropylthio)benzyl)-2,8-diazaspiro[4.5]decan-2-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((S)-1-(4-ethyl-3-fluorobenzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((3S)-1-(1-(3-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-1-((*S*)-1-(3-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-1-((*R*)-1-(3-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((3S)-1-(1-(2-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-1-((*S*)-1-(2-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-1-((*R*)-1-(2-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[3.4]octan-2-yl)morpholin-2-yl)acetamide;

N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-4-(spiro[3.4]octan-2-yl)morpholin-2-yl)acetamide;

N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-4-(spiro[3.4]octan-2-yl)morpholin-2-yl)acetamide;

(R)-2-(2-(3-fluoro-5-methylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(2-(2-(methylthio)benzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(2-(2-(isopropylthio)benzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[4.5]decan-8-yl)morpholin-2-yl)acetamide;

N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-4-(spiro[4.5]decan-8-yl)morpholin-2-yl)acetamide;

N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-4-(spiro[4.5]decan-8-yl)morpholin-2-yl)acetamide;

N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[3.5]nonan-7-yl)morpholin-2-yl)acetamide;

N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((R)-4-(spiro[3.5]nonan-7-yl)morpholin-2-yl)acetamide;

N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((S)-4-(spiro[3.5]nonan-7-yl)morpholin-2-yl)acetamide;

tert-butyl 4-(((S)-3-(2-((5-(((R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)-2-oxoethyl)piperidin-1-yl)methyl)piperidine-1-carboxylate;

2-(4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*R*)-4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((R)-4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((S)-4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-(((R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(4,4-dimethylcyclohexyl)morpholin-2-yl)acetamide;
N-(5-(((R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((S)-4-(4,4-dimethylcyclohexyl)morpholin-2-yl)acetamide;
N-(5-(((R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((R)-4-(4,4-dimethylcyclohexyl)morpholin-2-yl)acetamide;
2-(4-(2,4-dimethylpentan-3-yl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((S)-1-(3,5-difluorobenzyl)piperidin-3-yl)-N-(5-(((3S,4S)-4-fluoro-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-[4-(4,4-dimethylcyclohexyl)-1-methylpiperazin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(R)-4-(4,4-dimethylcyclohexyl)-1-methylpiperazin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(S)-4-(4,4-dimethylcyclohexyl)-1-methylpiperazin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[4-(4,4-dimethylcyclohexyl)thiomorpholin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(4-{spiro[4.5]decan-8-yl}thiomorpholin-2-yl)acetamide; and
2-(4-{bicyclo[2.2.2]octan-1-yl}morpholin-2-yl)-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
or a salt and/or solvate of any one thereof such as a pharmaceutically acceptable salt and/or solvate thereof.

In one embodiment there is provided a compound of formula (I), which is selected from the list consisting of:
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(3-(trifluoromethoxy)benzyl)piperazin-1-yl)acetamide;
(R)-N-(5-((1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(4-(trifluoromethoxy)benzyl)piperazin-1-yl)acetamide;
(R)-2-(4-(2-chloro-4-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-chloro-5-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(2-(trifluoromethoxy)benzyl)piperazin-1-yl)acetamide;

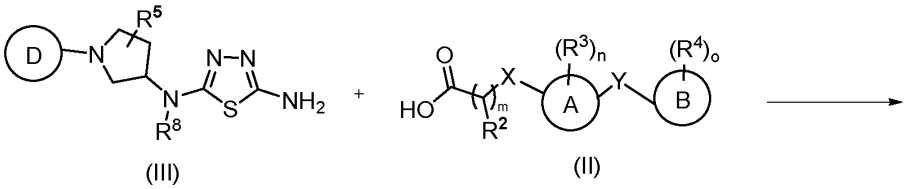
(R)-2-(4-(3-fluoro-4-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-bromo-5-fluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-methoxy-4-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(4-chloro-3-fluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-chloro-5-fluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3,4-difluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3,5-difluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3,5-difluoro-4-methoxybenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-(((3S,4S)-4-fluoro-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(4-(trifluoromethoxy)benzyl)piperazin-1-yl)acetamide;
(R)-2-(4-(2-chloro-5-(trifluoromethoxy)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-chloro-4-(trifluoromethoxy)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-(difluoromethoxy)-4-methylbenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
((R)-2-(4-(3,5-dichloro-4-methylbenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(2,4-dichloro-6-fluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(5-fluoro-2-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-fluoro-5-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-((7-fluoro-2,3-dihydro-1H-inden-5-yl)methyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(5-chloro-2-(difluoromethoxy)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(4-(2,3-difluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide; and
(R)-2-(4-(3-difluoromethoxy)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
or a salt and/or solvate of any one thereof such as a pharmaceutically acceptable salt and/or solvate thereof.

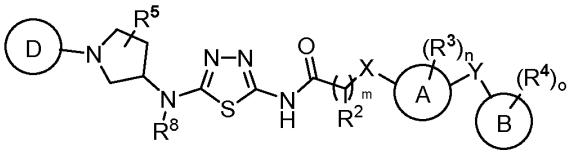
Compounds of formula (I) may be synthesised as shown in the schemes below and as shown in the Examples section. Example compounds may be synthesized using one or more of the schemes below. For each scheme, variables are as defined above unless otherwise stated.

One skilled in the art will appreciate that the compounds of formula (I) may be synthesised by one or more of the following schemes.

Scheme 1: Synthesis of compounds of formula (I)



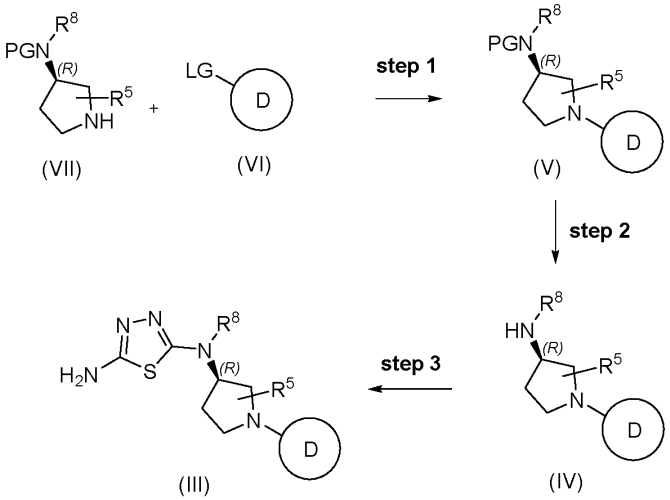
(III) (II)



(I)

Compounds of formula (I) may be prepared by coupling amine intermediate (III) with carboxylic acid (II) using a coupling agent such as T_3P, HATU or PyBOP in the presence of an organic base such as DIPEA in a solvent such as DMF.

Scheme 2: Synthesis of compounds of formula (III), wherein D is pyridazine



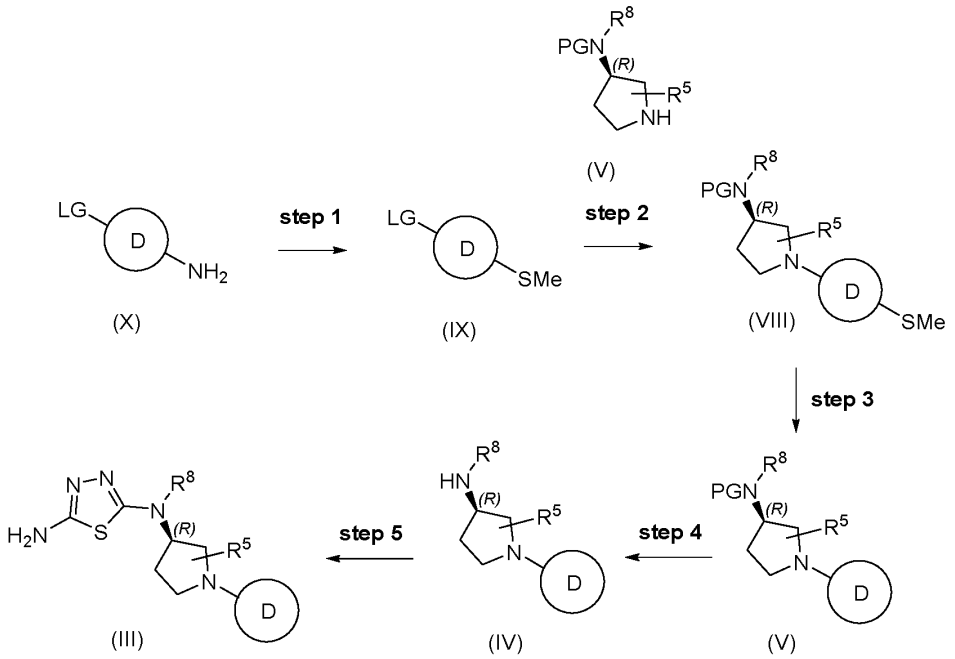
PG is a nitrogen protecting group such as Boc. Other nitrogen protecting groups are as described herein. LG is a leaving group such as halo e.g. chloro.

Step 1: Compounds of formula (VII) are reacted in the presence of an organic base such as DIPEA with compounds of formula (VI) to give compounds of formula (V).

Step 2: PG is removed under conditions known to the skilled person to give amines (IV). For example, if PG is Boc, this protecting group can be removed using neat TFA.

Step 3: Amines (IV) are coupled with 5-halo-1,3,4-thiadiazol-2-amine (wherein halo is suitably bromo) under basic conditions (such as DIPEA) to give compounds of formula (III).

Scheme 3: Synthesis of compounds of formula (III), wherein D is 1,2,4-triazine



PG is a nitrogen protecting group such as Boc. Other nitrogen protecting groups are as described herein. LG is a leaving group such as halo e.g. chloro.

Step 1: Compounds of formula (X) are reacted with a reducing agent (such as tert-butyl nitrite) with dimethyldisulfane to give compounds of formula (IX).

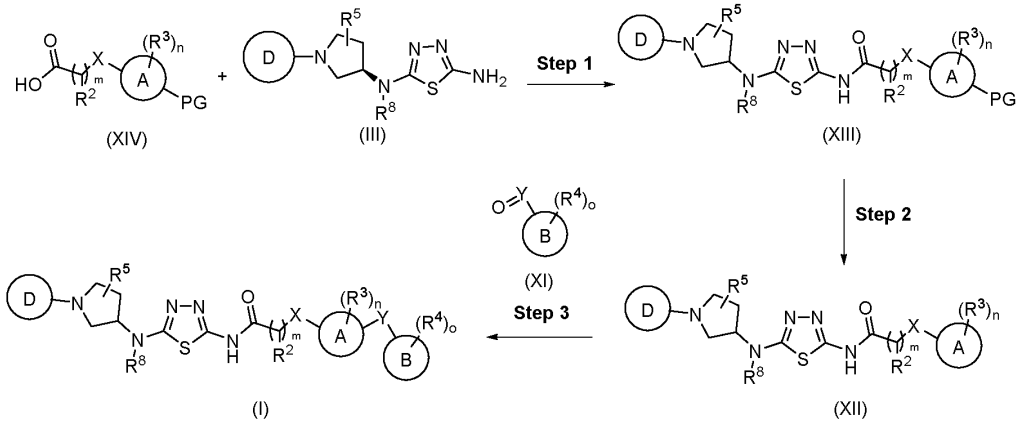
Step 2: Compounds of formula (IX) are reacted in the presence of an organic base such as DIPEA with compounds of formula (V) to give compounds of formula (VIII).

Step 3: Compounds of formula (VIII) are reacted with a reducing agent (such as Raney-Nickel) to give compounds of formula (V).

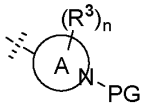
Step 4: PG is removed under conditions known to the skilled person to give amines (IV). For example, if PG is Boc, this protecting group can be removed using neat TFA.

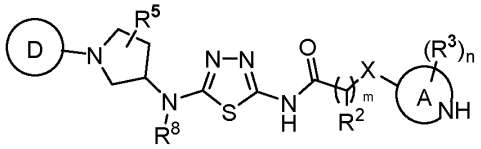
Step 5: Amines (IV) are coupled with 5-halo-1,3,4-thiadiazol-2-amine (wherein halo is suitably bromo) under basic conditions (such as DIPEA) to give compounds of formula (III).

Scheme 4: Synthesis of compounds of formula (I) wherein A is a nitrogen containing heterocyclyl or heterospirocycloalkyl



PG is a nitrogen protecting group such as Boc. Other nitrogen protecting groups are as described herein. The skilled person will appreciate that when PG is attached to ring A, PG is attached to a nitrogen atom in ring A as shown in the following structure:

 wherein indicates the connection to the remainder of the compound (e.g. any one of the compounds in Scheme 4). Furthermore, after Step 2 wherein PG is removed, the skilled person will appreciate that compounds of formula (XII) have the following structure:



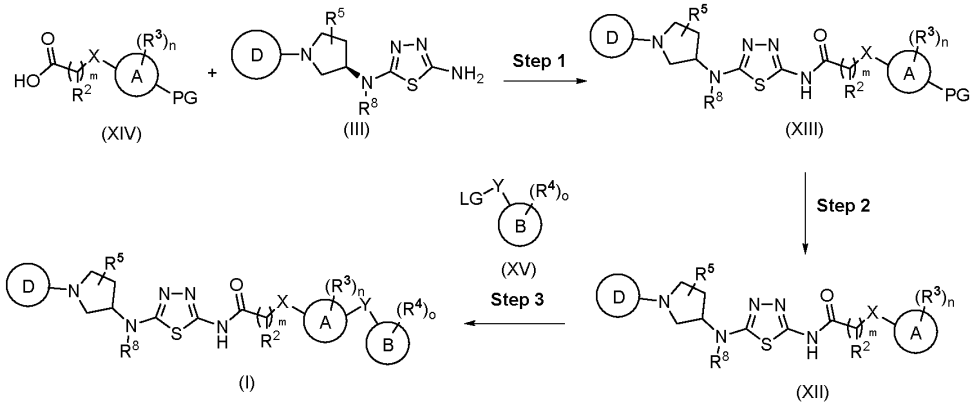
(XII-a)

Step 1: Compounds of formula (XIV) are coupled with amine intermediate (III) using a coupling agent such as T_3P, HATU or PyBOP in the presence of an organic base such as DIPEA in a solvent such as DMF to give compounds of formula (XIII).

Step 2: PG is removed under conditions known to the skilled person to give intermediate (XII). For example, if PG is Boc, this protecting group can be removed using neat TFA.

Step 3: Compounds of formula (XII) are reacted with carbonyl intermediate (XI) using a reducing agent (such as STAB) to give compounds of formula (I).

Scheme 5: Synthesis of compounds of formula (I) wherein A is a nitrogen containing heterocyclyl or heterospirocycloalkyl



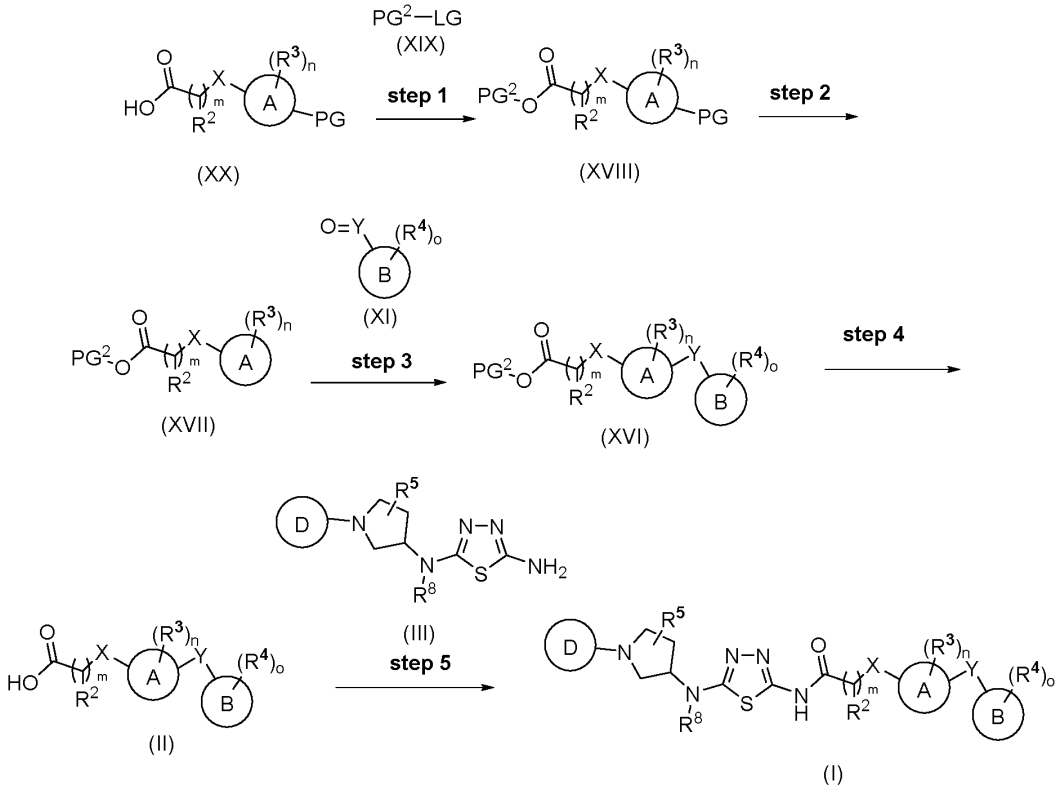
PG is a nitrogen protecting group such as Boc. Other nitrogen protecting groups are as described herein. LG is a leaving group such as halo e.g. chloro. The comments regarding ring A under Scheme 4 apply equally to ring A in Scheme 5.

Step 1: Compounds of formula (XIV) are coupled with amine intermediate (III) using a coupling agent such as T_3P, HATU or PyBOP in the presence of an organic base such as DIPEA in a solvent such as DMF to give compounds of formula (XIII).

Step 2: PG is removed under conditions known to the skilled person to give intermediate (XII). For example, if PG is Boc, this protecting group can be removed using neat TFA.

Step 3: Compounds of formula (XII) are reacted with alkyl or benzyl halide intermediate (XV) in the presence of an organic base such as TEA to give compounds of formula (I).

Scheme 6: Synthesis of compounds of formula (I) wherein A is a nitrogen containing heterocyclyl or heterospirocyclloalkyl



PG is a nitrogen protecting group such as Boc and PG^2 is a carboxylic acid protecting group such as methyl or benzyl. Other nitrogen protecting groups are as described herein. LG is a leaving group such as halo e.g. chloro. The comments regarding ring A under Scheme 4 apply equally to ring A in Scheme 6, see removal of PG in Step 2 to form compounds of formula (XVII).

Step 1: The carboxylic acid group in compounds of formula (XX) is protected with PG^2 under standard protection conditions known to the skilled person or as described in the Example section below.

Step 2: PG is removed under acidic conditions known to the skilled person to give intermediate (XVII). For example, if PG is Boc, this protecting group can be removed using HCl.

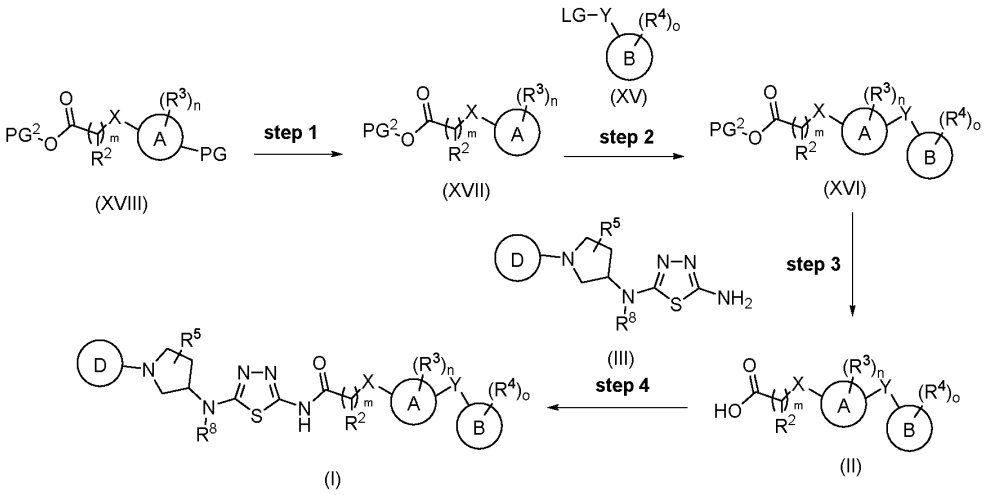
Step 3: Compounds of formula (XVII) are reacted with carbonyl intermediate (XI) using a reducing agent (such as STAB) to give compounds of formula (XVI).

Step 4: PG^2 is removed under conditions known to the skilled person to give intermediate (II). For example, if PG^2 is methyl, this protecting group can be removed using LiOH. Alternatively, if PG^2 is benzyl, this protecting group can be removed using Pd/C with hydrogen gas.

Step 5: Compounds of formula (II) are coupled with amine intermediate (III) to give compounds of formula (I) as described in Scheme 1.

In instances wherein the compound of formula (XVIII) is a readily available starting material, Step 1 of Scheme 6 is omitted.

Scheme 7: Synthesis of compounds of formula (I) wherein A is a nitrogen containing heterocyclyl or heterospirocyclloalkyl



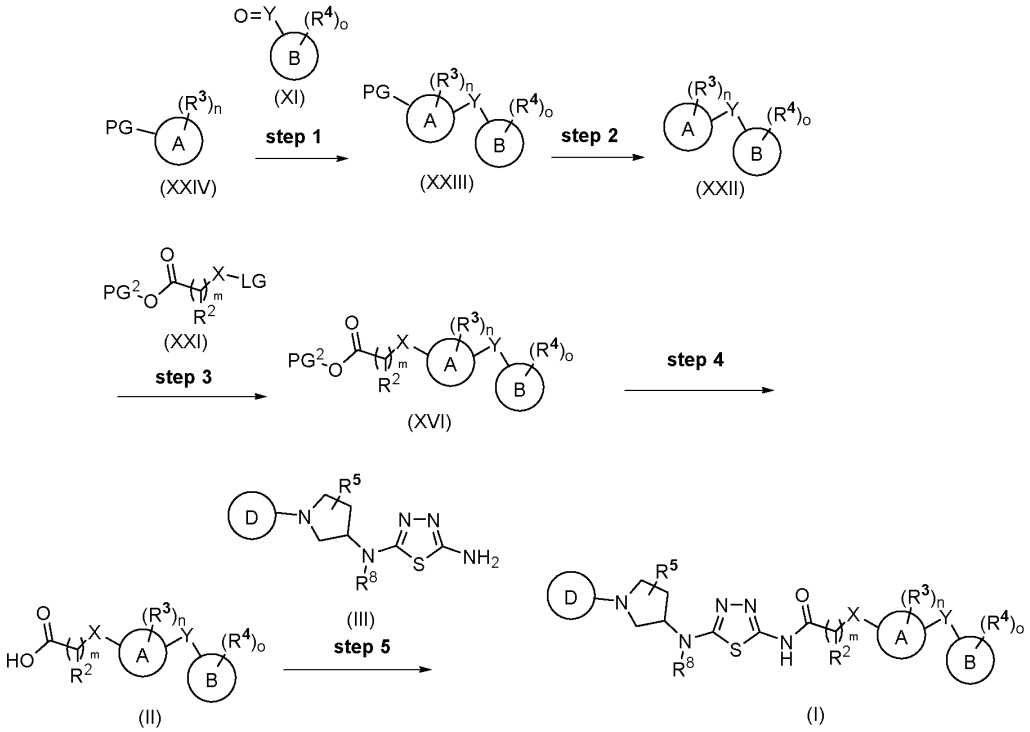
PG is a nitrogen protecting group such as Boc and PG^2 is a carboxylic acid protecting group such as methyl or benzyl. Other nitrogen protecting groups are as described herein. LG is a leaving group such as halo e.g. chloro. The comments regarding ring A under Scheme 4 apply equally to ring A in Scheme 7, see removal of PG in Step 1 to form compounds of formula (XVII).**Step 1:** PG is removed under conditions known to the skilled person to give intermediate (XVII). For example, if PG is Boc, this protecting group can be removed using HCl.

Step 2: Compounds of formula (XVII) are reacted with the alkyl or benzyl halide intermediate (XV) in the presence of an organic base such as TEA to give compounds of formula (XVI).

Step 3: PG^2 is removed under conditions known to the skilled person to give intermediate (II). For example, if PG^2 is methyl, this protecting group can be removed using LiOH.

Step 4: Compounds of formula (II) are coupled with amine intermediate (III) to give compounds of formula (I) as described in Scheme 1.

Scheme 8: Synthesis of compounds of formula (I) wherein A is a nitrogen containing heterocyclyl or heterospirocyclloalkyl



PG is a nitrogen protecting group such as Boc and PG^2 is a carboxylic acid protecting group such as methyl or benzyl. Other nitrogen protecting groups are as described herein. LG is a leaving group such as halo e.g. chloro. The comments regarding ring A under Scheme 4 apply equally to ring A in Scheme 8, see removal of PG in Step 2 to form compounds of formula (XXII). In addition, the skilled person will appreciate that ring A in compounds of formula (XXIV) must have an NH group present so that the compounds of formula (XXIV) can undergo reaction with aldehydes of formula (XI) in Step 1. Thus, this scheme is particularly suitable for the synthesis of compounds where ring A contains two or more N ring atoms e.g. A is piperazinyl.

Step 1: Compounds of formula (XXIV) are reacted with carbonyl intermediate (XI) using a reducing agent (such as STAB) to give compounds of formula (XXIII).

Step 2: Compounds of formula (XXIII) are reacted under acidic conditions (such as in the presence of TFA) to give compounds of formula (XXII).

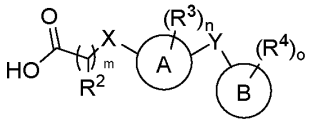
Step 3: Compounds of formula (XXII) are reacted with compounds of formula (XXI) under S_N2 reaction conditions to give compounds of formula (XVI).

Step 4: PG^2 is removed under conditions known to the skilled person to give compounds of formula (II). For example, if PG^2 is methyl, this protecting group can be removed using LiOH.

Step 5: Compounds of formula (II) are coupled with amine intermediate (III) to give compounds of formula (I) as described in Scheme 1.

Compounds of formula (II) may be synthesised as set out in Schemes 6 to 8. Otherwise, compounds of formula (II) may be synthesised for example as set out in the Example section below. All variables are as defined herein unless otherwise specified.

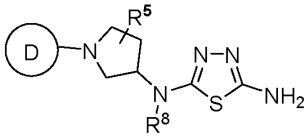
The invention provides a compound of formula (II):



(II)

or a salt, such as a pharmaceutically acceptable salt thereof. Suitably, R^2 is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, $NR^{2a}R^{2b}$ and C_{0-3}alkyleneC_{3-6}cycloalkyl wherein R^{2a} and R^{2b} are as defined elsewhere herein.

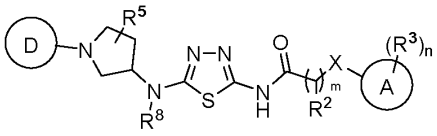
The invention also provides a compound of formula (III):



(III)

or a salt, such as a pharmaceutically acceptable salt thereof. Suitably, R^5 is H. Suitably R^8 is H. Most suitably, R^5 and R^8 are both independently H.

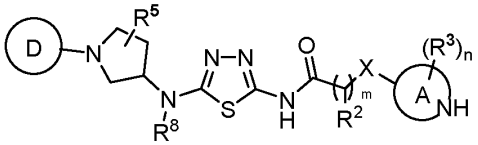
The invention also provides a compound of formula (XII):



(XII)

or a salt, such as a pharmaceutically acceptable salt thereof.

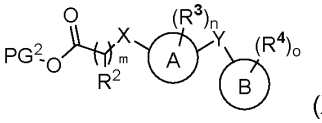
There is also provided a compound of formula (XII-a):



(XII-a)

or a salt, such as a pharmaceutically acceptable salt thereof.

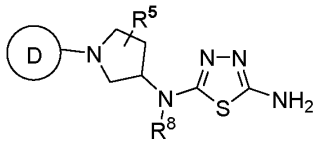
The invention also provides a compound of formula (XVI):



(XVI)

or a salt, such as a pharmaceutically acceptable salt thereof, wherein PG^2 is a carboxylic acid protecting group such as methyl or benzyl.

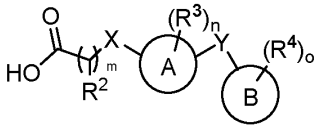
There is also provided a process for the preparation of a compound of formula (I), or a salt such as a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula (III):



(III)

or a salt such as a pharmaceutically acceptable salt thereof;

with a compound of formula (II):

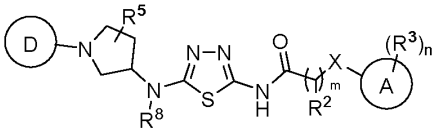


(II);

or a salt such as a pharmaceutically acceptable salt thereof;

wherein R^2, R^3, R^4, R^5, R^8, m, n, o, X, Y, A and B are as defined elsewhere herein.

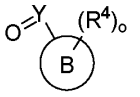
There is also provided a process for the preparation of a compound of formula (I), or a salt such as a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula (XII):



(XII);

or a salt such as a pharmaceutically acceptable salt thereof;

with a compound of formula (XI):

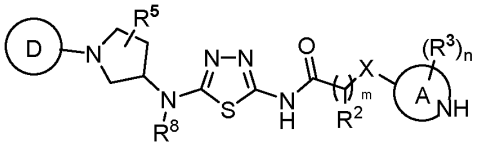


(XI)

or a salt such as a pharmaceutically acceptable salt thereof;

wherein R^2, R^3, R^4, R^5, R^8, m, n, o, X, Y, A and B are as defined elsewhere herein.

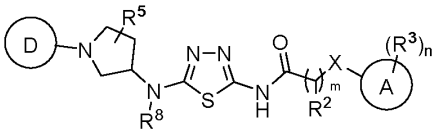
Suitably, the compound of formula (XII) is a compound of formula (XII-a):



(XII-a)

or a salt such as a pharmaceutically acceptable salt thereof.

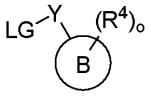
There is also provided a process for the preparation of a compound of formula (I), or a salt such as a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula (XII):



(XII);

or a salt such as a pharmaceutically acceptable salt thereof;

with a compound of formula (XV):

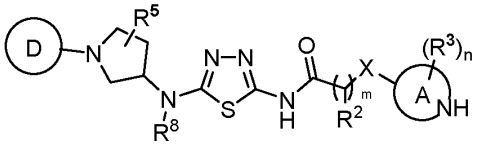


(XV)

or a salt such as a pharmaceutically acceptable salt thereof;

wherein R^2, R^3, R^4, R^5, R^8, m, n, o, X, Y, A and B are as defined elsewhere herein. LG is a leaving group such as halo e.g. chloro.

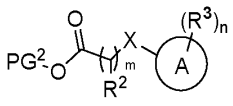
Suitably, the compound of formula (XII) is a compound of formula (XII-a):



(XII-a)

or a salt such as a pharmaceutically acceptable salt thereof.

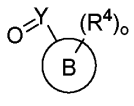
There is also provided a process for the preparation of a compound of formula (XVI), or a salt such as a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula (XVII):



(XVII);

or a salt such as a pharmaceutically acceptable salt thereof;

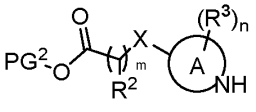
with a compound of formula (XI):


(XI)

or a salt such as a pharmaceutically acceptable salt thereof;

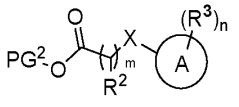
wherein R^2, R^3, R^4, m, n, o, X, Y, A and B are as defined elsewhere herein, and PG^2 is a carboxylic acid protecting group such as methyl or benzyl.

Suitably, the compound of formula (XVII) is a compound of formula (XVII-a):


(XVII-a)

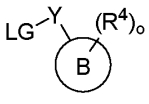
or a salt such as a pharmaceutically acceptable salt thereof.

There is also provided a process for the preparation of a compound of formula (XVI), or a salt such as a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula (XVII):


(XVII);

or a salt such as a pharmaceutically acceptable salt thereof;

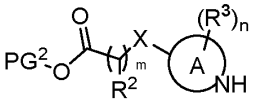
with a compound of formula (XV):


(XV)

or a salt such as a pharmaceutically acceptable salt thereof;

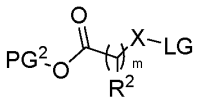
wherein R^2, R^3, R^4, m, n, o, X, Y, A and B are as defined elsewhere herein, PG^2 is a carboxylic acid protecting group such as methyl or benzyl and LG is a leaving group such as halo e.g. chloro.

Suitably, the compound of formula (XVII) is a compound of formula (XVII-a):


(XVII-a)

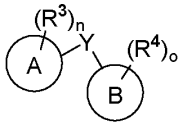
or a salt such as a pharmaceutically acceptable salt thereof.

There is also provided a process for the preparation of a compound of formula (XVI), or a salt such as a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula (XXI):


(XXI);

or a salt such as a pharmaceutically acceptable salt thereof;

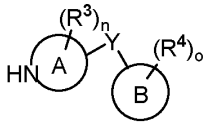
with a compound of formula (XXII):


(XXII)

or a salt such as a pharmaceutically acceptable salt thereof;

wherein R^2, R^3, R^4, m, n, o, X, Y, A and B are as defined elsewhere herein. PG^2 is a carboxylic acid protecting group such as methyl or benzyl. LG is a leaving group such as halo e.g. chloro.

Suitably, the compound of formula (XXII) is a compound of formula (XXII-a):


(XXII-a)

or a salt such as a pharmaceutically acceptable salt thereof.

It will be appreciated that for use in therapy the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art. Pharmaceutically acceptable salts include acid addition salts, suitably salts of compounds of the invention comprising a basic group such as an amino group, formed with inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid. Also included are salts formed with organic acids, e.g., succinic acid, maleic acid, acetic acid, fumaric acid, citric acid, tartaric acid, benzoic acid, p-toluenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid and 1,5-naphthalenedisulfonic acid. Other salts, e.g., oxalates or formates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention, as are basic addition salts such as sodium, potassium, calcium, aluminium, zinc, magnesium and other metal salts.

Pharmaceutically acceptable salts may also be formed with organic bases such as basic amines, e.g., with ammonia, meglumine, tromethamine, piperazine, arginine, choline, diethylamine, benzathine or lysine.

In one embodiment there is provided a compound of formula (I) in the form of a salt, such as a pharmaceutically acceptable salt. Alternatively, there is provided a compound of formula (I). When the compound contains a basic group as well as the free acid it may be zwitterionic.

Suitably, the compound of formula (I) is not in the form of a salt, e.g., is not in the form of a pharmaceutically acceptable salt.

Suitably, where the compound of formula (I) is in the form of a salt, the pharmaceutically acceptable salt is a basic addition salt such as a carboxylate salt formed with a group 1 metal (e.g., a sodium or potassium salt), a group 2 metal (e.g., a magnesium or calcium salt) or an ammonium salt of a basic amine (e.g., an NH_4^+ salt), such as a sodium salt.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form and, if crystalline, may optionally be solvated, e.g., as the hydrate. This invention includes within its scope stoichiometric solvates (e.g., hydrates) as well as compounds containing variable amounts of solvent (e.g., water). Suitably, the compound of formula (I) is not in the form of a solvate. Suitably, the compound of formula (I) or salt and/or solvate thereof is a solvate of the compound of formula (I). Suitably the solvate of the compound of formula (I) is a pharmaceutically acceptable solvate.

The invention extends to a pharmaceutically acceptable derivative thereof, such as a pharmaceutically acceptable prodrug of compounds of formula (I). Typical prodrugs of compounds of formula (I) which comprise a carboxylic acid include ester (e.g. C_{1-6} alkyl e.g. C_{1-4} alkyl ester) derivatives thereof. Thus, in one embodiment, the compound of formula (I) is provided as a pharmaceutically acceptable prodrug. In another embodiment, the compound of formula (I) is not provided as a pharmaceutically acceptable prodrug.

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

It is also to be understood that when the stereochemistry is undefined in the name of a compound of formula (I), each stereoisomer and all possible mixtures of the stereoisomers (including racemic mixtures) at the stereocentre(s) are included within the scope of the invention.

The present invention also includes all isotopic forms of the compounds provided herein, whether in a form (i) wherein all atoms of a given atomic number have a mass number (or mixture of mass numbers) which predominates in nature (referred to herein as the “natural isotopic form”) or (ii) wherein one or more atoms are replaced by atoms having the same atomic number, but a mass number different from the mass number of atoms which predominates in nature (referred to herein as an “unnatural variant isotopic form”). It is understood that an atom may naturally exists as a mixture of mass numbers. The term “unnatural variant isotopic form” also includes embodiments in which the proportion of an atom of given atomic number having a mass number found less commonly in nature (referred to herein as an “uncommon isotope”) has been increased relative to that which is naturally occurring e.g. to the level of >20%, >50%, >75%, >90%, >95% or> 99% by number of the atoms of that atomic number (the latter embodiment referred to as an "isotopically enriched variant form"). The term “unnatural variant isotopic form” also includes embodiments in which the proportion of an uncommon isotope has been reduced relative to that which is naturally occurring. Isotopic forms may include radioactive forms (i.e. they incorporate radioisotopes) and non-radioactive forms. Radioactive forms will typically be isotopically enriched variant forms.

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

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

In one embodiment, the compounds of formula (I) are provided in a natural isotopic form. In one embodiment, the compounds of formula (I) are provided in an unnatural variant isotopic form. In

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

In one embodiment, a compound of formula (I) is provided whereby a single atom of the compound exists in an unnatural variant isotopic form. In another embodiment, a compound of formula (I) is provided whereby two or more atoms exist in an unnatural variant isotopic form.

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

Therapeutic indications

Compounds of formula (I) are of use in therapy, particularly for treating or preventing fibrotic and/or inflammatory diseases, such as fibrotic and/or inflammatory diseases of the lung. Biological Example 1 shows that the compounds of the invention are GLS1 inhibitors in both a cell and enzyme assay, and thus may be expected to have utility in the treatment of diseases associated with inhibition of GLS1 such as fibrotic and/or inflammatory diseases, in particular fibrotic and/or inflammatory diseases of the lung. Biological Example 2 shows that compounds of the invention are expected to have superior pharmacokinetic properties compared with prior art compounds, and are thus more suitable for drug candidate development. In particular, Example 60 was shown to have higher lung concentration compared with prior art compounds. Biological Example 3 shows that compounds of the invention are expected to have improved solubility compared with prior art compounds such as Reference Example 3, and thus have preferred drug properties compared with prior art compounds.

Thus, in a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use as a medicament.

Also provided is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein. Thus, in a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use as a medicament.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use in treating or preventing fibrotic and/or inflammatory diseases.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use in treating fibrotic and/or inflammatory diseases.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, for use in preventing fibrotic and/or inflammatory diseases.

In a further aspect, the present invention provides a pharmaceutical composition as defined herein, for use in treating or preventing fibrotic and/or inflammatory diseases.

In a further aspect, the present invention provides a pharmaceutical composition as defined herein, for use in treating fibrotic and/or inflammatory diseases.

In a further aspect, the present invention provides a pharmaceutical composition as defined herein, for use in preventing fibrotic and/or inflammatory diseases.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, in the manufacture of a medicament for treating or preventing fibrotic and/or inflammatory diseases.

In a further aspect, the present invention provides the use of a compound of formula (I) or a

pharmaceutically acceptable salt and/or solvate thereof as defined herein, in the manufacture of a medicament for treating fibrotic and/or inflammatory diseases.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein, in the manufacture of a medicament for preventing fibrotic and/or inflammatory diseases.

In a further aspect, the present invention provides the use of a pharmaceutical composition as defined herein, in the manufacture of a medicament for treating or preventing fibrotic and/or inflammatory diseases.

In a further aspect, the present invention provides the use of a pharmaceutical composition as defined herein, in the manufacture of a medicament for treating fibrotic and/or inflammatory diseases.

In a further aspect, the present invention provides the use of a pharmaceutical composition as defined herein, in the manufacture of a medicament for preventing fibrotic and/or inflammatory diseases.

In a further aspect, the present invention provides a method of treating or preventing fibrotic and/or inflammatory diseases which comprises administering a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein.

In a further aspect, the present invention provides a method of treating fibrotic and/or inflammatory diseases which comprises administering a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein.

In a further aspect, the present invention provides a method of preventing fibrotic and/or inflammatory diseases which comprises administering a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof as defined herein.

In a further aspect, the present invention provides a method of treating or preventing fibrotic and/or inflammatory diseases which comprises administering a pharmaceutical composition as defined herein.

In a further aspect, the present invention provides a method of treating fibrotic and/or inflammatory diseases which comprises administering a pharmaceutical composition as defined herein.

In a further aspect, the present invention provides a method of preventing fibrotic and/or inflammatory diseases which comprises administering a pharmaceutical composition as defined herein.

In any one of the above embodiments, suitably the fibrotic and/or inflammatory disease is a fibrotic and/or inflammatory disease of the lung.

In any one of the above embodiments, the disease to be treated is a fibrotic disease of the lung. Alternatively, in any one of the above embodiments, the disease to be treated is an inflammatory disease of the lung. Alternatively, in any one of the above embodiments, the disease to be treated is a fibrotic and inflammatory disease of the lung.

In one embodiment, the fibrotic and/or inflammatory disease is an interstitial lung disease such as idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, lung cancer, radiation induced fibrosis, pulmonary hypertension, asthma, respiratory viral infection and long covid.

In one embodiment, the fibrotic and inflammatory disease is selected from the group consisting of diabetes, non-alcoholic fatty liver disease/cirrhosis, chronic kidney disease, osteoporosis, osteoarthritis and obesity.

In one embodiment, the fibrotic disease is fibrosis or non-alcoholic steatohepatitis.

In one embodiment, the inflammatory disease is selected from the group consisting of inflammation psoriasis, psoriatic arthritis, hidradenitis suppurativa, rheumatoid arthritis, ankylosing spondylitis and inflammatory bowel disease.

Suitably, the fibrotic and/or inflammatory disease is an interstitial lung disease such as idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, lung cancer, radiation induced fibrosis and pulmonary hypertension, asthma, respiratory viral infection and long covid.

For all aspects of the invention, suitably the compound is administered to a subject in need thereof, wherein the subject is suitably a human subject.

Administration

The compound of formula (I) is usually administered as a pharmaceutical composition. Thus, in

one embodiment, is provided a pharmaceutical composition comprising a compound of formula (I) or pharmaceutically acceptable salt and/or solvate thereof and one or more pharmaceutically acceptable diluents or carriers.

The compound of formula (I) may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal, intrathecal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

The compound of formula (I) may be administered topically to the target organ e.g. topically to the eye, lung, nose or skin. Hence the invention provides a pharmaceutical composition comprising a compound of formula (I) optionally in combination with one or more topically acceptable diluents or carriers.

A compound of formula (I) which is active when given orally can be formulated as a liquid or solid, e.g. as a syrup, suspension, emulsion, tablet, capsule or lozenge.

A liquid formulation will generally consist of a suspension or solution of the compound of formula (I) in a suitable liquid carrier(s). Suitably the carrier is non-aqueous e.g. polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

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

A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatine capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatine capsule.

Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels

and powders. Aerosol formulations typically comprise a solution or fine suspension of the compound of formula (I) in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a chlorofluorocarbon (CFC) or a hydrofluorocarbon (HFC). Aerosol dosage forms can also take the form of pump-atomisers.

Topical administration to the lung may be achieved by use of an aerosol formulation. Aerosol formulations typically comprise the active ingredient suspended or dissolved in a suitable aerosol propellant, such as a chlorofluorocarbon (CFC) or a hydrofluorocarbon (HFC).

Topical administration to the lung may also be achieved by use of a non-pressurised formulation such as an aqueous solution or suspension. These may be administered by means of a nebuliser e.g. one that can be hand-held and portable or for home or hospital use (i.e. non-portable). The formulation may comprise excipients such as water, buffers, tonicity adjusting agents, pH adjusting agents, surfactants and co-solvents.

Topical administration to the lung may also be achieved by use of a dry-powder formulation. The formulation will typically contain a topically acceptable diluent such as lactose, glucose or mannitol (preferably lactose).

The compound of the invention may also be administered rectally, for example in the form of suppositories or enemas, which include aqueous or oily solutions as well as suspensions and emulsions and foams. Such compositions are prepared following standard procedures, well known by those skilled in the art. For example, suppositories can be prepared by mixing the active ingredient with a conventional suppository base such as cocoa butter or other glycerides. In this case, the drug is mixed with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Generally, for compositions intended to be administered topically to the eye in the form of eye drops or eye ointments, the total amount of the compound of the present invention will be about 0.0001 to less than 4.0% (w/w).

Preferably, for topical ocular administration, the compositions administered according to the present invention will be formulated as solutions, suspensions, emulsions and other dosage forms.

The compositions administered according to the present invention may also include various other ingredients, including, but not limited to, tonicity agents, buffers, surfactants, stabilizing polymer, preservatives, co-solvents and viscosity building agents. Suitable pharmaceutical compositions of the present invention include a compound of the invention formulated with a tonicity agent and a buffer. The pharmaceutical compositions of the present invention may further optionally include a surfactant and/or a palliative agent and/or a stabilizing polymer.

Various tonicity agents may be employed to adjust the tonicity of the composition, preferably to that of natural tears for ophthalmic compositions. For example, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, simple sugars such as dextrose, fructose, galactose, and/or simply polyols such as the sugar alcohols mannitol, sorbitol, xylitol, lactitol, isomaltitol, maltitol, and hydrogenated starch hydrolysates may be added to the composition to approximate physiological tonicity. Such an amount of tonicity agent will vary, depending on the particular agent to be added. In general, however, the compositions will have a tonicity agent in an amount sufficient to cause the final composition to have an ophthalmically acceptable osmolality (generally about 150-450 mOsm, preferably 250-350 mOsm and most preferably at approximately 290 mOsm). In general, the tonicity agents of the invention will be present in the range of 2 to 4% w/w. Preferred tonicity agents of the invention include the simple sugars or the sugar alcohols, such as D-mannitol.

An appropriate buffer system (e.g. sodium phosphate, sodium acetate, sodium citrate, sodium borate or boric acid) may be added to the compositions to prevent pH drift under storage conditions. The particular concentration will vary, depending on the agent employed. Preferably however, the buffer will be chosen to maintain a target pH within the range of pH 5 to 8, and more preferably to a target pH of pH 5 to 7.

Surfactants may optionally be employed to deliver higher concentrations of compound of the present invention. The surfactants function to solubilise the compound and stabilise colloid dispersion, such as micellar solution, microemulsion, emulsion and suspension. Examples of surfactants which may optionally be used include polysorbate, poloxamer, polyosyl 40 stearate, polyoxyl castor oil, tyloxapol, Triton, and sorbitan monolaurate. Preferred surfactants to be employed in the invention have a hydrophile/lipophile/balance "HLB" in the range of 12.4 to 13.2 and are acceptable for ophthalmic use, such as Triton™ X-114 and tyloxapol.

Additional agents that may be added to the ophthalmic compositions of compounds of the present invention are demulcents which function as a stabilising polymer. The stabilizing polymer should be an ionic/charged example with precedence for topical ocular use, more specifically, a polymer that carries negative charge on its surface that can exhibit a zeta-potential of (–)10–50 mV for physical stability and capable of making a dispersion in water (i.e. water soluble). A preferred stabilising polymer of the invention would be polyelectrolyte, or polyelectrolytes if more than one, from the family of cross-linked polyacrylates, such as carbomers and Pemulen®, specifically Carbomer 974p (polyacrylic acid), at 0.1–0.5% w/w.

Other compounds may also be added to the ophthalmic compositions of the compound of the present invention to increase the viscosity of the carrier. Examples of viscosity enhancing agents include, but are not limited to polysaccharides, such as hyaluronic acid and its salts, chondroitin sulfate and its salts, dextrans, various polymers of the cellulose family; vinyl polymers; and acrylic acid polymers.

Topical ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, chlorobutanol, benzododecinium bromide, methyl paraben, propyl paraben, phenylethyl alcohol, edentate disodium, sorbic acid, polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0% w/v. Unit dose compositions of the present invention will be sterile, but typically unpreserved. Such compositions, therefore, generally will not contain preservatives.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the compound of formula (I) is formulated with a carrier such as sugar and acacia, tragacanth, or gelatine and glycerine.

Compositions suitable for transdermal administration include ointments, gels and patches.

The composition may contain from 0.1% to 100% by weight, for example from 10 to 60% by weight, of the compound of formula (I), depending on the method of administration. The composition may contain from 0% to 99% by weight, for example 40% to 90% by weight, of the carrier, depending on the method of administration. The composition may contain from 0.05mg to 1000mg, for example from 1.0 mg to 500 mg, such as from 1.0 mg to 50 mg, e.g. about 10 mg of the compound of formula (I), depending on the method of administration. The composition may contain from 50 mg to 1000 mg, for example from 100mg to 400mg of the carrier, depending on

the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide, suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 500mg, such as from 1.0 mg to 50 mg, e.g. about 10 mg and such unit doses may be administered more than once a day, for example two or three times a day. Such therapy may extend for a number of weeks or months.

In one embodiment of the invention, the compound of formula (I) is used in combination with a further therapeutic agent or agents. When the compound of formula (I) is used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route. Alternatively, the compounds may be administered separately.

Therapeutic agents which may be used in combination with the present invention include: corticosteroids (glucocorticoids), retinoids (e.g. acitretin, isotretinoin, tazarotene), anthralin, vitamin D analogues (e.g. cacitriol, calcipotriol), calcineurin inhibitors (e.g. tacrolimus, pimecrolimus), phototherapy or photochemotherapy (e.g. psoralen ultraviolet irradiation, PUVA) or other form of ultraviolet light irradiation therapy, ciclosporine, thiopurines (e.g. azathioprine, 6-mercaptopurine), methotrexate, anti-TNFα agents (e.g. infliximab, etanercept, adalimumab, certolizumab, golimumab and biosimilars), phosphodiesterase-4 (PDE4) inhibition (e.g. apremilast, crisaborole), anti-IL-17 agents (e.g. brodalumab, ixekizumab, secukinumab), anti-IL12/IL-23 agents (e.g. ustekinumab, briakinumab), anti-IL-23 agents (e.g. guselkumab, tildrakizumab), JAK (Janus Kinase) inhibitors (e.g. tofacitinib, ruxolitinib, baricitinib, filgotinib, upadacitinib), plasma exchange, intravenous immune globulin (IVIG), cyclophosphamide, anti-CD20 B cell depleting agents (e.g. rituximab, ocrelizumab, ofatumumab, obinutuzumab), anthracycline analogues (e.g. mitoxantrone), cladribine, sphingosine 1-phosphate receptor modulators or sphingosine analogues (e.g. fingolimod, siponimod, ozanimod, etrasimod), interferon beta preparations (including interferon beta 1b/1a), glatiramer, anti-CD3 therapy (e.g. OKT3), anti-CD52 targeting agents (e.g. alemtuzumab), leflunomide, teriflunomide, gold compounds, laquinimod, potassium channel blockers (e.g. dalfampridine/4-aminopyridine), mycophenolic acid, mycophenolate mofetil, purine analogues (e.g. pentostatin), mTOR (mechanistic target of rapamycin) pathway inhibitors (e.g. sirolimus, everolimus), anti-thymocyte globulin (ATG), IL-2 receptor (CD25) inhibitors (e.g. basiliximab, daclizumab), anti-IL-6 receptor or anti-IL-6 agents (e.g. tocilizumab, siltuximab), Bruton's tyrosine kinase (BTK) inhibitors (e.g. ibrutinib), tyrosine kinase inhibitors (e.g. imatinib, nintedanib), ursodeoxycholic acid, hydroxychloroquine, chloroquine, B cell activating factor (BAFF, also known as BLyS, B lymphocyte stimulator) inhibitors (e.g. belimumab, blisibimod), other B cell targeted therapy

including fusion proteins targeting both APRIL (A PRoliferation-Inducing Ligand) and BLyS (e.g. atacicept), PI3K inhibitors including pan-inhibitors or those targeting the p110δ and/or p110γ containing isoforms (e.g. idelalisib, copanlisib, duvelisib), interferon α receptor inhibitors (e.g. anifrolumab, sifalimumab), T cell co-stimulation blockers (e.g. abatacept, belatacept), thalidomide and its derivatives (e.g. lenalidomide), dapsone, clofazimine, leukotriene antagonists (e.g. montelukast), theophylline, anti-IgE therapy (e.g. omalizumab), anti-IL-5 agents (e.g. mepolizumab, reslizumab), long-acting muscarinic agents (e.g. tiotropium, aclidinium, umeclidinium), PDE4 inhibitors (e.g. roflumilast), riluzole, free radical scavengers (e.g. edaravone), proteasome inhibitors (e.g. bortezomib), complement cascade inhibitors including those directed against C5 (e.g. eculizumab), immunoadsor, antithymocyte globulin, 5-aminosalicylates and their derivatives (e.g. sulfasalazine, balsalazide, mesalamine), anti-integrin agents including those targeting α4β1 and/or α4β7 integrins (e.g. natalizumab, vedolizumab), anti-CD11-α agents (e.g. efalizumab), non-steroidal anti-inflammatory drugs (NSAIDs) including the salicylates (e.g. aspirin), propionic acids (e.g. ibuprofen, naproxen), acetic acids (e.g. indomethacin, diclofenac, etodolac), oxicams (e.g. meloxicam) and fenamates (e.g. mefenamic acid), selective or relatively selective COX-2 inhibitors (e.g. celecoxib, etroxicoxib, valdecoxib and etodolac, meloxicam, nabumetone), colchicine, IL-4 receptor inhibitors (e.g. dupilumab), topical/contact immunotherapy (e.g. diphenylcyclopropenone, squaric acid dibutyl ester), anti-IL-1 receptor therapy (e.g. anakinra), IL-1β inhibitor (e.g. canakinumab), IL-1 neutralising therapy (e.g. rilonacept), chlorambucil, specific antibiotics with immunomodulatory properties and/or ability to modulate NRF2 (e.g. tetracyclines including minocycline, clindamycin, macrolide antibiotics), anti-androgenic therapy (e.g. cyproterone, spironolactone, finasteride), pentoxifylline, ursodeoxycholic acid, obeticholic acid, fibrate, cystic fibrosis transmembrane conductance regulator (CFTR) modulators, VEGF (vascular endothelial growth factor) inhibitors (e.g. bevacizumab, ranibizumab, pegaptanib, aflibercept), pirfenidone, or mizoribine.

In one embodiment and suitably when the disease to be treated is lung cancer, the compounds of formula (I) may be administered as a combination therapy with radiation. It is understood that GLS1 inhibitors can augment radiation treatment (Fujimoto et al. 2022).

Compounds of formula (I) may display, or may be expected to have, one or more of the following desirable properties:

- low IC_{50} in the cellular assay of Biological Example 1;
- low IC_{50} in the enzyme assay of Biological Example 1;
- improved duration of action in the lung as shown in Biological Example 2;
- higher lung concentrations as shown in Biological Example 2;
- improved solubility as shown in Biological Example 3.

Abbreviations

ACN	Acetonitrile
aq.	Aqueous
BOC	tert-Butyloxycarbonyl
tBuOH	tert-Butanol
d	day/days
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCM	Dichloromethane
d.e.	Diastereomeric excess
Dioxane	1,4-Diethylene dioxide
DIPEA	N, N-Diisopropylethylamine
DMA	Dimethylacetamide
DMF	N, N-Dimethylformamide
DMSO	Dimethyl sulfoxide
EDTA	Ethylenediaminetetraacetic acid
ESI	Electrospray Ionisation
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
Et_2O	Diethyl ether
FA	Formic acid
h	Hour/hours
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HPLC	High Performance Liquid Chromatography
IPA	Isopropanol
IN	Intranasal
LCMS	Liquid Chromatography Mass Spectrometry
M	Molar concentration
MeOH	Methanol
MHz	Megahertz
min(s)	Minute(s)
NMR	Nuclear Magnetic Resonance
$Pd(dppf)Cl_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PE	Petroleum ether
pH	Potential of hydrogen (acidity/basicity)

PyBOP	Benzotriazol-1-yl-oxytripyrrolidino-phosphonium Hexafluorophosphate
RT	Retention time
r.t.	Room temperature
SFC	Supercritical Fluid Chromatography
STAB	Sodium triacetoxyborohydride
T_3P	Propylphosphonic anhydride solution
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
$Ti(O^iPr)_4$	Titanium(IV) isopropoxide
TLC	Thin Layer Chromatography
UPLC	Ultra Performance Liquid Chromatography

EXAMPLES

Analytical Equipment

Thin layer chromatography (TLC) was performed on silica gel plates (GF254, glass, silica gel size: 400~600 mesh). Spots were visualized by UV light (214 and 254 nm) or colour reagents (iodine, $KMnO_4$ aq.).

Bruker 400 MHz Avance III™ spectrometer fitted with a BBFO 5 mm probe, or a Bruker 500 MHz Avance III™ HD spectrometer equipped with a Bruker 5 mm SmartProbe™. ^1H chemical shifts are reported in δ values in ppm with the deuterated solvent as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), integration.

HPLC was performed according to methods described below:

Analytical Conditions

Method 1

Stationary phase:	Kinetex EVO C18 2.1 x 30 mm, 5 µm
Mobile Phase A:	0.025% $NH_3 \cdot H_2O$ in water(v/v)
Mobile Phase B:	Acetonitrile
Flow rate:	1.5 mL/min
Gradient program:	Time A% B%

0.00	95.00	5.00
0.80	5.00	95.00
1.20	5.00	95.00
1.21	95.00	5.00
1.55	95.00	5.00

Method 2

Stationary phase: Kinetex EVO C18 2.1 x 30 mm, 5 µm

Mobile Phase A: 0.0375% TFA in water (v/v)

Mobile Phase B: 0.01875% TFA in acetonitrile (v/v)

Flow rate: 1.5 mL/min

Gradient program:

Time	A%	B%
0.00	95.00	5.00
0.80	5.00	95.00
1.20	5.00	95.00
1.21	95.00	5.00
1.55	95.00	5.00

Method 3

Stationary phase: HALO C18 3.0 x 30 mm, 5 µm

Mobile Phase A: 0.0375% TFA in water (v/v)

Mobile Phase B: 0.01875% TFA in acetonitrile (v/v)

Flow rate: 1.5 mL/min

Gradient program:

Time	A%	B%
0.00	95.00	5.00
0.50	5.00	95.00
0.80	5.00	95.00
0.81	95.00	5.00
1.05	95.00	5.00

Method 4

Stationary phase: Agilent ZORBAX 5µm SB-Aq, 2.1*50mm

Mobile Phase A: 0.0375% TFA in water (v/v)

Mobile Phase B: 0.01875% TFA in acetonitrile (v/v)

Gradient program:

Time	A%	B%	Flow (mL/min)
0.00	99.00	1.00	0.8
0.40	99.00	1.00	0.8

3.40	10.00	90.00	0.8
3.90	0.00	100.00	0.8
3.91	99.00	1.00	0.8
4.00	99.00	1.00	1.0
4.50	99.00	1.00	1.0

Method 5

Stationary phase: Acquity UPLC BEH - Waters, 1.7µm C18 (2.1 x 100 mm), 130Å

Flow Rate 0.5 mL/min

Mobile Phase A: 0.1 % v/v water solution of formic acid

Mobile Phase B: 0.1 % v/v acetonitrile solution of formic acid

Gradient program:

Time	A%	B%
0.10	80.00	20.00
2.00	5.00	95.00
2.70	5.00	95.00
2.80	80.00	20.00

Method 6

Stationary phase: Gemini NX 3 µm C18 (4.6x150mm), 110Å

Mobile Phase A: 0.1% v/v water solution of formic acid

Mobile Phase B: 0.1% v/v acetonitrile solution of formic acid

Flow rate: 1 mL/min

Gradient program:

Time	A%	B%
0.00	100.00	0.00
7.50	70.00	30.00
8.00	70.00	30.00
8.50	5.00	95.00
9.75	5.00	95.00
10.25	100.00	0.00
12.00	100.00	0.00

Method 7

Stationary phase: Kinetex ® 2.6 µm XB-C18 (4.6x50mm), 100Å

Mobile Phase A: 0.1% v/v water solution of formic acid

Mobile Phase B: 0.1% v/v acetonitrile solution of formic acid

Flow rate: 1 mL/min

Gradient program:

Time	A%	B%
0.00	100.00	0.00

1.00	95.00	5.00
4.00	80.00	20.00
4.75	20.00	80.00
5.25	20.00	80.00
6.00	95.00	5.00
7.00	100.00	0.00

Method 8

Stationary phase: ACQUITY UPLC BEH C8 1.7 µm (2.1x150mm), 130Å

Mobile Phase A: 0.1% v/v water solution of formic acid

Mobile Phase B: 0.1% v/v acetonitrile solution of formic acid

Flow rate: 0.5 mL/min

Gradient program:

Time	A%	B%
0.00	100.00	0.00
6.00	80.00	20.00
6.80	80.00	20.00
7.00	5.00	95.00
8.10	5.00	95.00
8.50	95.00	5.00
10.00	95.00	5.00

Method 9

Stationary phase: Gemini NX 3 µm C18 (4.6x150mm), 110Å

Mobile Phase A: 0.05% v/v water solution of ammonium hydroxide

Mobile Phase B: acetonitrile

Flow rate: 1 mL/min

Gradient program:

Time	A%	B%
0.00	80.00	20.00
6.35	50.00	50.00
6.75	50.00	50.00
6.90	5.00	95.00
7.75	5.00	95.00
8.00	80.00	20.00
9.00	80.00	20.00

Method 10

Stationary phase: Lux i-Amylose-3 (4.6x250mm), 5 µm

Mobile Phase A: 60%, CO_2
Mobile Phase B: 40%, 1% ammonium hydroxide in methanol:acetonitrile (v/v, 1:1)
Flow rate: 3 mL/min
Gradient program:

Time	A%	B%
0.00	60.00	40.00
30.00	60.00	40.00

Method 11
Stationary phase: Lux Cellulose-1 (4.6x250mm), 5 µm
Mobile Phase A: 60%, CO_2
Mobile Phase B: 40%, 1% ammonium hydroxide in methanol:acetonitrile (v/v, 1:1)
Flow rate: 3 mL/min
Gradient program:

Time	A%	B%
0.00	60.00	40.00
30.00	60.00	40.00

Method 12
Stationary phase: Chiralpak AD-H (4.6x250mm), 5 µm
Mobile Phase A: 0.1% v/v ethanol solution of triethylamine
Mobile Phase B: *n*-hexane
Flow rate: 1 mL/min
Gradient program:

Time	A%	B%
0.00	40.00	60.00
20.00	40.00	60.00

Method 13
Stationary phase: Waters SunFire C18 150*4.6mm 5um
Mobile Phase A: 0.03% TFA in H_2O (v/v)
Mobile Phase B: 0.03% TFA in ACN(v/v)
Flow rate: 1.00 ml/min
Gradient program: 10% B hold for 1.8 min, increase to 95 % B within 10.2 min, hold at 95 % B for 3.0 min, then back to 10% B within 0.01 min

Method 14
Stationary phase: Waters SunFire C18 5µm 50*4.6mm
Mobile Phase A: 0.03%FA in H_2O (v/v)
Mobile Phase B: 0.03%FA in ACN (v/v)
Flow rate: 2.0 ml/min

Gradient program: 5% B hold for 0.2min, increase to 95 % B within 1.40 min, hold at 95 % B for 0.9 min, then back to 5% B within 0.01 min

Method 15

Stationary phase: Waters SunFire C18 5μm 50*4.6mm
Mobile Phase A: 0.1%FA in H_2O (v/v)
Mobile Phase B: 0.1%FA in ACN (v/v)
Flow rate: 2.0 ml/min
Gradient program: 5% B hold for 0.2min, increase to 95 % B within 1.40 min, hold at 95 % B for 0.9 min, then back to 5% B within 0.01 min

Method 16

Stationary phase: Waters XBridge C18 50*4.6mm 5um
Mobile Phase A: 0.1% $NH_3.H_2O$ in H_2O (v/v)
Mobile Phase B: Acetonitrile
Flow rate: 2.0 ml/min
Gradient program: 5% B hold for 0.2min, increase to 95 % B within 1.40 min, hold at 95 % B for 0.9 min, then back to 5% B within 0.01 min

Method 17

Stationary phase: Luna C18 30*2.0mm 3um
Mobile Phase A: 0.03%TFA in H_2O (v/v)
Mobile Phase B: 0.03%TFA in ACN (v/v)
Flow rate: 1.5 ml/min
Gradient program: 5% B increase to 95 % B within 0.7 min, hold at 95 % B for 0.4 min, back to 5% B within 0.01 min

Method 18

Stationary phase: Agilent Pursuit C18 20*2.0mm 5um
Mobile Phase A: 0.03%TFA in H_2O (v/v)
Mobile Phase B: 0.03%TFA in ACN (v/v)
Flow rate: 1.5 mL/min
Gradient program: 5% B increase to 95 % B within 0.7 min, hold at 95 % B for 0.4 min, then back to 5% B within 0.01 min

Method 19

Stationary phase:	ShimNex UP C18 50*4.6mm 5um
Mobile Phase A:	0.1%FA in H_2O (v/v)
Mobile Phase B:	0.1%FA in ACN (v/v)
Flow rate:	2.0 mL/min
Gradient program:	5% B hold for 0.2min, increase to 95 % B within 1.40 min, hold at 95 % B for 0.9 min, then back to 5% B within 0.01 min

Method 20

Stationary phase:	ShimNex UP C18 50*4.6mm 5um
Mobile Phase A:	0.03%FA in H_2O (v/v)
Mobile Phase B:	0.03%FA in ACN (v/v)
Flow rate:	2.0 mL/min
Gradient program:	5% B hold for 0.2min, increase to 95 % B within 1.40 min, hold at 95 % B for 0.9 min, then back to 5% B within 0.01 min

Method 21

Stationary phase:	Waters X Bridge C18, 50 x 4.6 mm, 5 μM
Flow Rate	2 mL/min
Mobile Phase A:	10mmol/L NH_4HCO_3 in H_2O
Mobile Phase B:	acetonitrile
Gradient program:	5% B hold for 0.2 min, increase to 95% B within 1.40 min, Hold at 95% B for 0.9 min, back to 5% B within 0.01min

Method 22

Stationary phase:	Agilent Pursuit XRs C18 30*2.0mm 5um
Mobile Phase A:	0.1%TFA in H_2O (v/v)
Mobile Phase B:	0.1%TFA in ACN (v/v)
Flow rate:	1.2 mL/min
Gradient program:	5% B increase to 95 % B within 1.40 min, hold at 95 % B for 0.5 min, then back to 5% B within 0.01 min

Method 23

Stationary phase:	Agilent Eclipse Plus C18 4.6*100mm 3.5um
Mobile Phase A:	0.1%TFA in H_2O (v/v)
Mobile Phase B:	0.1%TFA in ACN (v/v)
Flow rate:	1.5 mL/min

Gradient program: 5% B increase to 95 % B within 1.40 min, hold at 95 % B for 0.5 min, then back to 5% B within 0.01 min

Method 24

Stationary phase: Lux Cellulose-1 (4.6x250mm), 5 µm

Mobile Phase A: 70%, CO_2

Mobile Phase B: 30%, 1% ammonium hydroxide in methanol:acetonitrile (v/v, 1:1)

Flow rate: 3 mL/min

Gradient program:

Time	A%	B%
0.00	70.00	30.00
10.00	70.00	30.00

Method 25

Stationary phase: Lux Cellulose-1 (4.6x250mm), 5 µm

Mobile Phase A: 65%, CO_2

Mobile Phase B: 35%, 1% ammonium hydroxide in methanol:acetonitrile (v/v, 1:1)

Flow rate: 3 mL/min

Gradient program:

Time	A%	B%
0.00	65.00	35.00
10.00	65.00	35.00

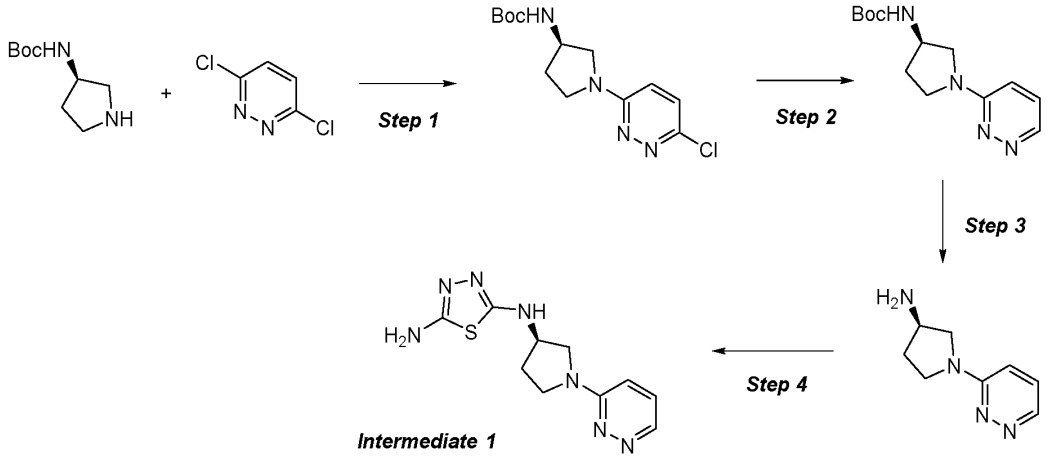
Commercial Materials

All starting materials are commercially available unless otherwise stated.

Synthesis of Intermediates

In the following general procedures, all variables are as defined herein.

INTERMEDIATE 1: *(R)-N²-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine*



Step 1: *tert-butyl (R)-(1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)carbamate*

Three reactions were run in parallel. To a solution of 3,6-dichloropyridazine (250 g, 1.68 mol, 1.0 *eq.)*, *tert*-butyl (*R*)-pyrrolidin-3-ylcarbamate (312 g, 1.68 mol, 1.0 *eq.)* in ACN (3.00 L) was added DIPEA (216 g, 1.68 mol, 292 mL, 1.0 *eq.)*. The mixture was stirred at 80 °C for 16 h. Water (4.50 L) was added into the reaction mixture with stirring before filtering. The filter cake was washed *in vacuo* with water (1.50 L) followed by PE (1.50 L). The filter cake was dried *in vacuo* to afford the *title compound* (1.16 kg, 76.8% yield) as a white solid without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 9.2 Hz, 1H), 6.62 (d, *J* = 9.6 Hz, 1H), 4.79 (br.s, 1H), 4.38 (br.s, 1H), 3.78 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.56-3.68 (m, 2H), 3.41 (dd, *J* = 10.8, 4.0 Hz, 1H), 2.25-2.37 (m, 1H), 1.97-2.08 (m, 1H), 1.45 (s, 9H). LCMS (Method 1, ESI) 299.0 $[MH]^+$, RT 0.866 minutes.

Step 2: *tert-butyl (R)-(1-(pyridazin-3-yl)pyrrolidin-3-yl)carbamate*

Three reactions were run in parallel. To a solution of *tert*-butyl (*R*)-(1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)carbamate (350 g, 1.17 mol, 1.00 *eq.)* in EtOH (3.00 L) was added Pd/C (30.0 g, 10.0% purity) and ammonium formate (738 g, 11.7 mol, 10.0 *eq.)*. The mixture was stirred at 70°C for 50 mins before filtering through a pad of celite. The filtrate was concentrated *in vacuo* and then re-treated with DCM (3.00 L). The mixture was filtered, and the filtrate was concentrated *in vacuo* to give the *title compound* (800 g, 85.5% yield) as a yellow solid without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 3.6 Hz, 1H), 7.17 (dd, *J* = 8.8, 4.4 Hz, 1H), 6.60 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.92 (br.s, 1H), 4.38 (br.s, 1H), 3.77 (q, *J* = 6.0 Hz, 1H), 3.56-3.69 (m, 2H), 3.42 (dd, *J* = 10.8, 4.4 Hz, 1H), 2.23-2.35 (m, 1H), 1.94-2.07 (m, 1H), 1.44 (s, 9 H). LCMS (Method 2, ESI) 265.1 $[MH]^+$, RT 0.343 minutes.

Step 3: *(R)-1-(pyridazin-3-yl)pyrrolidin-3-amine*

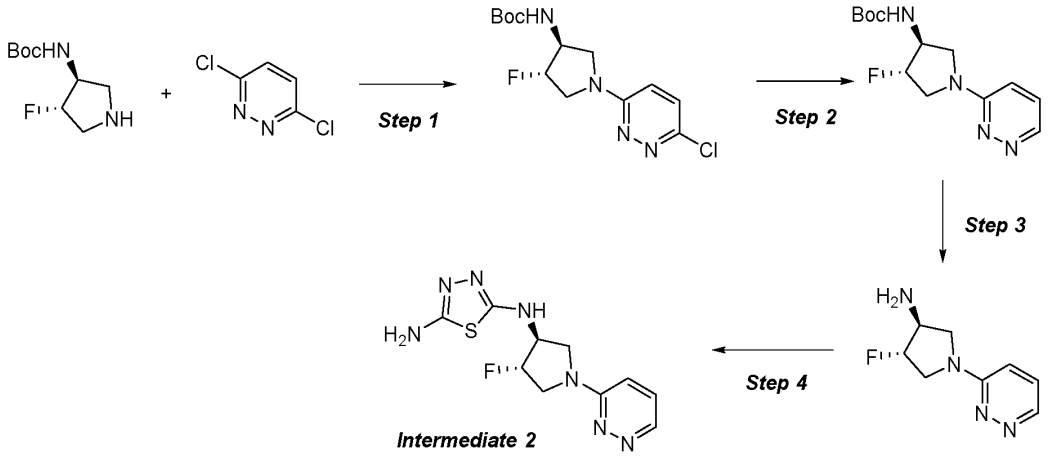
Two reactions were run in parallel. To a solution of *tert*-butyl (*R*)-(1-(pyridazin-3-yl)pyrrolidin-3-yl)carbamate (400 g, 1.51 mol, 1.00 *eq.)* in DCM (2.40 L) was added TFA (1.23 kg, 10.8 mol, 7.14 *eq.)*. The mixture was stirred at 25°C for 3 h. The reaction mixture was adjusted to pH = 7 by

addition of saturated aqueous Na_2CO_3 solution followed by concentrated *in vacuo*. The crude product was purified by reversed phase HPLC (0.1% $NH_3•H_2O$ condition) to afford the *title compound* (2.40 kg, 96.5% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (br.s, 1H), 7.32-7.35 (m, 1H), 6.84 (d, *J* = 9.2 Hz, 1H), 4.00-5.05 (br.s, 2H), 3.87 (br.s, 1H), 3.67-3.72 (m, 1H), 3.55-3.63 (m, 1H), 3.44-3.52 (m, 2H), 2.20-2.31 (m, 1 H), 1.98-2.08 (m, 1H). LCMS (An analogous method to Method 2, ESI) 165.1 $[MH]^+$, RT 0.654 minutes.

Step 4: *(R)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine*

Three reactions were run in parallel. To a solution of (*R*)-1-(pyridazin-3-yl)pyrrolidin-3-amine (581 g, 708 mmol, 20.0% purity, 1.00 *eq.)*, 5-bromo-1,3,4-thiadiazol-2-amine (153 g, 849 mmol, 1.20 *eq.)* in MeOH (3.00 L) was added DIPEA (137 g, 1.06 mol, 1.50 *eq.)*. The mixture was stirred at 45°C for 12 h before concentrated *in vacuo* to remove MeOH (*ca*. 2.0 L). The mixture was filtered and the filter cake was washed with MeOH (600 mL). The filter cake was then dried *in vacuo*. The crude product was triturated with water (750 mL x 2) and stirred at r.t. for 30 min. The mixture was filtered and the filter cake was triturated with MeOH (500 mL) at 40 °C for 30 min, then the mixture was cooled to r.t. and filtered. The filter cake was collected and dried *in vacuo* afford the *title compound* (252 g, 44.5% yield) as a grey solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (br.s, 1H), 7.30-7.34 (m, 1H), 7.08 (d, *J* = 5.2 Hz, 1H), 6.85 (d, = 8.8 Hz, 1H), 6.28 (br.s, 2H), 4.27 (br.d, *J* = 3.6 Hz, 1H), 3.70-3.72 (m, 1H), 3.53-3.54 (m, 2H), 3.44-3.47 (m, 1H), 2.22-2.29 (m, 1H), 1.99-2.08 (m, 1H). LCMS (Method 1, ESI) 264.0 $[MH]^+$, RT 0.725 minutes.

INTERMEDIATE 2: *N^2-[(3S,4S)-4-fluoro-1-(pyridazin-3-yl)pyrrolidin-3-yl]-1,3,4-thiadiazole-2,5-diamine*



Step 1: *tert-butyl N-[(3S,4S)-1-(6-chloropyridazin-3-yl)-4-fluoropyrrolidin-3-yl]carbamate*

To a stirred solution of *tert*-butyl *N*-[(3*S*,4*S*)-4-fluoropyrrolidin-3-yl]carbamate (0.9 g, 4.40 mmol, 1 *eq.*) in ethanol (18 mL) was added 3,6-dichloropyridazine (0.656 g, 4.40 mmol, 1 *eq.*) followed

by Et_3N (0.89 mL, 6.61 mmol, 1.5 *eq.*). The reaction mixture was then stirred at reflux for 16 h. The resulting mixture was diluted with EtOAc, washed with 0.1M HCl and brine, dried over sodium sulphate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica, 5-60% EtOAc in hexane) to afford the *title compound* (0.5 g, 34% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 9.4 Hz, 1H), 6.64 (d, *J* = 9.4 Hz, 1H), 5.22 (d, *J* = 50.8 Hz, 1H), 4.76 (s, 1H), 4.45 (s, 1H), 3.96-3.80 (m, 2H), 3.77 (s, 1H), 3.64 (d, *J* = 11.4 Hz, 1H), 1.44 (d, *J* = 7.9 Hz, 9H).

Step 2: *tert-butyl N-[(3S,4S)-4-fluoro-1-(pyridazin-3-yl)pyrrolidin-3-yl]carbamate*

To a solution of *tert*-butyl *N*-[(3*S*,4*S*)-1-(6-chloropyridazin-3-yl)-4-fluoropyrrolidin-3-yl] carbamate (0.25 g, 0.74 mmol, 1 *eq.*) in THF (15 mL) were added Pd/C (0.02 g, 10.0% purity) and ammonium formate (0.46 g, 7.41 mmol, 10 *eq.*). The mixture was stirred at 50 °C for 16 h and the reaction was filtered through a pad of *celite* and concentrated *in vacuo*. The crude compound (0.20 g, 87% yield) was used directly in the next step without any further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (d, *J* = 4.3 Hz, 1H), 7.37 (dd, *J* = 9.1, 4.4 Hz, 2H), 6.90 (d, *J* = 9.5 Hz, 1H), 5.16 (d, *J* = 52 hz, 1H), 4.27-4.14 (m, 1H), 3.87-3.67 (m, 3H), 3.51 (d, *J* = 11.2 Hz, 1H), 1.39 (s, 9H). UPLC (Method 5, ESI) 283.15 [MH]+, RT 1.67 minutes.

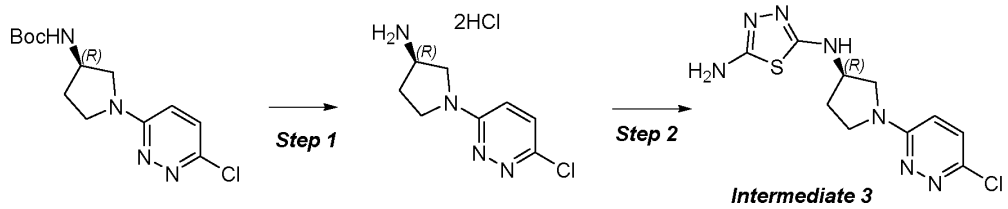
Step 3: *(3S,4S)-4-fluoro-1-(pyridazin-3-yl)pyrrolidin-3-amine hydrochloride*

To a solution of tert-butyl *N*-[(3*S*,4*S*)-4-fluoro-1-(pyridazin-3-yl)pyrrolidin-3-yl]carbamate (0.20 g, 0.65 mmol, 1 *eq.*) in DCM (10 mL) was added HCl solution in 1,4-dioxane (4 M, 0.96 mL, 3.86 mmol, 5 *eq.*). The reaction mixture was stirred at 55 °C for 38 h. The solvent was removed *in vacuo*, crude was washed with Et_2O to afford the *title compound* (1.97 g, 96% yield) as a white solid. ^{1}H NMR (300 MHz, D_2O) δ 8.60 (d, *J* = 4.7 Hz, 1H), 7.88 (dd, *J* = 9.5, 4.7 Hz, 1H), 7.60 (dd, *J* = 9.5, 1 hz, 1H), 5.67-5.44 (m, 1H), 4.38 -4.27 (m, 1H), 4.21-4.11 (m, 2H), 4.10-3.97 (m, 1H), 3.89 (dd, *J* = 12.7, 2.5 Hz, 1H), 3.59-3.51 (m, 1H). UPLC (Method 5, ESI) 183.05 [MH]+, RT 0.47 minutes.

Step 4: *N2-[(3S,4S)-4-fluoro-1-(pyridazin-3-yl)pyrrolidin-3-yl]-1,3,4-thiadiazole-2,5-diamine*

A mixture of (3*S*,4*S*)-4-fluoro-1-(pyridazin-3-yl)pyrrolidin-3-amine hydrochloride (0.19 g, 0.61 mmol, 1 *eq.*), 2-amino-5-bromo-1,3,4-thiadiazole (0.33 g, 1.82 mmol, 3 *eq.*) and potassium carbonate anhydrous (0.42 g, 3.04 mmol, 5 *eq.*) in anhydrous DMF (7 mL) was heated at 60°C for 10 h. The solvent was removed *in vacuo*, and the crude material was purified by flash chromatography (silica, 0-10% MeOH in DCM) to afford the *title compound* (0.11 g, 58% yield) as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (d, *J* = 4.1 Hz, 1H), 7.39 (dd, *J* = 9.2, 4.5 Hz, 1H), 7.22 (d, *J* = 5.4 Hz, 1H), 6.95 (d, *J* = 9.1 Hz, 1H), 6.42 (s, 2H), 5.36 (d, *J* = 51.4 Hz, 1H), 4.43-4.30 (m, 1H), 3.88-3.61 (m, 4H). UPLC (Method 5, ESI) 282.05 [MH]+, RT 0.51 minutes.

INTERMEDIATE 3: *(R)-N²-(1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine*



Intermediate 3

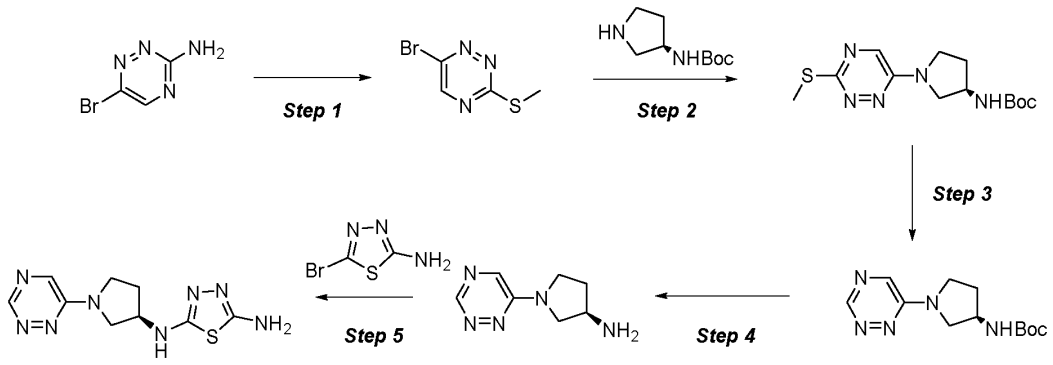
Step 1: *(R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-amine, dihydrochloride*

To a solution of *tert*-butyl (*R*)-(1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)carbamate (50.0 g, 167 mmol, 1.00 *eq.*) in EtOAc (400 mL) was added HCl/EtOAc (4 M, 227 mL, 5.43 *eq.*) at 0 °C. The mixture was stirred at r.t. for 4 h before filtering. The filter cake was dried *in vacuo* to afford the *title compound* (40.0 g, 147 mmol, 88.0% yield) as a white solid without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 3H), 7.75-7.78 (m. 1H), 7.41-7.44 (m, 1H), 3.98-4.03 (m, 1H), 3.76-3.84 (m, 3H), 3.63-3.73 (m, 1H), 2.26-2.51 (m, 2H). LCMS (Method 3, ESI) 199.1 $[MH]^+$, RT 0.211 minutes.

Step 2: *(R)-N²-(1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine*

To a solution of (*R*)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-amine, dihydrochloride (8.00 g, 29.5 mmol, 1.00 *eq.*) in ACN (69.0 mL) was added 5-bromo-1,3,4-thiadiazol-2-amine (6.89 g, 38.3 mmol, 1.30 *eq.*) and DIPEA (15.2 g, 117 mmol, 20.5 mL, 4.00 *eq.*). The mixture was stirred at 45 °C for 12 h. The mixture was filtered, and the filter cake was dried *in vacuo*. The crude product was purified by normal phase chromatography (column: Welch Ultimate XB-CN 250*70*10 μm; mobile phase: [Hexane-EtOH (0.1% $NH_3.H_2O$)]; B%: 20%-60%,15 min). The solvent was removed *in vacuo* to afford the *title compound* (25.2 g,77.2 mmol, 38.3% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, *J* = 9.2 Hz, 1H), 7.13 (d, *J* = 6 Hz, 1H), 7.69 (d, *J* = 9.6 Hz, 1H), 6.35 (s, 2H), 4.24-4.28 (m, 1H), 3.67-3.71 (m, 1H), 3.46-3.55 (m, 3H), 2.20-2.26 (m, 1H), 2.00-2.06 (m, 1H). LCMS (Method 4, ESI) 298.1/300.0 $[MH]^+$, RT 1.123 minutes.

INTERMEDIATE 4: *(R)-N2-(1-(1,2,4-triazin-6-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine*



Intermediate 4

Step 1: *6-bromo-3-(methylthio)-1,2,4-triazine*

To a mixture of 6-bromo-1,2,4-triazin-3-amine (15.0 g, 0.86 mol, 1.0 *eq.*) and 1,2-dimethyldisulfane (76 mL, 8.6 mmol, 10 *eq.*) in anhydrous ACN (60 mL) was added *tert*-butyl nitrite (63 mL, 0.51 mol, 6 *eq.*) dropwise and the reaction mixture was stirred at r.t. for 1 h. MeOH (6 mL) was added and the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 20% of EtOAc in PE) to afford the *title compound* (12.0 g, 42%) as a yellow oil. LCMS (Method 3, ESI):206.0 $[M+H]^+$, RT 0.373 minutes.

Step 2: *tert-butyl (R)-(1-(3-(methylthio)-1,2,4-triazin-6-yl)pyrrolidin-3-yl)carbamate*

To a stirred solution of 6-bromo-3-(methylthio)-1,2,4-triazine (12.0 g, 48.0 mmol, 1.0 *eq.*) in butan-l-ol (20 mL) were added *tert*-butyl (*R*)-pyrrolidin-3-ylcarbamate (9.82 g, 52.8 mmol, 1.1 *eq.*) and DIPEA (2.32 g, 134.0 mmol, 3.0 *eq.*). The resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was concentrated *in vacuo.* The residue was purified by reverse column chromatography (0-90% ACN in H_2O) then by flash chromatography (silica, 20% of EtOAc in PE) to afford the *title compound* (9.8 g, 65% yield) as a yellow solid. LCMS (Method 15, ESI): 312.1 $[M+H]^+$, RT 1.583 minutes. 1H MR (400 MHz, $CDCl_3$) 1.46 (9H, s), δ 1.96-2.09 (1H, m), 2.26-2.41 (1H, m), 2.63 (3H, s), 3.43 (1H, m), 3.58-3.72 (2H, m), 3.80 (1H, m), 4.39 (1H, s), 4.66 (1H, s), 7.91 (1H, s).

Step 3: *tert-butyl (R)-(1-(1,2,4-triazin-6-yl)pyrrolidin-3-yl)carbamate*

To a stirred solution of *tert*-butyl (*R*)-(1-(3-(methylthio)-1,2,4-triazin-6-yl)pyrrolidin-3-yl)carbamate (1.0 g, 3.20 mmol, 1.0 *eq.*) in EtOH (15 mL) and water (5 mL) was added Raney-Nickel (5 g, wet) and the mixture was refluxed for 48 h. The reaction mixture was filtered and to the filtrate was added MnO_2 (5.5 g, 64 mmol, 20 *eq.*). The resulting suspension was stirred at 25°C for 30 min. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by reverse column chromatography (0-90% ACN in H_2O) to afford the *title compound* (280 mg, 32% yield) as a yellow solid. LCMS (An analogous method to Method 21, ESI): 266.1 $[M+H]^+$,

RT 1.272 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.24 (s, 1H), 7.24 (d, *J* = 6.2 Hz, 1H), 4.16 (d, *J* = 4.8 Hz, 1H), 3.74-3.43 (m, 3H), 3.35 (dd, *J* = 11.1, 4.4 Hz, 1H), 2.15 (td, *J* = 13.2, 7.0 Hz, 1H), 1.93 (td, *J* = 12.9, 5.7 Hz, 1H), 1.39 (s, 9H).

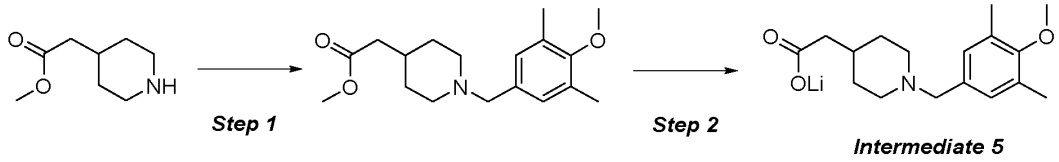
Step 4: *Preparation of (R)-1-(1,2,4-triazin-6-yl)pyrrolidin-3-amine*

To a stirred solution of *tert*-butyl (*R*)-(1-(1,2,4-triazin-6-yl)pyrrolidin-3-yl)carbamate (280 mg, 1.02 mmol, 1.0 *eq.*) in DCM (5 mL) was added HCl/dioxane (5 mL, 4M) and the resulting mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated *in vacuo.* The residue was basified with aqueous sodium carbonate solution (2N, 1.5 mL). the mixture was concentrated *in vacuo* and the residue was washed with MeOH (15 mL x 3). The organic layer was concentrated *in vacuo* to afford the *title compound* (260 mg as crude) as a yellow solid. LCMS (An analogous method to Method 15, ESI): 166.3 $[M+H]^+$, RT 0.243 minutes.

Step 5: *(R)-N2-(1-(1,2,4-triazin-6-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine*

To a stirred solution of (*R*)-1-(1,2,4-triazin-6-yl)pyrrolidin-3-amine (260 mg crude, 1.02 mmol, 1.0 *eq.*) in DMF (5 mL) was added 5-bromo-1,3,4-thiadiazol-2-amine (456 mg, 2.55 mmol, 2.5 *eq.*) and $NaHCO_3$ (257 mg, 3.06 mmol, 3.0 *eq.*). The resulting mixture was stirred at 80°C for 4 h. The reaction mixture was concentrated *in vacuo.* The residue was purified by flash chromatography (silica, 10% of EtOAc in PE) to afford the *title compound* (150 mg, 0.56 mmol, 55% yield over two steps) as a yellow solid. LCMS (An analogous method to Method 21, ESI): 265.0 $[M+H]^+$, RT 0.532 minutes.

INTERMEDIATE 5: *lithio 2-{1-[(4-methoxy-3,5-dimethylphenyl)methyl]piperidin-4-yl}acetate*



Intermediate 5

Step 1: *methyl 2-{1-[(4-methoxy-3,5-dimethylphenyl)methyl]piperidin-4-yl}acetate*

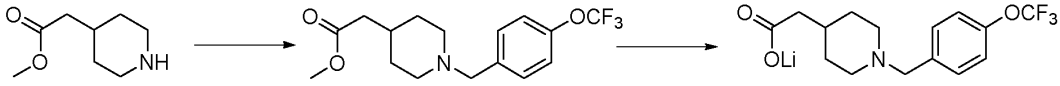
To a stirred solution of methyl (piperidin-4-yl)acetate hydrochloride (280 mg, 1.44 mmol, 0.95 *eq.*) in MeOH (25 mL) was added 3,5-dimethyl-4-methoxybenzaldehyde (250 mg, 1.52 mmol, 1.0 *eq.*) and the reaction mixture was stirred at r.t. under argon for 2 h. Sodium cyanoborohydride (136 mg, 2.28 mmol, 1.5 *eq.*) was added and the reaction mixture was stirred at r.t. for 16 h before the solvent was removed *in vacuo*. Crude mixture was re-dissolved in DCM and saturated aqueous sodium bicarbonate solution was added. Stirring was continued for 15 min and phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the *title compound* (210 mg,

40% yield) without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 2H), 3.83-3.76 (m, 3H), 3.76 – 3.68 (m, 3H), 3.38 – 3.29 (m, 1H), 2.35 (s, 6H), 2.31 – 2.22 (m, 5H), 1.56 (s, 7H). UPLC (Method 20, ESI) 306.10 $[MH]^+$, RT 2.10 min.

Step 2: *lithio 2-{1-[(4-methoxy-3,5-dimethylphenyl)methyl]piperidin-4-yl}acetate*

To a stirred solution of methyl 2-{1-[(4-methoxy-3,5-dimethylphenyl)methyl]piperidin-4-yl}acetate (210 mg, 0.63 mmol, 1 *eq.*) in a mixture of THF (4.6 mL) and water (3.2 mL) was added lithium hydroxide monohydrate (52 mg, 1.22 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (120 mg, 43% yield) without further purification. UPLC (An analogous method to Method 5, ESI) 292.10 $[MH]^+$, RT 1.76 min.

INTERMEDIATE 6: *lithio 2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate*



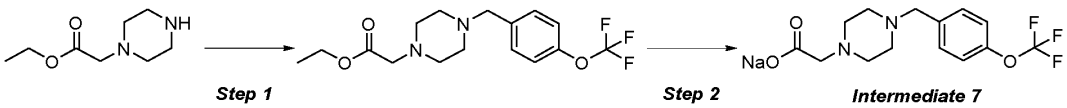
Step 1: *methyl 2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate*

To a solution of methyl (piperidin-4-yl)acetate hydrochloride (170 mg, 0.88 mmol, 0.9 *eq.*) and anhydrous potassium carbonate (470 mg, 3.43 mmol, 3.5 *eq.*) in ACN (25 mL) was added 4-(trifluoromethoxy)benzyl bromide (0.16 mL, 0.98 mmol, 1.0 *eq.*). The reaction mixture was stirred at r.t. for 3 h before it was filtered and concentrated *in vacuo* to afford the *title compound* (450 mg, quantitative yield) without further purification. UPLC (An analogous method to Method 5, ESI) 332.25 $[MH]^+$, RT 2.05 min.

Step 2: *lithio 2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate*

To a stirred solution of methyl 2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate (450 mg, 0.95 mmol, 1 *eq.*) in MeOH (10 mL) was added lithium hydroxide monohydrate (790 mg, 1.9 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 56 h and the solvent was removed *in vacuo* to afford the *title compound* (420 mg, 62% yield) without further purification. UPLC (An analogous method to Method 5, ESI) 318.25 $[MH]^+$, RT 1.88 min.

INTERMEDIATE 7: *sodium 2-(4-{[4-(trifluoromethoxy)phenyl]methyl}piperazin-1-yl)acetate*



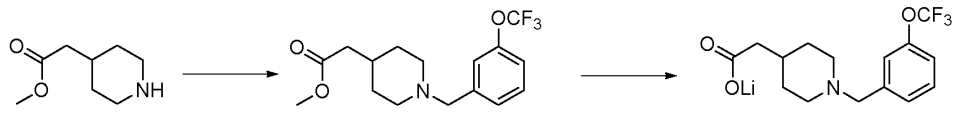
Step 1: *ethyl 2-(4-{[4-(trifluoromethoxy)phenyl]methyl}piperazin-1-yl)acetate*

To a stirred solution of 1-(ethoxycarbonylmethyl)piperazine (200 mg, 1.16 mmol, 1 *eq.*) in ACN (5.8 mL), was added Et_3N (486 µL, 3.48 mmol, 3 *eq.*) followed by 4-(trifluoromethoxy)benzyl bromide (296 mg, 1.161 mmol, 1 *eq.*). The reaction mixture was stirred at r.t. for 16 h and the solvent was removed *in vacuo*. The crude material was re-dissolved in DCM and saturated aqueous sodium bicarbonate solution was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the *title compound* (346 mg, 86% yield) as a yellow oil without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.51 (s, 2H), 3.20 (s, 2H), 2.68 – 2.57 (m, 4H), 2.57 – 2.45 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H). UPLC (An analogous method to Method 5, ESI) 347.25 $[MH]^+$, RT 1.64 min.

Step 2: *sodium 2-(4-{[4-(trifluoromethoxy)phenyl]methyl}piperazin-1-yl)acetate*

To a stirred solution of ethyl 2-(4-{[4-(trifluoromethoxy)phenyl]methyl}piperazin-1-yl)acetate (346 mg, 1.00 mmol, 1 *eq.*) in MeOH (5.0 mL) was added aqueous sodium hydroxide solution (1M, 2.0 mL, 2.00 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (400 mg, quantitative yield, 80% purity) as a yellow solid without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.45 – 7.37 (m, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.45 (s, 2H), 2.61 (s, 2H), 2.45 – 2.29 (m, 8H). UPLC (An analogous method to Method 5, ESI) 319.10 $[MH]^+$, RT 1.55 min.

INTERMEDIATE 8: *lithio 2-(1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate*



Step 1 *Step 2* ***Intermdiate 8***

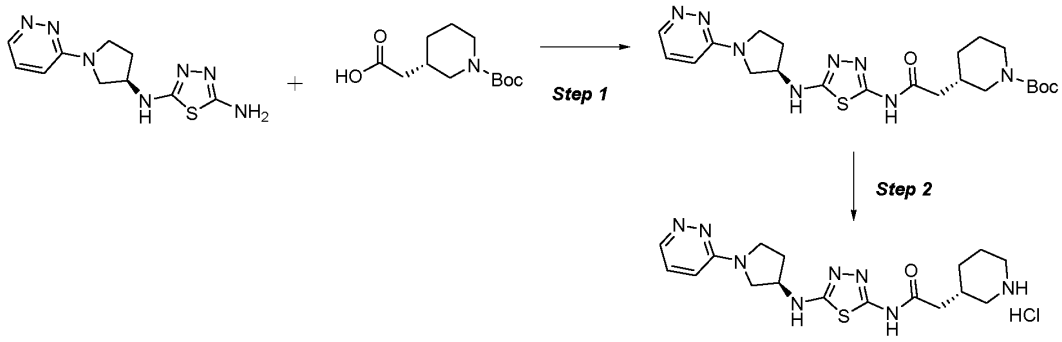
Step 1: *methyl 2-(1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate*

To a stirred solution of 3-(trifluoromethoxy)benzaldehyde (154 µL, 1.05 mmol, 1.0 *eq.*) in MeOH (5.3 mL) was added methyl (piperidin-4-yl)acetate hydrochloride (224 mg, 1.16 mmol, 1.1 *eq.*). The reaction mixture was stirred at r.t. for 15 min and then sodium cyanoborohydride (94 mg, 1.58 mmol, 1.5 *eq.*) was added. The reaction mixture was stirred at r.t. for 16 h before concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-10% MeOH/ DCM) to afford the *title compound* (175 mg, 40% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.44 (t, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.27 – 7.17 (m, 2H), 3.57 (s, 3H), 3.48 (s, 2H), 2.83 – 2.57 (m, 2H), 2.23 (d, *J* = 6.7 Hz, 2H), 1.93 (td, *J* = 12.1, 2.3 Hz, 2H), 1.80 – 1.43 (m, 2H), 1.38 – 1.08 (m, 3H). UPLC (An analogous method to Method 5, ESI) 332.25 $[MH]^+$, RT 1.98 min.

Step 2: *lithio 2-(1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate*

To a stirred solution of methyl 2-(1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate (165 mg, 0.39 mmol, 1 *eq.*) in MeOH (2.0 mL) was added aqueous sodium hydroxide solution (1M, 0.79 mL, 0.79 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 16 h before removed *in vacuo* to afford the *title compound* (190 mg, quantitative yield) without further purification. UPLC (An analogous method to Method 5, ESI) 318.20 $[MH]^+$, RT 1.76.

INTERMEDIATE 9: *2-[(3S)-piperidin-3-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide hydrochloride*



Intermediate 9

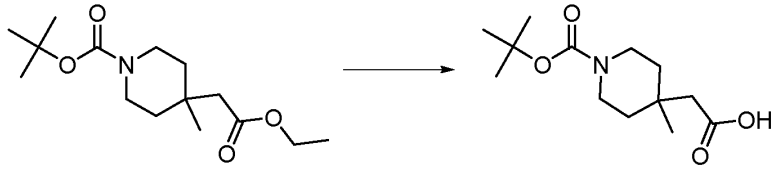
Step 1: *tert-butyl (3S)-3-{[(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamoyl]methyl}piperidine-1-carboxylate*

To a stirred solution of *(R)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine (*prepared according to the procedure of *Intermediate 1)* (250 mg, 0.94 mmol, 1.0 *eq.*) in anhydrous DMF (18.7 mL) was added 2-[(3*S*)-1-[(*tert*-butoxy)carbonyl]piperidin-3-yl]acetic acid (220 mg, 0.94 mmol, 1.0 *eq.*), DIPEA (0.82 mL, 4.67 mmol, 5.0 *eq.*) and 1-propylphosphonic acid cyclic anhydride (50+% soln. in DMF, 0.82 mL, 2.81 mmol, 3.0 *eq.*). The reaction mixture was stirred at r.t. for 16 h. The reaction mixture was diluted with DCM and saturated aqueous sodium bicarbonate solution was added. Stirring was continued for 15 min and phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-10% MeOH in DCM) to give the *title compound* (340 mg, 74% yield) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.62 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.44 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.71 – 3.63 (m, 3H), 3.61 – 3.46 (m, 3H), 2.88 – 2.74 (m, 1H), 2.33 – 2.23 (m, 3H), 2.13 – 2.01 (m, 1H), 1.92 – 1.77 (m, 1H), 1.76 – 1.65 (m, 1H), 1.63 – 1.52 (m, 1H), 1.36 (s, 11H). UPLC (An analogous method to Method 5, ESI) 489.3 $[MH]^+$, RT 1.78 min.

Step 2: *2-[(3S)-piperidin-3-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide hydrochloride*

To a stirring solution of *tert*-butyl (3*S*)-3-{[(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamoyl]methyl}piperidine-1-carboxylate (340 mg, 0.69 mmol, 1 *eq.*) in anhydrous MeOH (7.0 mL) was added HCl in dioxane (4M, 1.74 mL, 6.96 mmol, 30 *eq.*) and the mixture was stirred at r.t. for 16 h. Solvent was removed *in vacuo* to give the *title compound* (350 mg, 99% yield, 75% purity) as a yellow solid. UPLC (An analogous method to Method 5, ESI) 388.95 $[MH]^+$, RT 0.64 min.

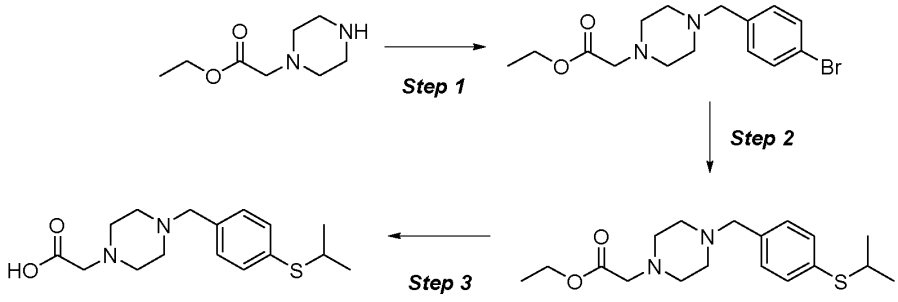
INTERMEDIATE 10: *2-{1-[(tert-butoxy)carbonyl]-4-methylpiperidin-4-yl}acetic acid*



Intermediate 10

To a stirred solution of *tert*-butyl 4-(2-ethoxy-2-oxo-ethyl)-4-methyl-piperidine-1-carboxylate (1.0 g, 3.50 mmol, 1 *eq.*) in MeOH (17.5 mL) was added aqueous sodium hydroxide solution (1M, 7.0 mL, 7.00 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 16 h before concentrated *in vacuo*. Crude was dissolved in water and acidified with 10% aqueous potassium bisulphate solution till pH = 3. Aqueous phase was extracted with EtOAc (3x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the *title compound* (1.0 g, quantitative yield, 90% purity) as a colourless oil without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.03 (s, 1H), 3.44 – 3.36 (m, 2H), 3.29 – 3.16 (m, 2H), 2.18 (s, 2H), 1.50 – 1.40 (m, 2H), 1.38 (s, 9H), 1.35 – 1.24 (m, 2H), 1.01 (s, 3H). UPLC (An analogous method to Method 5, ESI) 256.20 $[MH]^-$, RT 1.55 min.

INTERMEDIATE 11: *2-(4-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperazin-1-yl)acetic acid*



Intermediate 11

Step 1: *ethyl 2-{4-[(4-bromophenyl)methyl]piperazin-1-yl}acetate*

To a mixture of 4-bromobenzyl bromide (500 mg, 2.00 mmol, 1 *eq.*) and anhydrous potassium carbonate (830 mg, 6.00 mmol, 3 *eq.*) in ACN (20.0 mL) at -10°C under argon was added

dropwise a solution of ethyl 2-(piperazin-1-yl)acetate (370 µL, 2.20 mmol, 1.1 *eq.*) in ACN (1.0 mL). The reaction mixture was stirred at r.t. for 16 h. Then, it was filtered and concentrated *in vacuo.* The crude material was dissolved in DCM and saturated aqueous sodium bicarbonate solution was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the *title compound* (680 mg, quantitative yield) without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.58 – 7.43 (m, 2H), 7.29 – 7.21 (m, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.41 (s, 2H), 3.18 (s, 2H), 2.49 – 2.43 (m, 4H), 2.42 – 2.23 (m, 4H), 1.17 (t, *J* = 7.1 Hz, 3H).

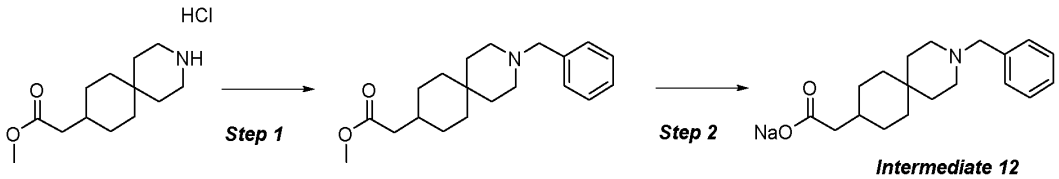
Step 2: *ethyl 2-(4-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperazin-1-yl)acetate*

A solution of ethyl 2-{4-[(4-bromophenyl)methyl]piperazin-1-yl}acetate (100 mg, 0.28 mmol, 1.0 *eq.*), propane-2-thiol (28 µL, 0.30 mmol, 1.1 *eq.*) in anhydrous dioxane (4.0 mL) was purged with argon for 10 min. Tris(dibenzylideneacetone)dipalladium(0) (25 mg, 0.03 mmol, 0.1 *eq.*) and XantPhos (16 mg, 0.03 mmol, 0.1 *eq.*) were then added and the mixture was purged with argon for 5 min. After that, DIPEA (150 µL, 0.83 mmol, 3.0 *eq.*) was added and the mixture was purged with argon for 5 min. The reaction mixture was heated at 100°C for 16 h. Then, it was filtered through a pad of Celite®, washed with MeOH and the organic layer was concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-5% MeOH in DCM) to afford the *title compound* (80 mg, 81% yield). ^{1}H NMR (300 MHz, methanol-d_4) δ 7.38 – 7.33 (m, 2H), 7.30 – 7.25 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.52 (s, 2H), 3.46 – 3.34 (m, 1H), 3.23 (s, 2H), 2.76 – 2.43 (m, 8H), 1.29 – 1.22 (m, 9H). UPLC (An analogous method to Method 5, ESI) 338.0 $[MH]^+$, RT 1.73 min.

Step 3: *2-(4-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperazin-1-yl)acetic acid*

To a stirred solution of ethyl 2-(4-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperazin-1-yl)acetate (260 mg, 0.73 mmol, 1 *eq.*) in MeOH (15.0 mL) was added lithium hydroxide monohydrate (160 mg, 6.60 mmol, 9 *eq.*). The reaction mixture was stirred at 40°C for 48 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (230 mg, quantitative yield) without further purification. UPLC (An analogous method to Method 5, ESI) 307.8 $[MH]^-$, RT 1.32 min.

INTERMEDIATE 12: *sodium 2-{3-benzyl-3-azaspiro[5.5]undecan-9-yl}acetate*



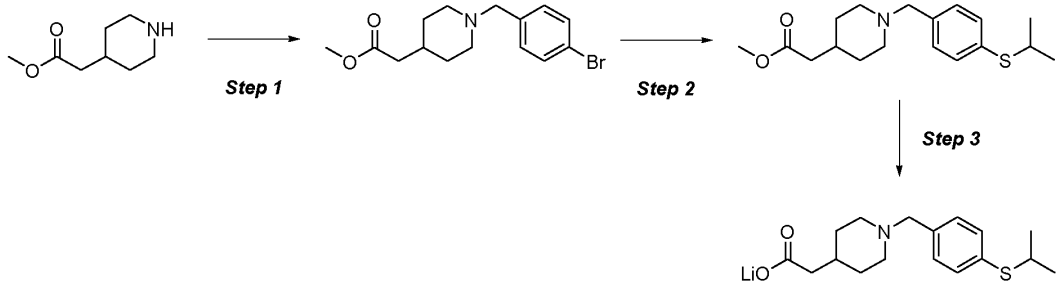
Step 1: *methyl 2-{3-benzyl-3-azaspiro[5.5]undecan-9-yl}acetate*

To a stirred solution of methyl 2-{3-azaspiro[5.5]undecan-9-yl}acetate hydrochloride (730 mg, 2.79 mmol, 1.0 *eq.*) in ACN (13.9 mL) was added benzyl bromide (570 mg, 3.35 mmol, 1.2 *eq.*) followed by Et_3N (1.13 g, 1.55 mL, 11.15 mmol, 4.0 *eq.*). The reaction mixture was stirred at r.t. for 16 h and the solvent was removed *in vacuo*. The crude material was purified by flash chromatography (silica, 0-10% MeOH in DCM) to afford the *title compound* (810 mg, 70% yield, 64% purity). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.46 (m, 2H), 7.43 – 7.32 (m, 3H), 3.91 (s, 2H), 3.65 (s, 3H), 2.93 – 2.60 (m, 4H), 2.20 (d, *J* = 7.0 Hz, 2H), 1.88 – 1.79 (m, 2H), 1.79 – 1.61 (m, 5H), 1.60 – 1.51 (m, 2H), 1.21 – 1.04 (m, 4H). UPLC (An analogous method to Method 5, ESI) 316.5 $[MH]^+$, RT 1.62 min.

Step 2: *sodium 2-{3-benzyl-3-azaspiro[5.5]undecan-9-yl}acetate*

To a stirred solution of methyl 2-{3-benzyl-3-azaspiro[5.5]undecan-9-yl}acetate (300 mg, 0.67 mmol, 1 *eq.*) in MeOH (3.3 mL), was added aqueous sodium hydroxide solution (1M, 1.33 mL, 1.33 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 16 h and aqueous sodium hydroxide solution (1 M, 0.67 mL, 0.67 mmol, 1 *eq.*) was added. Stirring was continued at r.t. for an additional 16 h. After completion, solvent was concentrated *in vacuo* to afford the *title compound* (400 mg, quantitative yield) without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.36 – 7.16 (m, 5H), 3.42 (s, 2H), 2.34 – 2.22 (m, 4H), 1.77 – 1.69 (m, 2H), 1.60 – 1.38 (m, 7H), 1.32 – 1.20 (m, 2H), 1.07 – 0.90 (m, 4H). UPLC (An analogous method to Method 5, ESI) 302.35 $[MH]^+$, RT 1.48 min.

INTERMEDIATE 13: *lithio 2-(1-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-4-yl)acetate*



Intermediate 13

Step 1: *methyl 2-{1-[(4-bromophenyl)methyl]piperidin-4-yl}acetate*

To a solution of 4-bromobenzyl bromide (500 mg, 2.0 mmol, 1.0 *eq.*) and anhydrous potassium carbonate (830 mg, 6.0 mmol, 3.0 *eq.*) in ACN (20.0 mL) at -10°C was added a solution of methyl (piperidin-4-yl)acetate hydrochloride (430 µL, 2.2 mmol, 1.1 *eq.*) in ACN (1.0 mL) dropwise under argon. The reaction mixture was stirred at r.t. for 16 h before filtered and concentrated *in vacuo.* Crude reaction was dissolved in DCM and saturated aqueous sodium bicarbonate solution was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was

extracted with DCM (3x). Combined organic layers were washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo.* Crude material was purified by flash chromatography (silica, 5% MeOH in DCM) to afford the *title compound* (620 mg, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 2H), 7.22 – 7.15 (m, 2H), 3.66 (s, 3H), 3.42 (s, 2H), 2.87 – 2.77 (m, 2H), 2.23 (d, *J* = 7.0 Hz, 2H), 1.97 (td, *J* = 11.7, 2.3 Hz, 2H), 1.85 – 1.72 (m, 1H), 1.72 – 1.63 (m, 2H), 1.39 – 1.19 (m, 2H).

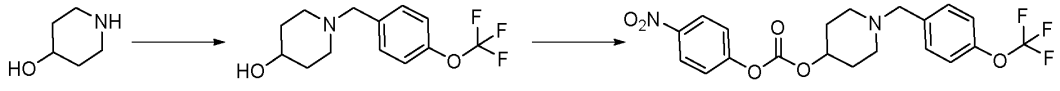
Step 2: *methyl 2-(1-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-4-yl)acetate*

A solution of methyl 2-{1-[(4-bromophenyl)methyl]piperidin-4-yl}acetate (200 mg, 0.58 mmol, 1.0 *eq.*), propane-2-thiol (59 µL, 0.64 mmol, 1.1 *eq.*) in anhydrous dioxane (4.0 mL) was purged with argon for 10 min. Then, Tris(dibenzylideneacetone)dipalladium(0) (34 mg, 0.06 mmol, 0.1 *eq.*) and XantPhos (34m g, 0.06 mmol, 0.1 *eq.*) were added and mixture was purged with argon for 5 min. After that, DIPEA (304 µL, 1.74 mmol, 3.0 *eq.*) was added and the mixture was purged with argon for another 5 min. The reaction was heated at 120°C for 16 h. Then, it was filtered through a pad of Celite®, washed with MeOH and concentrated *in vacuo.* Crude material was purified by flash chromatography (silica, 0-5% MeOH in DCM) to afford the *title compound* (180 mg, 91% yield). ^{1}H NMR (300 MHz, methanol-d_4) δ 7.42 – 7.37 (m, 2H), 7.36 – 7.30 (m, 2H), 3.80 (s, 2H), 3.65 (s, 3H), 3.45 (hept, *J* = 6.7 Hz, 1H), 3.20 – 3.05 (m, 2H), 2.54 – 2.36 (m, 2H), 2.30 (d, *J* = 6.8 Hz, 2H), 1.97 – 1.75 (m, 3H), 1.49 – 1.33 (m, 2H), 1.28 (d, *J* = 6.7 Hz, 6H). UPLC (An analogous method to Method 5, ESI) 324.1 $[MH]^+$, RT 1.83 min.

Step 3: *lithio 2-(1-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-4-yl)acetate*

To a stirred solution of methyl 2-(1-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-4-yl)acetate (260 mg, 0.77 mmol, 1 *eq.*) in MeOH (15.0 mL) was added lithium hydroxide monohydrate (160 mg, 6.60 mmol, 9 *eq.*). The reaction mixture was stirred at 45°C for 48 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (0.24 g, quantitative yield) without further purification. UPLC (An analogous method to Method 5, ESI) 308.9 $[MH]^-$, RT 1.33 min.

INTERMEDIATE 14: *4-nitrophenyl 1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl carbonate*



Step 1 ***Step 2*** ***Intermediate 14***

Step 1: *1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-ol*

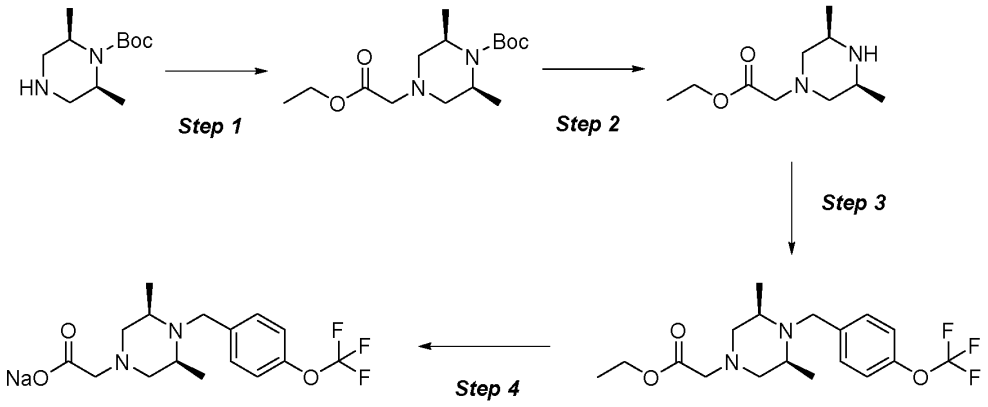
To a stirred solution of piperidin-4-ol (2.00 g, 19.77 mmol, 1 *eq.*) in ACN (60.0 mL) was added 4-(trifluoromethoxy)benzyl bromide (20.01 g, 19.77 mmol, 1 *eq.*) followed by Et_3N (27.56 mL, 197.73 mmol, 10 *eq.*). The reaction mixture was stirred at r.t. for 16 h. Then, it was filtered and concentrated *in vacuo.* Crude material was purified by flash chromatography (silica, 0-5% MeOH

in DCM) to afford the *title compound* (2.02 g, 27% yield, 74% purity). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.49 – 7.39 (m, 2H), 7.37 – 7.27 (m, 2H), 4.60 (bs, 1H), 3.58 – 3.39 (m, 3H), 2.81 – 2.58 (m, 2H), 2.23 – 1.85 (m, 2H), 1.76 – 1.63 (m, 2H), 1.49 – 1.31 (m, 2H). UPLC (An analogous method to Method 5, ESI) 276.0 $[MH]^+$, RT 1.75 minutes.

Step 2: *4-nitrophenyl 1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl carbonate*

To a stirred solution of 1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-ol (0.74 g, 2.69 mmol, 1 *eq.*) and DIPEA (0.94 mL, 5.38 mmol, 2.0 *eq.*) in anhydrous DMF (30.0 mL) under argon at 0°C, a solution of 4-nitrophenyl chloroformate (1.03 g, 5.11 mmol 1.9 *eq.*) in anhydrous DMF (30.0 mL) was added dropwise. The solution was stirred at 0°C for 1 h, warmed to r.t. and stirred for 16 h. The solvent was removed *in vacuo* and the crude residue was purified by flash chromatography (silica, 0-30% EtOAc in hexanes) to afford the *title compound* (106 mg, 7% yield, 73% purity). UPLC (An analogous method to Method 5, ESI) 441.35 $[MH]^+$, RT 2.51 min.

INTERMEDIATE 15: *sodium 2-[(3R,5S)-3,5-dimethyl-4-{[4-trifluoromethoxy)phenyl]methyl}piperazin-1-yl]acetate*



Intermediate 15

Step 1: *tert-butyl (2R,6S)-4-(2-ethoxy-2-oxoethyl)-2,6-dimethylpiperazine-1-carboxylate*

To a stirred solution of (2*R*,6*S*)-*tert*-butyl 2,6-dimethylpiperazine-1-carboxylate (474 mg, 2.21 mmol, 1 *eq.*) in ACN (10.0 mL), was added ethyl bromoacetate (489 µL, 4.42 mmol, 2 *eq.*) followed by Et_3N (1.23 mL, 8.84 mmol, 4 *eq.*). The reaction mixture was stirred at r.t. for 16 h. After completion, it was concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-5% MeOH in DCM) to afford the *title compound* (664 mg, 95% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.09 (q, *J* = 7.1 Hz, 2H), 3.99 – 3.89 (m, 2H), 3.22 (s, 2H), 2.64 (d, *J* = 11.3 Hz, 2H), 2.23 (dd, *J* = 11.3, 4.5 Hz, 2H), 1.40 – 1.38 (m, 9H), 1.22 – 1.16 (m, 9H). UPLC (An analogous method to Method 5, ESI) 301.3 $[MH]^+$, RT 2.76 min.

Step 2: *ethyl 2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]acetate*

To a stirred solution of *tert*-butyl (2*R*,6*S*)-4-(2-ethoxy-2-oxoethyl)-2,6-dimethylpiperazine -1-carboxylate (664 mg, 2.10 mmol, 1 *eq.*) in DCM (10.0 mL) at 0ºC was added HCl in dioxane (4M, 5.30 mL, 20.99 mmol, 10 *eq.*). The reaction mixture was stirred at r.t. for 16 h before concentrated *in vacuo* to afford the *title compound* (675 mg, quantitative yield, 90% purity). ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.15 (q, *J* = 7.1 Hz, 2H), 3.56 (s, 2H), 3.50 – 3.38 (m, 3H), 3.29 – 3.20 (m, 2H), 2.82 – 2.68 (m, 2H), 1.27 – 1.19 (m, 9H).

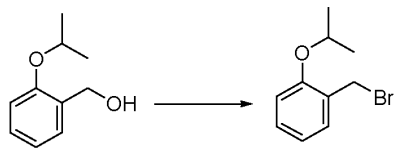
Step 3: *ethyl 2-[(3R,5S)-3,5-dimethyl-4-{[4-(trifluoromethoxy)phenyl]methyl}piperazin -1-yl]acetate*

To a stirred solution of ethyl 2-[(3*R*,5*S*)-3,5-dimethylpiperazin-1-yl]acetate (595 mg, 2.67 mmol, 1.0 *eq.*) in ACN (12.0 mL) was added 4-(trifluoromethoxy)benzyl bromide (642 µL, 4.01 mmol, 1.5 *eq.*) followed by Et_3N (1.50 mL, 10.70 mmol, 10.0 *eq.*). The reaction mixture was stirred at r.t. for 16 h before concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-50% EtOAc in cyclohexane) to afford the *title compound* (54 mg, 5% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.48 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 2H), 3.14 (s, 2H), 2.76 – 2.66 (m, 2H), 2.58 (ddd, *J* = 9.3, 6.2, 2.9 Hz, 2H), 2.06 – 1.93 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.1 Hz, 6H).

Step 4: *sodium 2-[(3R,5S)-3,5-dimethyl-4-{[4-(trifluoromethoxy)phenyl]methyl}piperazin-1-yl]acetate*

To a stirred solution of ethyl 2-[(3*R*,5*S*)-3,5-dimethyl-4-{[4-(trifluoromethoxy)phenyl]methyl} piperazin-1-yl]acetate (54 mg, 0.14 mmol, 1 *eq.*) in THF (0.8 mL), was added aqueous sodium hydroxide solution (0.9M, 300 µL, 0.27 mmol, 2 *eq.*) at r.t. and the reaction mixture was stirred at 60°C for 16 h. After completion, solvent was concentrated *in vacuo* to afford the *title compound* (59 mg, quantitative yield, 94% purity). UPLC (An analogous method to Method 5, ESI) 347.7 $[MH]^-$, RT 1.35 min.

INTERMEDIATE 16: *1-(bromomethyl)-2-(propan-2-yloxy)benzene*

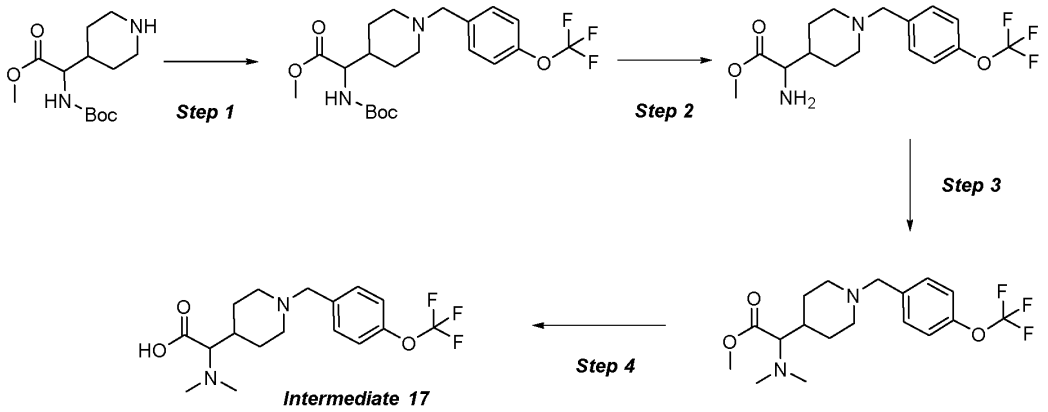


Intermediate 16

To a solution of [2-(propan-2-yloxy)phenyl]methanol (0.15 g, 0.90 mmol, 1.0 *eq.*) in anhydrous DCM (6.0 mL) under argon at 0°C, phosphorus tribromide (0.318 g, 1.17 mmol, 1.3 *eq.*) was added dropwise. The solution was stirred at 0°C for 5 h, warmed to r.t. and stirred for 16 h. The

reaction mixture was neutralised to pH = 7 by addition of saturated aqueous sodium bicarbonate solution, diluted with water and extracted with DCM (3x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to give the *title compound* (150 mg, 67% yield) without any further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.38 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.29 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.03 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.88 (td, *J* = 7.4, 1.1 Hz, 1H), 4.69 (p, *J* = 6.1 Hz, 1H), 4.62 (s, 2H), 1.30 (d, *J* = 6.0 Hz, 6H). UPLC (An analogous method to Method 5, ESI) 229.05 $[MH]^+$, RT 1.87 min.

INTERMEDIATE 17: *2-(dimethylamino)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetic acid*



Step 1: *methyl 2-{[(tert-butoxy)carbonyl]amino}-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}-piperidin-4-yl)acetate*

To a stirred solution of methyl 2-{[(*tert*-butoxy)carbonyl]amino}-2-(piperidin-4-yl)acetate (250 mg, 0.92 mmol, 1.0 *eq.*) and anhydrous potassium carbonate (380 mg, 2.75 mmol, 3.0 *eq.*) in ACN (10.0 mL) at -5°C under argon, a solution of 4-(trifluoromethoxy)benzyl bromide (260 µL, 1.01 mmol, 1.1 *eq.*) in ACN (1.5 mL) was added dropwise. The reaction mixture was stirred at -5°C for 1 h, then warmed up to r.t. and stirred for 3 h. Then, it was filtered and the filtrate concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 3% MeOH in DCM) to afford the *title compound* (350 mg, 77% yield, 90% purity). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 2H), 7.20 – 7.12 (m, 2H), 5.16 – 4.95 (m, 1H), 4.34 – 4.23 (m, 1H), 3.74 (s, 4H), 3.57 – 3.38 (m, 2H), 3.01 – 2.77 (m, 2H), 2.07 – 1.86 (m, 2H), 1.84 – 1.70 (m, 1H), 1.65 – 1.50 (m, 3H), 1.43 (s, 9H). UPLC An analogous method to Method 5, ESI) 447.3 $[MH]^+$, RT 4.27 min.

Step 2: *methyl 2-amino-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate hydrochloride*

To a stirred solution of methyl 2-{[(*tert*-butoxy)carbonyl]amino}-2-(1-{[4-(trifluoromethoxy) phenyl]methyl}-piperidin-4-yl)acetate (350 mg, 0.71 mmol, 1 *eq.*) in Et_2O (14.0 mL) was added

HCl solution in Et_2O (2M, 2.12 mL, 4.23 mmol, 6 *eq.*). The reaction mixture was stirred at r.t. for 16 h. HCl solution in Et_2O (2M, 2.12 mL, 4.23 mmol, 6 *eq.*) was added and the mixture was stirred at 45°C for 16 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (270 mg, quantitative yield) without further purification. ^{1}H NMR (300 MHz, Deuterium Oxide) δ 7.61 – 7.53 (m, 2H), 7.47 – 7.38 (m, 2H), 4.34 (s, 2H), 4.13 (d, *J* = 5.4 Hz, 1H), 3.86 (s, 3H), 3.68 – 3.50 (m, 2H), 3.16 – 2.96 (m, 2H), 2.43 – 2.25 (m, 1H), 2.13 – 1.95 (m, 2H), 1.93 – 1.71 (m, 1H), 1.71 – 1.50 (m, 1H).

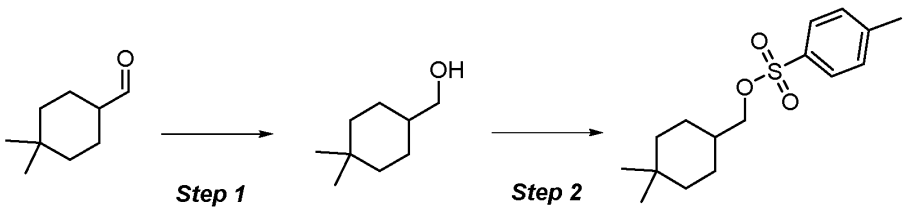
Step 3: *methyl 2-(dimethylamino)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate*

To a stirred solution of methyl 2-amino-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate hydrochloride (270 mg, 0.70 mmol, 1 *eq.*) in MeOH (13.5 mL) was added formaldehyde solution (37 wt. % in H_2O, contains 10-15% MeOH as stabilizer, 720 µL, 7.10 mmol, 10 *eq.*). The reaction mixture was stirred at r.t. for 1 h. Acetic acid (1.0 mL) was then added and stirring was continued at 45°C for 3 h. Then, sodium cyanoborohydride (63 mg. 1.06 mmol, 1.5 *eq.*) was added. The reaction mixture was stirred at r.t. for 16 h before concentrated *in vacuo*. Crude material was washed with saturated aqueous sodium bicarbonate solution and extracted with DCM (3x). Combined organic layer were dried over sodium sulphate, filtered and concentrated *in vacuo* to give the *tittle compound* (264 mg, 92% yield) without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 2H), 7.20 – 7.12 (m, 2H), 3.68 (s, 3H), 3.63 – 3.42 (m, 2H), 2.97 – 2.85 (m, 3H), 2.28 (s, 6H), 2.14 – 1.84 (m, 3H), 1.84 – 1.68 (m, 1H), 1.54 – 1.45 (m, 1H), 1.45 – 1.26 (m, 2H). UPLC (An analogous method to Method 5, ESI) 375.25 $[MH]^+$, RT 1.18 min.

Step 4: *2-(dimethylamino)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetic acid*

To a solution of methyl 2-(dimethylamino)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl} piperidin-4-yl)acetate (290 mg, 0.65 mmol, 1 *eq.*) in MeOH (17.0 mL) was added lithium hydroxide monohydrate (47 mg, 1.95 mmol, 3 *eq.*) and the reaction mixture was stirred at 60°C for 72 h and then at 80°C for another 72 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (300 mg, quantitative yield) without further purification. ^{1}H NMR (300 MHz, Deuterium Oxide) δ 7.39 – 7.30 (m, 2H), 7.29 – 7.20 (m, 2H), 3.48 (s, 2H), 2.98 – 2.74 (m, 2H), 2.66 (d, *J* = 10.4 Hz, 1H), 2.17 (s, 6H), 2.11 – 1.93 (m, 2H), 1.81 – 1.65 (m, 1H), 1.66 – 1.53 (m, 1H), 1.52 – 1.41 (m, 1H), 1.29 – 1.01 (m, 2H). UPLC (An analogous method to Method 5, ESI) 361.20 $[MH]^+$, RT 1.39 min.

INTERMEDIATE 18: *(4,4-dimethylcyclohexyl)methyl 4-methylbenzene-1-sulfonate*



Intermediate 18

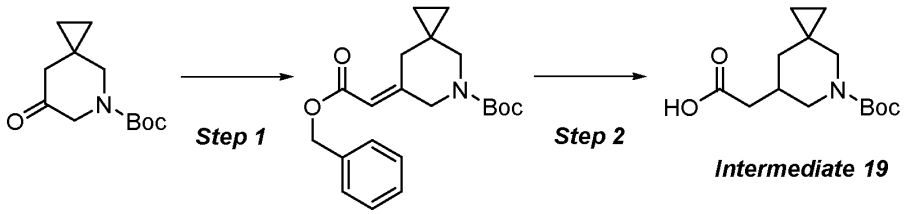
Step 1: *(4,4-dimethylcyclohexyl)methanol*

To a solution of 4,4-dimethylcyclohexane-1-carbaldehyde (150 mg, 1.07 mmol, 1 *eq.*) in MeOH (7.5 mL) at 0 °C was added sodium borohydride (120 mg, 3.21 mmol, 3 *eq.*). The reaction mixture was stirred at 0 °C for 10 min and concentrated *in vacuo*. Crude was re-dissolved in DCM and washed with brine. Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to give the *title compound* (120 mg, 75% yield) without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50 (d, *J* = 6.3 Hz, 2H), 1.64 – 1.58 (m, 2H), 1.47 – 1.39 (m, 3H), 1.31 – 1.07 (m, 4H), 0.93 (s, 3H), 0.90 (s, 3H).

Step 2: *(4,4-dimethylcyclohexyl)methyl 4-methylbenzene-1-sulfonate*

To a solution of *p*-toluenesulfonyl chloride (160 mg, 0.84 mmol, 1.05 *eq.*) in DCM (7.0 mL) was added a solution of (4,4-dimethylcyclohexyl)methanol (120 mg, 0.80 mmol, 1.0 *eq.*) and Et_3N (340 µL, 2.40 mmol, 3.0 *eq.*) in DCM (5.0 mL). The reaction mixture was stirred at r.t. for 5 d with addition of *p*-toluenesulfonyl chloride (400 mg, 2.40 mmol, 3 *eq.*) and Et_3N (1.02 mL, 7.20 mmol, 9 *eq.*). After completion, the reaction mixture was poured into H_2O and extracted with DCM. Combined organic phases were washed with 1M aqueous HCl solution, saturated aqueous sodium bicarbonate solution, water and then dried over sodium sulphate, filtered and concentrated *in vacuo* to give the *title compound* (180 mg, 76% yield) without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.72 (m, 2H), 7.42 – 7.30 (m, 2H), 3.84 (d, *J* = 6.2 Hz, 2H), 2.45 (s, 3H), 1.55 – 1.47 (m, 3H), 1.40 – 1.31 (m, 2H), 1.20 – 1.00 (m, 4H), 0.88 (s, 3H), 0.82 (s, 3H). UPLC (An analogous method to Method 5, ESI) 293.20 $[MH]^-$, RT 4.59 min.

INTERMEDIATE 19: *2-{5-[(tert-butoxy)carbonyl]-5-azaspiro[2.5]octan-7-yl}acetic acid*



Intermediate 19

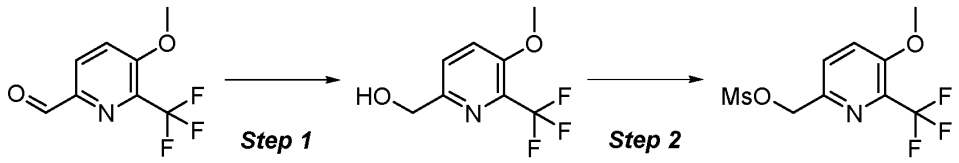
Step 1: *tert-butyl (7E)-7-[2-(benzyloxy)-2-oxoethylidene]-5-azaspiro[2.5]octane-5-carboxylate*

To a solution of benzyl 2-(dimethoxyphosphoryl)acetate (1.72 g, 6.66 mmol, 1.5 *eq.*) in anhydrous THF (6.0 mL) at 0°C sodium hydride (60 % dispersion in mineral oil, 0.16 g, 6.66 mmol, 1.5 *eq.*) was added. The resulting mixture was transferred at 0°C to a solution of *tert*-butyl 7-oxo-5-azaspiro[2.5]octane-5-carboxylate (1.00 g, 4.44 mmol, 1 *eq.*) in anhydrous THF (30.0 mL) and the solution was stirred at r.t. for 5 h. After completion, solvent was removed *in vacuo* and the crude mixture was re-dissolved in EtOAc. Saturated aqueous sodium bicarbonate solution was added, and the layers were separated. Aqueous phase was extracted with EtOAc (2x). Combined organic phases were dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 5-10% EtOAc in cyclohexane) to afford the *title compound* (0.74 g, 44% yield, 85% purity). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 5H), 5.17 (s, 1H), 5.13 (s, 2H), 4.03 (s, 2H), 3.27 (s, 2H), 2.80 (d, *J* = 1.6 Hz, 2H), 1.44 (s, 9H), 0.55 – 0.47 (m, 2H), 0.43 – 0.37 (m, 2H). UPLC (An analogous method to Method 5, ESI) 358.10 $[MH]^+$, RT 4.35 min.

Step 2: *2-{5-[(tert-butoxy)carbonyl]-5-azaspiro[2.5]octan-7-yl}acetic acid*

To a solution of *tert*-butyl 7-[2-(benzyloxy)-2-oxoethylidene]-5-azaspiro[2.5]octane-5-carboxylate (800 mg, 2.11 mmol, 1 *eq.*) in MeOH (14.1 mL) under argon was added palladium on carbon (10% wet., 62 mg, 0.32 mmol, 15% w/w). The reaction was evacuated and backfilled with hydrogen 3 times before stirred at r.t. for 16 h under hydrogen atmosphere. The reaction mixture was then stirred at 40°C for 16 h under hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite® and concentrated *in vacuo* to give (590 mg, 77% yield, 74% purity) without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 – 3.74 (m, 1H), 3.27 – 3.06 (m, 2H), 2.95 (dd, *J* = 13.2, 8.1 Hz, 1H), 2.49 – 2.34 (m, 1H), 2.34 – 2.10 (m, 2H), 1.45 (s, 11H), 0.54 – 0.40 (m, 2H), 0.40 – 0.20 (m, 2H). UPLC (An analogous method to Method 5, ESI) 270.25 $[MH]^+$, RT 4.47 min.

INTERMEDIATE 20: *[5-methoxy-6-(trifluoromethyl)pyridin-2-yl]methyl methanesulfonate*



Intermediate 20

Step 1: *[5-methoxy-6-(trifluoromethyl)pyridin-2-yl]methanol*

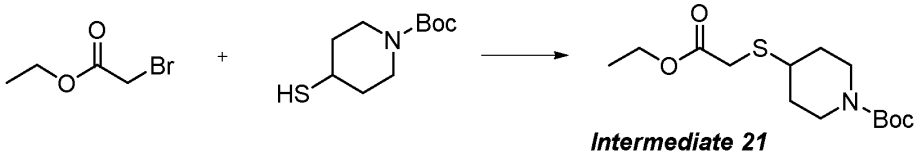
To a solution of 5-methoxy-6-(trifluoromethyl)pyridine-2-carbaldehyde (250 mg., 1.22 mmol, 1 *eq.*) in MeOH (12.5 mL) was added sodium borohydride (140 mg, 3.66 mmol, 3 *eq.*) at 0°C. The reaction mixture was stirred at 0°C for 10 min and concentrated *in vacuo*. The obtained crude was dissolved in DCM and washed with brine. Combined organic layers were dried over sodium

sulphate, filtered and concentrated *in vacuo* to give the *title compound* (250 mg, quantitative yield) without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.36 (m, 2H), 4.75 (s, 2H), 3.94 (s, 3H). UPLC (An analogous method to Method 5, ESI) 208.60 $[MH]^+$, RT 1.44 min.

Step 2: *[5-methoxy-6-(trifluoromethyl)pyridin-2-yl]methyl methanesulfonate*

To a stirred solution of [5-methoxy-6-(trifluoromethyl)pyridin-2-yl]methanol (240 mg, 1.16 mmol., 1.0 *eq.*) and Et_3N (490 µL, 3.48 mmol, 3.0 *eq.*) in DCM (12.0 mL) at 0 °C under argon was slowly added methanesulfonyl chloride (140 µL, 1.74 mmol, 1.5 *eq.*). The reaction mixture was stirred at 0 °C for 30 min. Then, it was poured into saturated aqueous sodium bicarbonate solution. Aqueous layer was extracted with DCM (2x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to give the *title compound* (250 mg, quantitative yield, 90% purity) which was used in the next step without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.6 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 3.99 (s, 3H), 3.17 (s, 2H), 3.15 (s, 3H). UPLC (An analogous method to Method 5, ESI) 308.9 $[MH+Na]^+$, RT 1.53 min.

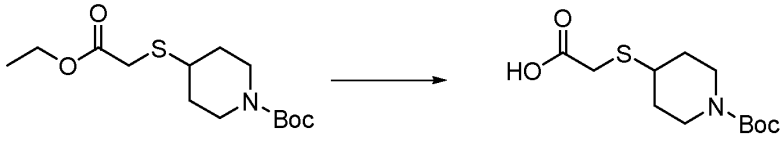
INTERMEDIATE 21: *tert-butyl 4-[(2-ethoxy-2-oxoethyl)sulfanyl]piperidine-1-carboxylate*



Intermediate 21

To a mixture of *tert*-butyl 4-sulfanylpiperidine-1-carboxylate (5.00 g, 23 mmol, 1 *eq.*) and anhydrous potassium carbonate (4.77 g, 34.5 mmol, 1.5 *eq.*) in ACN (250.0 mL) a solution of ethyl bromoacetate (2.67 mL, 24.16 mmol, 1.05 *eq.*) in ACN (10.0 mL) was added under argon. The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was removed *in vacuo* and the crude mixture was re-dissolved in EtOAc and washed with saturated aqueous sodium bicarbonate solution. Aqueous layer was extracted with EtOAc (2x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to give the *title compound* (7.1 g, quantitative yield, 95% purity) without any further purification. ^{1}H NMR (400 MHz, Methanol-d_4) δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.99 – 3.88 (m, 2H), 3.32 (s, 2H), 3.06 – 2.88 (m, 3H), 2.01 – 1.90 (m, 2H), 1.45 (s, 9H), 1.43 – 1.36 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). UPLC (An analogous method to Method 5, ESI) 203.9 $[MH - Boc]^+$, RT 2.5 min.

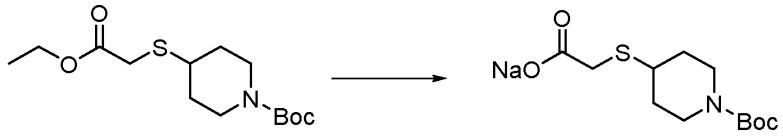
INTERMEDIATE 22: *2-({1-[(tert-butoxy)carbonyl]piperidin-4-yl}sulfanyl)acetic acid*



Intermediate 22

To a stirred solution of tert-butyl 4-[(2-ethoxy-2-oxoethyl)sulfanyl]piperidine-1-carboxylate *Intermediate 21* (1.55 g, 4.85 mmol, 1 *eq.*) in MeOH (23.3 mL), at r.t. was added aqueous sodium hydroxide solution (1M, 24.3 mL, 24.27 mmol, 5 *eq.*). The resulting mixture was stirred at 45°C for 16 h before concentrated *in vacuo*. Crude product was then diluted with water and acidified with 1M aqueous HCl solution till pH = 5. The precipitate was filtered off, washed with excess of ACN and concentrated *in vacuo* to afford the *title compound* (1.7 g, 89% yield, 70% purity). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 – 3.75 (m, 2H), 2.95 (s, 2H), 2.93 – 2.76 (m, 3H), 1.91 – 1.81 (m, 2H), 1.38 (s, 9H), 1.34 – 1.15 (m, 2H). UPLC (An analogous method to Method 5, ESI) 273.9 [MH]$^-$, RT 2.06 min.

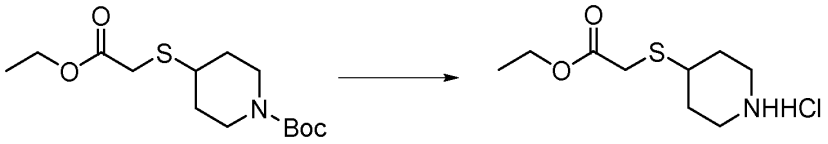
INTERMEDIATE 23: *Sodium 2-({1-[(tert-butoxy)carbonyl]piperidin-4-yl}sulfanyl)acetate*



Intermediate 23

To a stirred solution of tert-butyl 4-[(2-ethoxy-2-oxoethyl)sulfanyl]piperidine-1-carboxylate (prepared according to the procedure of *Intermediate 21)* (525 mg, 1.55 mmol, 1 *eq.*) in THF (8.0 mL) at r.t. was added aqueous sodium hydroxide solution (1.2M, 2.5 mL, 3.11 mmol, 2 *eq.*). The reaction mixture was stirred at 60°C for 16 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (776 mg, quantitative yield, 89% purity). UPLC (An analogous method to Method 5, ESI) 274.7 [MH]$^-$, RT 1.28 min.

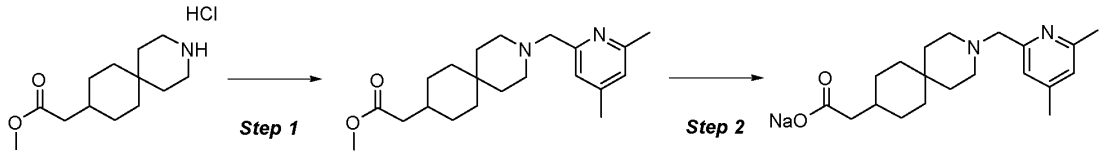
INTERMEDIATE 24: *ethyl 2-(piperidin-4-ylsulfanyl)acetate hydrochloride*



Intermediate 24

To a solution of *tert-butyl 4-[(2-ethoxy-2-oxoethyl)sulfanyl]piperidine-1-carboxylate (prepared according to the procedure of Intermediate 21)* (2.45 g, 7.67 mmol, 1 *eq.*) in DCM (50.0 mL) was added a solution of HCl in dioxane (4M, 5.75 mL, 23.01 mmol, 3 *eq.*). The reaction mixture was stirred at 40°C for 16 h. After completion, solvent was removed *in vacuo* to give the *title compound* (1.90 g, quantitative yield) without any further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 – 8.57 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.42 (s, 2H), 3.23 (dt, *J* = 12.9, 4.2 Hz, 2H), 3.14 – 2.99 (m, 1H), 2.98 – 2.80 (m, 2H), 2.15 – 1.94 (m, 2H), 1.76 – 1.49 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H). UPLC (An analogous method to Method 5, ESI) 204.00 [MH]+, RT 1.04 min.

INTERMEDIATE 25: *sodium 2-{3-[(4,6-dimethylpyridin-2-yl)methyl]-3-azaspiro[5.5]undecan-9-yl}acetate*



Intermediate 25

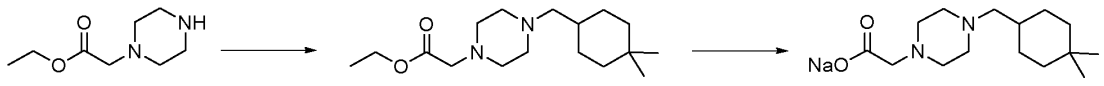
Step 1: *methyl 2-{3-[(4,6-dimethylpyridin-2-yl)methyl]-3-azaspiro[5.5]undecan-9-yl}acetate*

To a solution of methyl 2-(3-azaspiro[5.5]undecan-9-yl)acetate hydrochloride (240 mg, 0.92 mmol, 1.0 *eq.*) in ACN (4.6 mL) was added Et_3N (510 µL, 3.67 mmol, 4.0 *eq.*) and the resulting mixture was stirred for 5 min. 2-(bromomethyl)-4,6-dimethylpyridine (200 mg, 1.01 mmol, 1.1 *eq.*) was then added and the reaction stirred at r.t. for 16 h. After completion, it was concentrated *in vacuo* and the crude product was purified by flash chromatography (silica, 0-10% MeOH in DCM) to afford the *title compound* (309 mg, 97% yield). UPLC (An analogous method to Method 5, ESI) 345.45 [MH]+, RT 1.91 min.

Step 2: *ethyl 2-(piperidin-4-ylsulfanyl)acetate hydrochloride*

To a stirred solution of ethyl sodium 2-{3-[(4,6-dimethylpyridin-2-yl)methyl]-3-azaspiro[5.5]undecan-9-yl}acetate (300 mg, 0.86 mmol, 1 *eq.*) in MeOH (18.0 mL) was added aqueous sodium hydroxide solution (1M, 2.59 mL, 2.59 mmol, 3 *eq.*). The reaction mixture was stirred at 50°C for 5 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (570 mg, 54% purity) without further purification. UPLC (An analogous method to Method 5, ESI) 331.40 $[MH]^+$, RT 1.59 min.

INTERMEDIATE 26: *sodium 2-{4-[(4,4-dimethylcyclohexyl)methyl]piperazin-1-yl}acetate*



Intermediate 26

Step 1: *ethyl 2-{4-[(4,4-dimethylcyclohexyl)methyl]piperazin-1-yl}acetate*

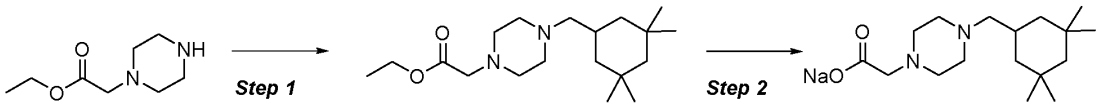
To a stirred solution of 1-(ethoxycarbonylmethyl)piperazine (100 mg, 0.58 mmol, 1 *eq.*) in ACN (2.9 mL) was added Et_3N (243 µL, 1.74 mmol, 3 *eq.*) followed by 4-(bromomethyl)-1,1-dimethylcyclohexane (119 mg, 0.58 mmol, 1 *eq.*). The reaction mixture was stirred at r.t. for 16 h and then at 50°C for 16 h. The solvent was removed *in vacuo* and the crude was dissolved in DCM. Saturated aqueous sodium bicarbonate solution was added, mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the *title compound* (74 mg, 41% yield) as a yellow oil without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.1 Hz, 2H), 3.21 (s, 2H), 2.80 – 2.16 (m, 8H), 1.70 –

1.52 (m, 3H), 1.48 – 1.33 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.33 – 1.22 (m, 1H), 1.21 – 1.05 (m, 4H), 0.89 (s, 3H), 0.86 (s, 3H).

Step 2: *sodium 2-{4-[(4,4-dimethylcyclohexyl)methyl]piperazin-1-yl}acetate*

To a stirred solution of ethyl 2-{4-[(4,4-dimethylcyclohexyl)methyl]piperazin-1-yl}acetate (74 mg, 0.24 mmol, 1 *eq.*) in MeOH (1.2 mL) was added aqueous sodium hydroxide solution (1M, 0.474 mL, 0.47 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (80 mg, quantitative yield, 80% purity) as a yellow solid without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.57 (s, 2H), 2.43 – 2.33 (m, 4H), 2.31 – 2.23 (m, 4H), 2.05 (d, *J* = 7.1 Hz, 2H), 1.58 – 1.47 (m, 2H), 1.37 – 1.27 (m, 3H), 1.18 – 1.03 (m, 3H), 1.02 – 0.95 (m, 1H), 0.87 (s, 3H), 0.84 (s, 3H). UPLC (An analogous method to Method 5, ESI) 269.30 $[MH]^+$, RT 1.50 min.

INTERMEDIATE 27: *sodium 2-{4-[(3,3,5,5-tetramethylcyclohexyl)methyl]piperazin-1-yl}acetate*



Intermediate 27

Step 1: *ethyl 2-{4-[(3,3,5,5-tetramethylcyclohexyl)methyl]piperazin-1-yl}acetate*

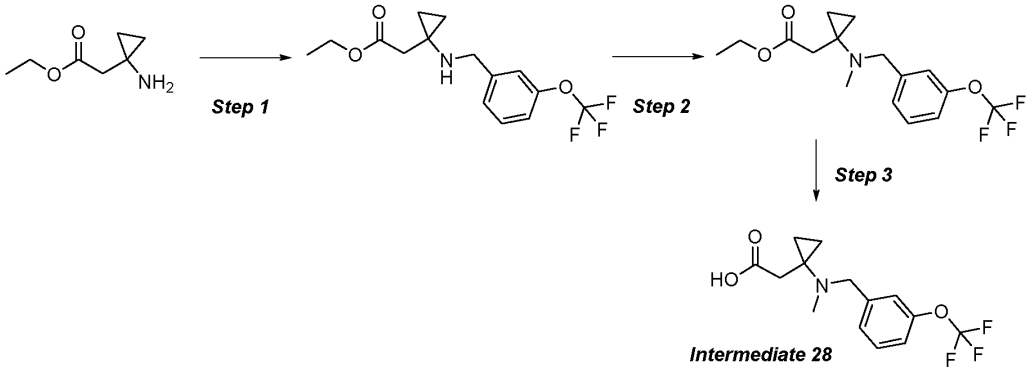
To a stirred solution of 1-(ethoxycarbonylmethyl)piperazine (150 mg, 0.87 mmol, 1 *eq.*) in ACN (4.4 mL) was added Et_3N (364 µL, 2.61 mmol, 3 *eq.*) followed by 5-(bromomethyl)-1,1,3,3-tetramethylcyclohexane (203 mg, 0.87 mmol, 1 *eq.*). The reaction mixture was stirred at 50°C for 16 h and the solvent was removed *in vacuo*. The crude was re-dissolved in DCM and saturated aqueous sodium bicarbonate solution was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-2% MeOH in DCM) to afford the *title compound* (130 mg, 22% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H), 3.22 (s, 2H), 2.76 – 2.33 (m, 6H), 2.29 – 2.05 (m, 2H), 1.96 – 1.73 (m, 1H), 1.62 – 1.44 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.33 – 1.19 (m, 3H), 0.99 (s, 6H), 0.88 (s, 6H), 0.87 – 0.81 (m, 1H), 0.72 – 0.65 (m, 1H). UPLC (An analogous method to Method 5, ESI) 325.45 $[MH]^+$, RT 1.89 min.

Step 2: *sodium 2-{4-[(3,3,5,5-tetramethylcyclohexyl)methyl]piperazin-1-yl}acetate*

To a stirred solution of ethyl 2-{4-[(3,3,5,5-tetramethylcyclohexyl)methyl]piperazin-1-yl}acetate (130 mg, 0.38 mmol, 1 *eq.*) in MeOH (1.9 mL) was added aqueous sodium hydroxide solution (1M, 750 µL, 0.75 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was concentrated *in vacuo* to afford the *title compound* (120 mg, quantitative yield) as a

yellow solid without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (s, 2H), 2.46 – 2.34 (m, 4H), 2.33 – 2.20 (m, 4H), 2.01 (d, *J* = 7.1 Hz, 2H), 1.88 – 1.74 (m, 1H), 1.50 – 1.39 (m, 2H), 1.28 – 1.16 (m, 2H), 0.95 (s, 6H), 0.85 (s, 6H), 0.59 (t, *J* = 12.5 Hz, 2H). UPLC (An analogous method to Method 5, ESI) 297.30 [MH]$^+$, RT 1.78 min.

INTERMEDIATE 28: *2-{1-[methyl({[3-(trifluoromethoxy)phenyl]methyl})amino]cyclopropyl}acetic acid*



Step 1: *ethyl 2-{1-({[3-(trifluoromethoxy)phenyl]methyl}amino)cyclopropyl]acetate*

To a solution of ethyl 2-(1-aminocyclopropyl)acetate hydrochloride (180 mg, 2.78 mmol, 1.0 *eq.*) in MeOH (12.5 mL) at 0°C under argon was added 3-(trifluoromethoxy)benzaldehyde (410 µL, 2.78 mmol, 1.0 *eq.*). Acetic acid were added dropwise until pH ~ 4.5. The reaction mixture was stirred for 30 min. at r.t. and sodium cyanoborohydride (250 mg, 4.18 mmol, 1.5 *eq.*) was added. The reaction mixture was stirred at 0°C for 1 h and then at r.t. for 16 h. Another portions of 3-(trifluoromethoxy)benzaldehyde (100 µL, 0.70 mmol, 0.25 *eq.*) and sodium cyanoborohydride (50 mg, 0.80 mmol, 0.3 *eq.*) were added and stirring was continued for 30 min. After completion, solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with saturated sodium carbonate solution. Organic layer was separated, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude product was purified by flash chromatography (silica, 5-10% EtOAc in cyclohexane) to afford the *title compound* (590 mg, 63% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 1H), 7.26 – 7.22 (m, 1H), 7.19 (s, 1H), 7.12 – 7.05 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 2H), 2.49 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.83 – 0.73 (m, 2H), 0.58 – 0.47 (m, 2H). UPLC (An analogous method to Method 5, ESI) 318.30 [MH]$^+$, RT 2.28 min.

Step 2: *ethyl 2-{1-[methyl({[3-(trifluoromethoxy)phenyl]methyl})amino]cyclopropyl}acetate*

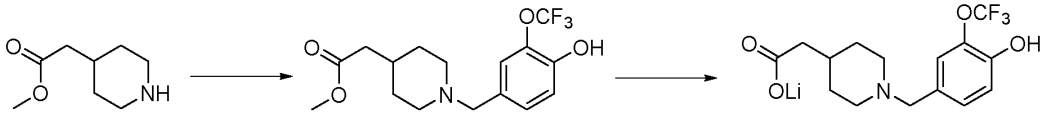
To a solution of ethyl 2-[1-({[3-(trifluoromethoxy)phenyl]methyl}amino)cyclopropyl]acetate (570 mg, 1.71 mmol, 1 *eq.*) in MeOH (14.5 mL) were added paraformaldehyde (154 mg, 5.12 mmol, 2 *eq.*) and acetic acid (*ca.* 200 µL). The reaction mixture was stirred for 30 min, then sodium cyanoborohydride (200 mg, 3.41 mmol, 2 *eq.*) was added and the reaction mixture was heated up to 70°C for 16 h before concentrated *in vacuo*. The crude mixture was re-dissolved in DCM

and washed with saturated aqueous sodium bicarbonate solution. Aqueous layer was extracted with DCM (2x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to give the *title compound* (550 mg, quantitative yield) without any further purification. ^{1}H NMR (300 MHz, methanol-d_4) δ 7.40 – 7.33 (m, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.15 – 7.08 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 2H), 2.58 (s, 2H), 2.22 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.80 – 0.68 (m, 4H). UPLC (An analogous method to Method 5, ESI) 332.25 $[MH]^+$, RT 2.87 min.

Step 3: *2-{1-[methyl({[3-(trifluoromethoxy)phenyl]methyl})amino]cyclopropyl}acetic acid*

To a solution of ethyl 2-{1-[methyl({[3-(trifluoromethoxy)phenyl]methyl})amino]-cyclopropyl}acetate (550 mg, 1.58 mmol, 1 *eq.*) in MeOH (27.0 mL) was added aqueous sodium hydroxide solution (1M, 4.73 mL, 4.73 mmol, 3 *eq.*) and the reaction mixture was stirred at r.t. for 16 h. Aqueous sodium hydroxide solution (1M, 4.73 mL, 4.73 mmol, 3 *eq.*) was added to the reaction mixture which was stirred at 45°C for 3 h. After completion, solvent was removed *in vacuo*. Aqueous residue was neutralised by 1M aqueous HCl solution to pH~7 and concentrated *in vacuo*. Residual was then washed with ACN, filtered and concentrated *in vacuo* to give the *title compound* (490 mg, quantitative yield) without any further purification. ^{1}H NMR (300 MHz, methanol-d_4) δ 7.41 (t, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.24 – 7.13 (m, 2H), 3.93 (s, 2H), 2.61 (s, 2H), 2.34 (s, 3H), 0.93 – 0.73 (m, 4H). UPLC (An analogous method to Method 5, ESI) 304.20 $[MH]^+$, RT 1.64 min.

INTERMEDIATE 29: *sodium 2-(1-{[4-hydroxy-3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate*



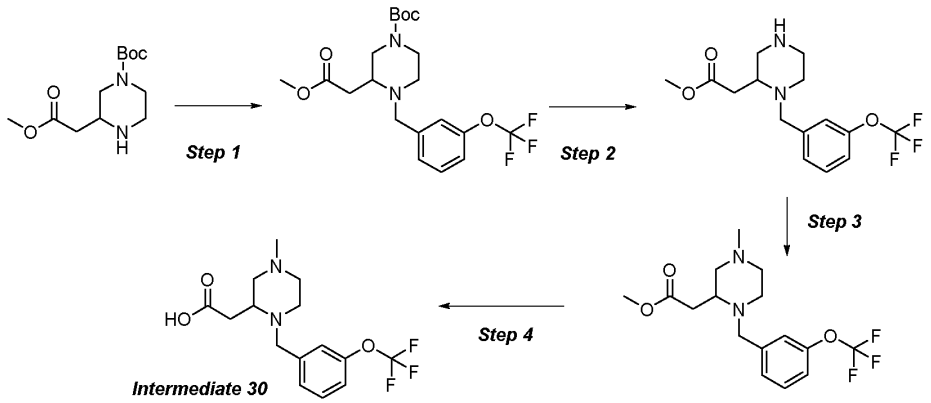
Step 1: *methyl 2-(1-{[4-hydroxy-3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate*

To a stirred solution of methyl 2-(piperidin-4-yl)acetate (500 mg, 2.58 mmol, 1.0 *eq.*) and 4-hydroxy-3-(trifluoromethoxy)benzaldehyde (530 mg, 2.58 mmol, 1.0 *eq.*) in MeOH (12.9 mL) was added 10 drops of glacial acetic acid. The reaction mixture was stirred at r.t. for 30 min and then STAB (230 mg, 3.87 mmol, 1.5 *eq.*) was added. The reaction mixture was stirred at r.t. for 56 h. After completion, it was concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-5% MeOH in DCM) to afford the *title compound* (123 mg, 95% yield, 86% purity). UPLC (An analogous method to Method 5, ESI) 348.15 $[MH]^+$, RT 1.77 min.

Step 2: *sodium 2-(1-{[4-hydroxy-3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate*

To a stirred solution of methyl 2-(1-{[4-hydroxy-3-(trifluoromethoxy)phenyl]methyl} piperidin-4-yl)acetate (120 mg, 0.33 mmol, 1 *eq.*) in MeOH (6.1 mL), was added aqueous sodium hydroxide solution (1M, 660 µL, 0.66 mmol, 2 *eq.*). The reaction mixture was stirred at 40°C for 16 h. Another portion of aqueous sodium hydroxide solution (1M, 660 µL, 0.66 mmol, 2 *eq.*) was added and stirring was continued at 40°C for 16 h. Another portion of aqueous sodium hydroxide solution (1M, 660 µL, 0.66 mmol, 2 *eq.*) was added and stirring was continued at 40°C for 16 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (160 mg, 75% purity) without further purification. UPLC (An analogous method to Method 5, ESI) 334.15 $[MH]^+$, RT 1.38 min.

INTERMEDIATE 30: *2-(4-methyl-1-{[3-(trifluoromethoxy)phenyl]methyl}piperazin-2-yl)acetic acid*



Step 1: *tert-butyl 3-(2-methoxy-2-oxoethyl)-4-{[3-(trifluoromethoxy)phenyl]methyl} piperazine-1-carboxylate*

To a mixture of *tert*-butyl 3-(2-methoxy-2-oxoethyl)piperazine-1-carboxylate (380 mg, 1.47 mmol, 1 *eq.*) and 3-(trifluoromethoxy)benzaldehyde (240 µL, 1.62 mmol, 1.1 *eq.*) in MeOH (10.0 mL) under argon was added acetic acid (*ca.* 200 µL) to achieve pH~4. The reaction mixture was stirred at r.t. for 30 min. Sodium cyanoborohydride (170 mg, 2.94 mmol, 2 *eq.*) was added and the reaction mixture was stirred at r.t. for 2 h. Then, 3-(trifluoromethoxy) benzaldehyde (240 µL, 1.62 mmol, 1.1 *eq.*) and sodium cyanoborohydride (170 mg, 2.94 mmol, 2 *eq.*) were added and the mixture was stirred at 50°C for 5 h before concentrated *in vacuo*. The crude material was dissolved in EtOAc and washed with saturated aqueous sodium bicarbonate solution. Aqueous layer was washed with EtOAc (3x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude product was purified by flash chromatography (silica, 100% DCM) to afford the *title compound* (420 mg, 63% yield). ^{1}H NMR (300 MHz, methanol-d_4) δ 7.44 – 7.36 (m, 1H), 7.36 – 7.31 (m, 1H), 7.28 (s, 1H), 7.21 – 7.11 (m, 1H), 3.88 – 3.75 (m, 1H), 3.68 (s, 3H), 3.66 – 3.49 (m, 3H), 3.46 – 3.37 (m, 1H), 3.26 – 3.13 (m, 1H), 3.10 – 3.00 (m, 1H), 2.72 – 2.46 (m, 3H), 2.41 – 2.26 (m, 1H), 1.45 (s, 9H). UPLC (An analogous method to Method 5, ESI) 433.25 $[MH]^+$, RT 3.66 min.

Step 2: *methyl 2-(1-{[3-(trifluoromethoxy)phenyl]methyl}piperazin-2-yl)acetate*

To a solution of *tert*-butyl 3-(2-methoxy-2-oxoethyl)-4-{[3-(trifluoromethoxy)phenyl]methyl} piperazine-1-carboxylate (420 mg, 0.93 mmol, 1 *eq.*) in DCM (40.0 mL) was added HCl solution in dioxane (4M, 4.14 mL, 8.31 mmol, 9 *eq.*). The reaction mixture was refluxed for 80 h. After completion, solvent was removed *in vacuo* to give the *title compound* (360 mg, quantitative yield) without any further purification. ^{1}H NMR (300 MHz, Deuterium Oxide) δ 7.59 – 7.51 (m, 1H), 7.46 – 7.35 (m, 3H), 4.53 (d, *J* = 13.2 Hz, 1H), 3.95 (d, *J* = 13.2 Hz, 1H), 3.87 – 3.77 (m, 1H), 3.76 (s, 3H), 3.73 – 3.62 (m, 1H), 3.58 – 3.46 (m, 1H), 3.44 – 3.23 (m, 3H), 3.18 – 2.96 (m, 3H). UPLC (An analogous method to Method 5, ESI) 333.10 $[MH]^+$, RT 2.41 min.

Step 3: *methyl 2-(4-methyl-1-{[3-(trifluoromethoxy)phenyl]methyl}piperazin-2-yl)acetate*

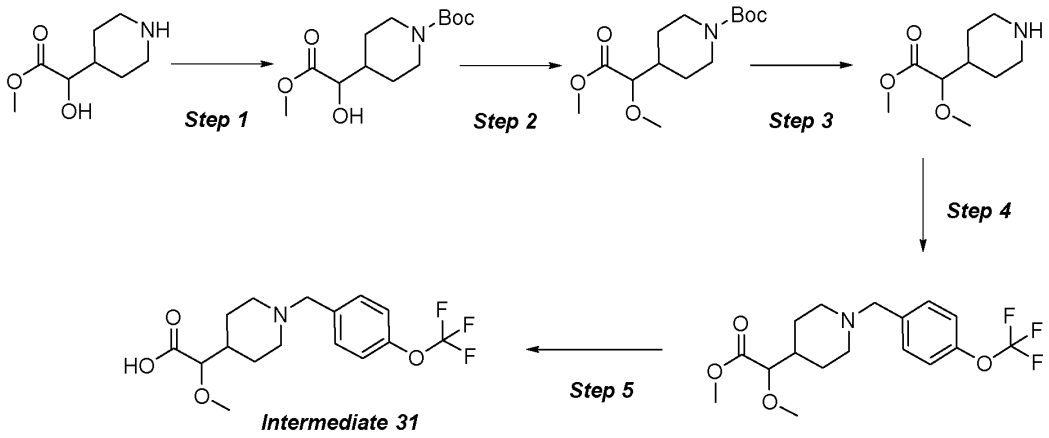
To a solution of methyl 2-(1-{[3-(trifluoromethoxy)phenyl]methyl}piperazin-2-yl)acetate hydrochloride (350 mg, 0.82 mmol, 1 *eq.*) in MeOH (9.0 mL) were added paraformaldehyde (74 mg, 2.46 mmol, 3 *eq.*) and acetic acid (*ca.* 200 µL). The reaction mixture was stirred for 10 min before the addition of sodium cyanoborohydride (98 mg, 1.64 mmol, 2 *eq.*). The reaction mixture was stirred at 50 °C for 1 h and concentrated *in vacuo*. After completion, solvent was removed *in vacuo*. Crude mixture was dissolved in DCM and washed with saturated aqueous sodium bicarbonate solution. Aqueous layer was washed with DCM (2x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to give the *title compound* (280 mg, quantitative yield, 98% purity) without any further purification. ^{1}H NMR (300 MHz, CDCl3) δ 7.32 (t, *J* = 7.8 Hz, 1H), 7.24 – 7.16 (m, 2H), 7.13 – 7.06 (m, 1H), 4.01 – 3.81 (m, 1H), 3.68 (s, 3H), 3.38 (d, *J* = 13.6 Hz, 1H), 3.26 – 3.11 (m, 1H), 2.82 – 2.24 (m, 11H). UPLC (An analogous method to Method 5, ESI) 347.25 $[MH]^+$, RT 1.81 min.

Step 4

2-(4-methyl-1-{[3-(trifluoromethoxy)phenyl]methyl}piperazin-2-yl)acetic acid

To a stirred solution of methyl 2-(4-methyl-1-{[3-(trifluoromethoxy)phenyl]methyl}piperazin-2-yl)acetate (280 mg, 0.73 mmol, 1 *eq.*) in MeOH (14.0 mL) was added aqueous sodium hydroxide solution (1M, 2.18 mL, 2.18 mmol, 3 *eq.*) and the reaction mixture was stirred at 40°C for 16 h. After completion, solvent was concentrated *in vacuo*. Aqueous residue was neutralised with 1M aqueous HCl solution to pH~7 and concentrated *in vacuo*. Residual was washed with ACN, filtered and concentrated *in vacuo* to give the *title compound* (260 mg, quantitative yield, 98% purity) without any further purification. ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.48 – 7.34 (m, 2H), 7.32 (s, 1H), 7.22 – 7.16 (m, 1H), 4.12 (d, *J* = 13.1 Hz, 1H), 3.52 (d, *J* = 13.7 Hz, 1H), 3.39 – 3.33 (m, 1H), 3.24 – 2.85 (m, 5H), 2.77 (s, 3H), 2.67 (dd, *J* = 15.8, 4.4 Hz, 1H), 2.61 – 2.47 (m, 2H). UPLC (An analogous method to Method 5, ESI) 333.25 $[MH]^+$, RT 1.64 min.

INTERMEDIATE 31: *2-methoxy-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetic acid*



Step 1

tert-butyl 4-(1-hydroxy-2-methoxy-2-oxoethyl)piperidine-1-carboxylate

To a stirred solution of methyl 2-hydroxy-2-(piperidin-4-yl)acetate hydrochloride (400 mg, 1.91 mmol, 1 *eq.*) and di-*tert*-butyl dicarbonate (460 mg, 2.10 mmol, 1.1 *eq.*) in DCM (40.0 mL) was added Et_3N (1.07 mL, 7.63 mmol, 4 *eq.*) under argon and the reaction mixture was stirred at r.t. for 16 h. Then, it was quenched with 0.01M aqueous HCl solution and extracted with DCM (3x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude product was purified by flash chromatography (silica, 50% cyclohexene in EtOAc) to afford the *title compound* (240 mg, 44% yield, 95% purity). ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.40 (d, *J* = 6.0 Hz, 1H), 4.00 – 3.92 (m, 2H), 3.88 (t, *J* = 5.7 Hz, 1H), 3.63 (s, 3H), 2.72 – 2.55 (m, 2H), 1.83 – 1.67 (m, 1H), 1.53 – 1.42 (m, 2H), 1.38 (s, 9H), 1.26 – 1.09 (m, 2H). UPLC (An analogous method to Method 5, ESI) 174.1 $[MH\text{-}Boc]^+$, RT 0.54 min.

Step 2

tert-butyl 4-(1,2-dimethoxy-2-oxoethyl)piperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-(1-hydroxy-2-methoxy-2-oxoethyl)piperidine-1-carboxylate (220 mg, 0.76 mmol, 1 *eq.*) in DMF (20.0 mL) at 0°C was added sodium hydride (60% dispersion in mineral oil, 34 mg, 0.84 mmol, 1.1 *eq.*). The reaction mixture was stirred for 10 min, then methyl iodide (52 µL, 0.84 mmol, 1.1 *eq.*) was added at the same temperature. The reaction mixture was stirred at r.t. for 30 min. Then, it was quenched with water and extracted with EtOAc. Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to give the *title compound* (220 mg, quantitative yield, 90% purity) without any further purification. ^{1}H NMR (300 MHz, CDCl3) δ 4.25 – 4.02 (m, 2H), 3.77 (s, 3H), 3.56 (d, *J* = 5.9 Hz, 1H), 3.37 (s, 3H), 2.74

– 2.56 (m, 2H), 1.96 – 1.79 (m, 1H), 1.73 – 1.60 (m, 1H), 1.56 – 1.47 (m, 1H), 1.44 (s, 9H), 1.40 – 1.27 (m, 2H). UPLC (An analogous method to Method 5, ESI) 188.1 $[MH\text{-}Boc]^+$, RT 2.26 min.

Step 3

methyl 2-methoxy-2-(piperidin-4-yl)acetate

To a stirred solution of *tert*-butyl 4-(1,2-dimethoxy-2-oxoethyl)piperidine-1-carboxylate (220 mg, 0.69 mmol, 1 *eq.*) in DCM (20.0 mL) was added HCl solution in Et_2O (2M, 1.03 mL, 2.07 mmol, 3 *eq.*). The reaction mixture was stirred at r.t. for 16 h. Then, HCl solution in dioxane (4M, 3.00 mL, 12.0 mmol, 18 *eq.*) was added and reaction mixture was stirred at 60°C for 16 h. After completion, solvent was removed *in vacuo* to give the *title compound* (150 mg, quantitative yield, 95% purity) without any further purification. ^{1}H NMR (300 MHz, Deuterium Oxide) δ 3.92 (d, *J* = 5.0 Hz, 1H), 3.80 (s, 3H), 3.49 – 3.40 (m, 2H), 3.38 (s, 3H), 3.06 – 2.89 (m, 2H), 2.21 – 2.05 (m, 1H), 1.96 – 1.77 (m, 2H), 1.77 – 1.50 (m, 2H). UPLC (An analogous method to Method 5, ESI) 188.1 $[MH]^+$, RT 0.80 min.

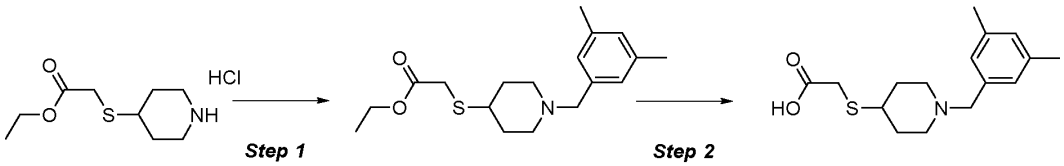
Step 4: *methyl 2-methoxy-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetate*

To a solution of methyl 2-methoxy-2-(piperidin-4-yl)acetate hydrochloride (150 mg, 0.64 mmol, 1 *eq.*) and anhydrous potassium carbonate (310 mg, 2.23 mmol, 3.5 *eq.*) in ACN (15.0 mL) was added 4-(trifluoromethoxy)benzyl bromide (120 µL, 0.76 mmol, 1.2 *eq.*) under argon. The reaction mixture was stirred at r.t. for 4 h before filtered and the filtrate was concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 3% MeOH in DCM) to afford the *title compound* (190 mg, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 2H), 7.20 – 7.11 (m, 2H), 3.76 (s, 3H), 3.56 (d, *J* = 5.9 Hz, 1H), 3.52 – 3.46 (m, 1H), 3.36 (s, 3H), 3.06 – 2.71 (m, 2H), 2.14 – 1.85 (m, 2H), 1.82 – 1.67 (m, 2H), 1.63 – 1.43 (m, 4H). UPLC (An analogous method to Method 5, ESI) 362.25 $[MH]^+$, RT 1.77 min.

Step 5: *2-methoxy-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetic acid*

To a stirred solution of methyl 2-methoxy-2-(1-{[4-(trifluoromethoxy)phenyl]methyl} piperidin-4-yl)acetate (190 mg, 0.5 mmol, 1 *eq.*) in MeOH (10 mL) was added aqueous sodium hydroxide solution (1M, 2.99 mL, 2.99 mmol, 6 *eq.*) and the reaction mixture was stirred at 45 °C for 16 h. After completion, solvent was concentrated *in vacuo*. Aqueous residue was neutralised with 1M aqueous HCl solution to pH~7 and concentrated *in vacuo*. Residual was washed with ACN, filtered and concentrated *in vacuo* to give the *title compound* (180 mg, quantitative yield, 90% purity) without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 4.08 – 4.02 (m, 1H), 3.67 – 3.43 (m, 3H), 3.38 (s, 3H), 2.66 – 2.37 (m, 2H), 2.21 – 1.75 (m, 6H). UPLC (An analogous method to Method 5, ESI) 348.20 $[MH]^+$, RT 1.60 min.

INTERMEDIATE 32: *2-({1-[(3,5-dimethylphenyl)methyl]piperidin-4-yl}sulfanyl)acetic acid*



Step 1 ***Step 2*** ***Intermediate 32***

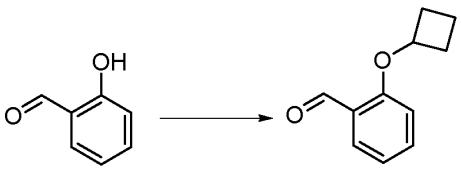
Step 1: *ethyl 2-({1-[(3,5-dimethylphenyl)methyl]piperidin-4-yl}sulfanyl)acetate*

To a solution of *ethyl 2-(piperidin-4-ylsulfanyl)acetate hydrochloride (prepared according to the procedure of Intermediate 24)* (58 mg, 0.20 mmol, 1 *eq.*) and anhydrous potassium carbonate (98 mg, 0.71 mmol, 3.5 *eq.*) in ACN (6.0 mL) was added 3,5-dimethylbenzyl bromide (49 µL, 0.24 mmol, 1.2 *eq.*) under argon. The reaction mixture was stirred at r.t. for 16 h before filtered and the filtrate was concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 3% MeOH in DCM) to afford the *title compound* (65 mg, 80% yield, 80% purity). UPLC (An analogous method to Method 5, ESI) 322.55 $[MH]^+$, RT 1.96 min.

Step 2: *2-({1-[(3,5-dimethylphenyl)methyl]piperidin-4-yl}sulfanyl)acetic acid*

To a mixture of ethyl 2-({1-[(3,5-dimethylphenyl)methyl]piperidin-4-yl}sulfanyl)acetate (65 mg, 0.16 mmol, 1 *eq.*) in MeOH (7.0 mL) was added a solution of sodium hydroxide (1M, 490 µL, 0.49 mmol, 3 *eq.*), and the reaction mixture was stirred at 40 C° for 16 h. After completion, solvent was concentrated *in vacuo*. Aqueous residue was neutralised with 1M aqueous HCl solution and concentrated *in vacuo*. Residual was washed with ACN, filtered and concentrated *in vacuo* to give the *title compound* (55 mg, quantitative yield) without any further purification. UPLC (An analogous method to Method 5, ESI) 294.5 $[MH]^+$, RT 1.67 min.

INTERMEDIATE 33: *2-cyclobutoxybenzaldehyde*

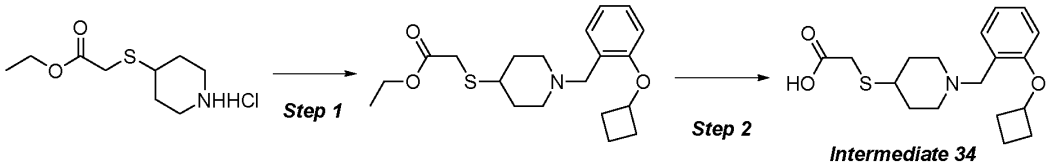


Intermediate 33

To a stirred solution of salicylaldehyde (2.00 g, 16.38 mmol, 1 *eq.*) in anhydrous DMF (40.0 mL) was added anhydrous potassium carbonate (4.53 g, 32.75 mmol, 2 *eq.*) followed by bromocyclobutane (4.42 g, 32.75 mmol, 2 *eq.*). The reaction mixture was stirred at 85°C for 16 h. The mixture was concentrated *in vacuo* and purified by flash chromatography (silica, 15% EtOAc in hexanes) to afford the *title compound* (2.88 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53

– 10.48 (m, 1H), 7.83 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.54 – 7.45 (m, 1H), 7.04 – 6.96 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 4.75 (p, *J* = 6.9 Hz, 1H), 2.55 – 2.45 (m, 2H), 2.30 – 2.19 (m, 2H), 1.97 – 1.88 (m, 1H), 1.80 – 1.69 (m, 1H). UPLC (An analogous method to Method 5, ESI) 177.0 $[MH]^+$, RT 2.48 min.

INTERMEDIATE 34: *2-({1-[(2-cyclobutoxyphenyl)methyl]piperidin-4-yl}sulfanyl)acetic acid*



Intermediate 34

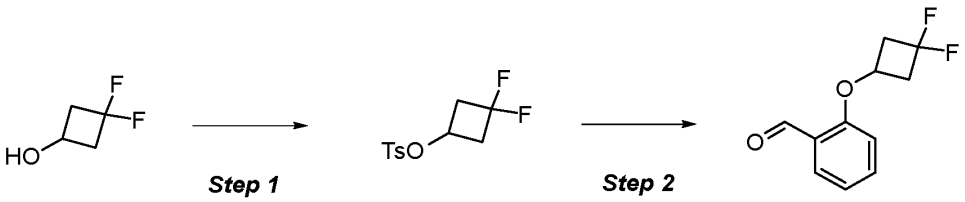
Step 1: *ethyl 2-({1-[(2-cyclobutoxyphenyl)methyl]piperidin-4-yl}sulfanyl)acetate*

To a solution of *ethyl 2-(piperidin-4-ylsulfanyl)acetate hydrochloride (prepared according to the procedure of Intermediate 24)* (55 mg, 0.79 mmol, 1.0 *eq.*) and Et_3N (190 µL, 1.43 mmol, 1.8 *eq.*) in DCE (10.0 mL) was added 2-cyclobutoxybenzaldehyde *(prepared according to the procedure of Intermediate 33)* (220 mg, 1.18 mmol, 1.5 *eq.*). The reaction mixture was stirred at r.t. for 40 min and sodium cyanoborohydride (140 mg, 2.38 mmol, 3.0 *eq.*) was added. After completion, solvent was removed *in vacuo* and the crude mixture was dissolved in DCM and washed with saturated aqueous sodium bicarbonate solution. Aqueous layer was extracted with DCM (2x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude product was purified by flash chromatography (silica, 25% EtOAc in hexanes) to afford the *title compound* (200 mg, 35% yield, 50% purity). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.28 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.20 (td, *J* = 8.1, 1.7 Hz, 1H), 6.89 (td, *J* = 7.5, 0.9 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 4.68 (p, *J* = 7.2 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.60 (s, 2H), 3.28 (s, 2H), 2.98 – 2.87 (m, 2H), 2.85 – 2.75 (m, 1H), 2.53 – 2.41 (m, 2H), 2.26 – 2.18 (m, 2H), 2.18 – 2.08 (m, 2H), 2.02 – 1.93 (m, 2H), 1.91 – 1.81 (m, 1H), 1.81 – 1.69 (m, 1H), 1.66 – 1.54 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). UPLC (An analogous method to Method 5, ESI) 364.6 [MH]+, RT 2.01 min.

Step 2: *2-({1-[(2-cyclobutoxyphenyl)methyl]piperidin-4-yl}sulfanyl)acetic acid*

To a solution of ethyl 2-({1-[(2-cyclobutoxyphenyl)methyl]piperidin-4-yl}sulfanyl)acetate (0.20 g, 0.28 mmol, 1 *eq.*) in MeOH (10.0 mL) was added aqueous sodium hydroxide solution (1M, 1.65 mL, 1.65 mmol, 6 *eq.*) and the reaction mixture was stirred at 45°C for 1 h. After completion, solvent was concentrated *in vacuo*. Aqueous residue was neutralised with 1 M aqueous HCl solution and concentrated *in vacuo*. Residual was washed with ACN, filtered and concentrated *in vacuo* to give the *title compound* (100 mg, quantitative yield, 90% purity) without any further purification. UPLC (An analogous method to Method 5, ESI) 336.6 [MH]+, RT 1.72 min.

INTERMEDIATE 35: *2-(3,3-difluorocyclobutoxy)benzaldehyde*



Intermediate 35

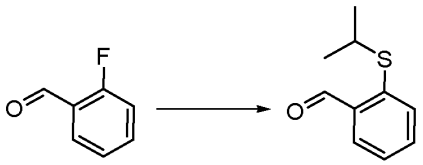
Step 1: *3,3-difluorocyclobutyl 4-methylbenzene-1-sulfonate*

To a solution of *p*-toluenesulfonyl chloride (880 mg, 4.63 mmol, 2 *eq.*) in anhydrous DCM (7.5 mL), a solution of 3,3-difluorocyclobutanol (250 mg, 2.31 mmol, 1 *eq.*) and Et_3N (27.6 mL, 197.73 mmol, 10 *eq.*) in anhydrous DCM (7.5 mL) was added slowly at 0°C under argon. The resulting mixture was warmed to r.t. and stirred for 16 h. Then, it was then poured into water and extracted with DCM (3x). Combined organic layers were washed with 1M aqueous HCl solution, saturated aqueous sodium bicarbonate solution and water. Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo.* Crude residue was purified by flash chromatography (silica, 10% EtOAc in hexanes) to afford the *title compound* (470 mg, 74% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 – 7.78 (m, 2H), 7.53 – 7.46 (m, 2H), 4.87 – 4.77 (m, 1H), 3.08 – 2.96 (m, 2H), 2.79 – 2.66 (m, 2H), 2.43 (s, 3H).

Step 2: *2-(3,3-difluorocyclobutoxy)benzaldehyde*

To a stirred solution of salicylaldehyde (830 mg, 6.77 mmol, 1.1 *eq.*) in anhydrous DMF (51.0 mL) was added anhydrous potassium carbonate (2.55 g, 18.47 mmol, 3.0 *eq.*) followed by 3,3-difluorocyclobutyl 4-methylbenzene-1-sulfonate (250 mg, 2.31 mmol, 1 *eq.*). The reaction mixture was stirred at 90°C for 16 h before concentrated *in vacuo*. Crude product was triturated with ACN and filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography (silica, 0-20% EtOAc in cyclohexane) to afford the *title compound* (220 mg, 15% yield, 87% purity). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 – 10.39 (m, 1H), 7.72 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.16 – 7.09 (m, 2H), 5.00 – 4.89 (m, 1H), 3.31 – 3.20 (m, 2H), 2.91 – 2.77 (m, 2H).

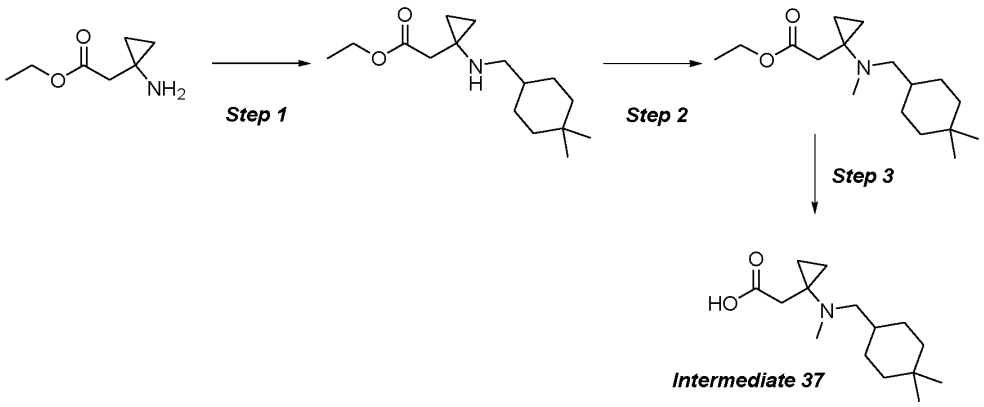
INTERMEDIATE 36: *2-(propan-2-ylsulfanyl)benzaldehyde*



Intermediate 36

To a stirred solution of 2-fluorobenzaldehyde (425 µL, 3.83 mmol, 1.0 *eq.*) in DMF (10.0 mL) was added propane-2-thiol (533 µL, 5.74 mmol, 1.5 *eq.*) followed by anhydrous potassium carbonate (800 mg, 5.74 mmol, 2.0 *eq.*). The reaction mixture was stirred at 80°C for 16 h. After completion, solvent was removed *in vacuo* and the crude mixture was dissolved in DCM. Water was added and the layers were separated. Aqueous layer was extracted with DCM (2x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the *title compound* (572 mg, 82% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 7.86 (dd, J = 7.6, 1.5 Hz, 1H), 7.68 – 7.57 (m, 2H), 7.46 – 7.39 (m, 1H), 3.59 (hept, J = 6.7 Hz, 1H), 1.28 (d, J = 6.7 Hz, 6H). UPLC (An analogous method to Method 5, ESI) 180.70 $[MH]^+$, RT 3.56 min.

INTERMEDIATE 37: *2-(1-{[(4,4-dimethylcyclohexyl)methyl](methyl)amino}cyclopropyl)acetic acid*



Step 1: *ethyl 2-(1-{[(4,4-dimethylcyclohexyl)methyl]amino}cyclopropyl)acetate*

To a solution of ethyl 2-(1-aminocyclopropyl)acetate hydrochloride (200 mg, 1.11 mmol, 1.0 *eq.*) and anhydrous potassium carbonate (460 mg, 3.34 mmol, 3.0 *eq.*) in ACN (8.0 mL) was added 4-(bromomethyl)-1,1-dimethylcyclohexane (240 µL, 0.67 mmol, 1.2 *eq.*) under argon. The reaction mixture was stirred at 75°C for 20 h. Then, it was filtered and the filtrate was concentrated *in vacuo* to give the *title compound* (210 mg, 45% purity) without any further purification. UPLC (An analogous method to Method 5, ESI) 268.25 $[MH]^+$, RT 2.46 min.

Step 2: *ethyl 2-(1-{[(4,4-dimethylcyclohexyl)methyl](methyl)amino}cyclopropyl)acetate*

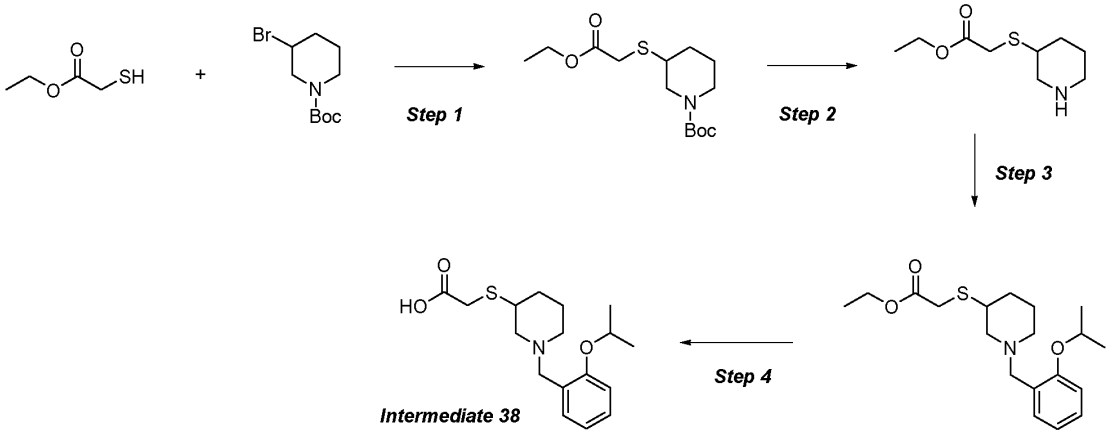
To a solution of ethyl 2-(1-{[(4,4-dimethylcyclohexyl)methyl]amino}cyclopropyl)acetate (210 mg, 0.35 mmol, 1 *eq.*) in DCE (5.0 mL) was added paraformaldehyde (104 mg, 3.45 mmol, 10 *eq.*). The reaction mixture was stirred for 10 min, then STAB (365 mg, 1.72 mmol, 5 *eq.*) was added and the reaction mixture was heated up to 80°C for 16 h. After completion, solvent was removed *in vacuo* and the crude mixture was dissolved in DCM and washed with saturated aqueous sodium bicarbonate solution. Aqueous layer was extracted with DCM (2x). Combined organic phases were dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude product was

purified by flash chromatography (silica, 10% EtOAc in cyclohexane) to afford the *title compound* (45 mg, 43% purity). UPLC (An analogous method to Method 5, ESI) 282.15 $[MH]^+$, RT 2.54 min.

Step 3: *2-(1-{[(4,4-dimethylcyclohexyl)methyl](methyl)amino}cyclopropyl)acetic acid*

To a solution of ethyl 2-(1-{[(4,4-dimethylcyclohexyl)methyl](methyl)amino}cyclopropyl)-acetate (45 mg, 0.07 mmol, 1 *eq.*) in MeOH (5.0 mL) was added aqueous sodium hydroxide solution (1M, 340 µL, 0.34 mmol, 5 *eq.*). The reaction mixture was stirred at r.t. for 16 h and then at 50°C for 4 h. After completion, solvent was removed *in vacuo*. Aqueous residue was neutralised with 1 M aqueous HCl solution and concentrated *in vacuo*. Residual was washed with ACN, filtered and concentrated *in vacuo* to give the *title compound* (30 mg, quantitative yield) without any further purification. UPLC (An analogous method to Method 5, ESI) 254.1 $[MH]^+$, RT 1.79 min.

INTERMEDIATE 38: *2-[(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-3-yl)sulfanyl]acetic acid*



Step 1: *tert-butyl 3-[(2-ethoxy-2-oxoethyl)sulfanyl]piperidine-1-carboxylate*

To a stirred solution of ethyl thioglycolate (1.25 mL, 11.36 mmol, 1.5 *eq.*) in DMF (40.0 mL), was added 1-Boc-3-bromopiperidine (2.00 g, 7.57 mmol, 1.0 *eq.*) followed by potassium carbonate (2.09 g, 15.14 mmol, 2.0 *eq.*). The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was removed *in vacuo* and the crude mixture was re-dissolved in DCM. Water was added and the layers were separated. Aqueous phase was extracted with DCM (3x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude product was purified by flash chromatography (silica, 0-30% EtOAc in cyclohexane) to afford the *title compound* (272 mg, 9% yield, 80% purity). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.14 – 4.05 (m, 2H), 3.93 – 3.80 (m, 1H), 3.58 – 3.49 (m, 1H), 3.32 (s, 2H), 3.05 – 2.94 (m, 1H), 2.91 – 2.81 (m, 1H), 2.03 – 1.88 (m, 1H), 1.71 – 1.60 (m, 1H), 1.50 – 1.30 (m, 1H), 1.39 (s, 9H), 1.30 – 1.14 (m, 5H). UPLC (An analogous method to Method 5, ESI) 325.90 $[MNa]^+$, RT 3.69 min.

Step 2: *ethyl 2-(piperidin-3-ylsulfanyl)acetate*

To a solution of *tert*-butyl 3-[(2-ethoxy-2-oxoethyl)sulfanyl]piperidine-1-carboxylate (252 mg, 1.51 mmol, 1.0 *eq.)* in DCM (5.0 mL) at 0°C was added TFA (254 µL, 3.32 mmol, 5.0 *eq.)*. The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was concentrated *in vacuo* to afford the *title compound* (333 mg, 31% purity). UPLC (An analogous method to Method 5, ESI) 204.10 $[MH]^+$, RT 0.94 min.

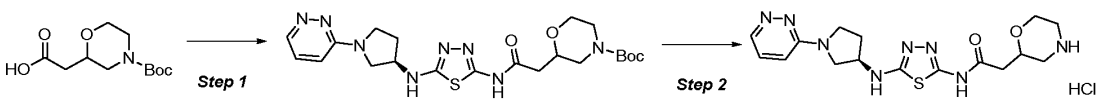
Step 3: *ethyl 2-[(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-3-yl)sulfanyl]acetate*

To a solution of ethyl 2-(piperidin-3-ylsulfanyl)acetate (293 mg, 0.45 mmol, 1.0 *eq.)* in DCE (3.0 mL) was added Et_3N (249 µL, 1.79 mmol, 4.0 *eq.)*. The resulting mixture was stirred for 5 min. After that 2-(propan-2-yloxy)benzaldehyde (110 mg, 0.67 mmol, 1.5 *eq.)* was added and the reaction mixture was stirred for 30 min. Then, STAB (284 mg, 1.34 mmol, 3.0 *eq.)* was added and the mixture was stirred at r.t. for 3 h before filtered and concentrated *in vacuo.* Crude product was purified by flash chromatography (silica, 0-80% EtOAc in cyclohexane) to afford the *title compound* (146 mg, 86% yield, 92% purity). UPLC (An analogous method to Method 5, ESI) 352.55 $[MH]^+$, RT 2.58 min.

Step 4: *2-[(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-3-yl)sulfanyl]acetic acid*

To a stirred solution of ethyl 2-[(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-3-yl) sulfanyl]acetate (126 mg, 0.33 mmol, 1 *eq.*) in THF (1.9 mL) at r.t. was added aqueous sodium hydroxide solution (1.7 M, 630 µL, 0.99 mmol, 3 *eq.*). The resulting mixture was stirred at 60°C for 16 h before concentrated *in vacuo*. Crude product was then dissolved in water and acidified with 1M aqueous HCl solution till pH = 5. The precipitate was filtered off. The obtained solid was washed with excess of ACN and the filtrate concentrated *in vacuo* to afford the *title compound* (135 mg, 91% yield, 72% purity). ^1H NMR (400 MHz, DMSO-d_6) δ 7.49 – 7.39 (m, 1H), 7.37 – 7.32 (m, 1H), 7.10 – 7.05 (m, 1H), 7.00 – 6.91 (m, 1H), 4.74 – 4.60 (m, 1H), 4.19 – 3.81 (m, 2H), 3.16 – 2.98 (m, 3H), 2.79 – 2.57 (m, 2H), 2.00 – 1.89 (m, 1H), 1.86 – 1.75 (m, 1H), 1.74 – 1.61 (m, 1H), 1.39 – 1.32 (m, 1H), 1.37 – 1.24 (m, 8H). UPLC (Method 21, ESI) 324.45 $[MH]^+$, RT 2.08 min.

INTERMEDIATE 39: *2-(morpholin-2-yl)-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide hydrochloride*



Intermediate 39

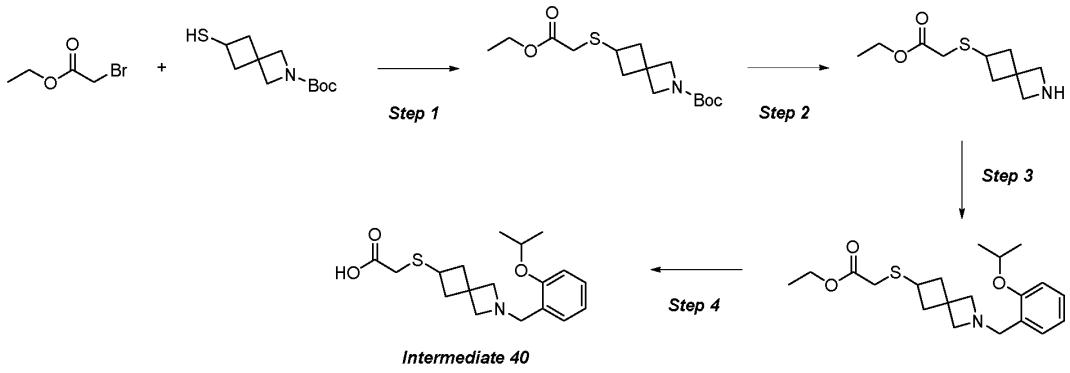
Step 1: *tert-butyl 2-{[(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamoyl]methyl}morpholine-4-carboxylate*

To a stirred solution of 2-{4-[(*tert*-butoxy)carbonyl]morpholin-2-yl}acetic acid (2.00 g, 8.15 mmol, 1.0 *eq.*) and DIPEA (4.26 mL, 3.16 g, 24.46 mmol, 3.0 *eq.*) in anhydrous DMF (40.0 mL) was added 1-propylphosphonic acid cyclic anhydride (50% sol. in DMF, 10.38 mL, 5.19 g, 16.31 mmol, 2.0 *eq.*) and the reaction mixture was stirred at r.t. for 15 min. (R)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine *(prepared according to the procedure of Intermediate 1)* (2.58 g, 16.31 mmol, 1.2 *eq.*) was added and stirring was continued at r.t. for 16 h. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (silica, 0-15% MeOH in DCM) to afford the *title compound* (1.04 g, 24% yield, 94% purity). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.01 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.65 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.1, 1.3 Hz, 1H), 4.43 – 4.33 (m, 1H), 3.88 – 3.64 (m, 6H), 3.63 – 3.46 (m, 4H), 3.35 (td, *J* = 11.5, 2.7 Hz, 1H), 2.60 – 2.55 (m, 2H), 2.36 – 2.23 (m, 1H), 2.14 – 2.01 (m, 1H), 1.40 (s, 9H). UPLC (An analogous method to Method 5, ESI) 491.55 $[MH]^+$, RT 1.91 min.

Step 2: *2-(morpholin-2-yl)-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide hydrochloride*

To a stirring solution of *tert*-butyl 2-{[(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamoyl]methyl}morpholine-4-carboxylate (4.29 g, 8.66 mmol, 1 *eq.*) in MeOH (214.5 mL) was added HCl solution in dioxane (4M, 21.64 mL, 86.57 mmol, 10 *eq.*) at 0°C and the mixture was stirred at r.t. for 16 h. Crude material was purified by reverse phase flash chromatography (C-18 silica, 0-100% ACN in 0.1% FA in H_2O sol.). Obtained fraction was triturated with 1:1 mixture of ACN and Et_2O to afford the *title compound* (3.59 g, 93% yield, 88% purity). UPLC (An analogous method to Method 5, ESI) 390.90 $[MH]^+$, RT 0.65 min.

INTERMEDIATE 40: *2-[(2-{[2-(propan-2-yloxy)phenyl]methyl}-2-azaspiro[3.3]heptan-6-yl)sulfanyl]acetic acid*



Intermediate 40

Step 1: *tert-butyl 6-[(2-ethoxy-2-oxoethyl)sulfanyl]-2-azaspiro[3.3]heptane-2-carboxylate*

To a stirred solution of ethyl bromoacetate (362 µL, 3.27 mmol, 1.5 *eq.*) in DMF (10.0 mL), was added *tert*-butyl 6-sulfanyl-2-azaspiro[3.3]heptane-2-carboxylate (500 mg, 2.18 mmol, 1.0 *eq.*) followed by potassium carbonate (600 mg, 4.36 mmol, 2.0 *eq.*). The reaction mixture was then stirred at r.t. for 16 h. After completion, solvent was removed *in vacuo* and the crude mixture was re-dissolved in EtOAc, filtered and concentrated *in vacuo*. Crude product was purified by flash chromatography (silica, 0-35% EtOAc in cyclohexane) to afford the *title compound* (671 mg, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.08 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 2H), 3.77 (s, 2H), 3.39 (p, *J* = 7.6 Hz, 1H), 3.27 (s, 2H), 2.57 – 2.52 (m, 2H), 2.10 – 1.99 (m, 2H), 1.35 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H). UPLC (An analogous method to Method 5, ESI) 315.85 $[MH]^+$, RT 2.54 min.

Step 2: *ethyl 2-{2-azaspiro[3.3]heptan-6-ylsulfanyl}acetate*

To a solution of *tert*-butyl 3-[(2-ethoxy-2-oxoethyl)sulfanyl]piperidine-1-carboxylate (350 mg, 1.11 mmol, 1.0 *eq.)* in DCM (7.0 mL) was added TFA (425 µL, 5.55 mmol, 5.0 *eq.)* at 0°C. The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (796 mg, 53% purity). UPLC (An analogous method to Method 5, ESI) 216.10 $[MH]^+$, RT 1.30 min.

Step 3: *ethyl 2-[(2-{[2-(propan-2-yloxy)phenyl]methyl}-2-azaspiro[3.3]heptan-6-yl)sulfanyl] acetate*

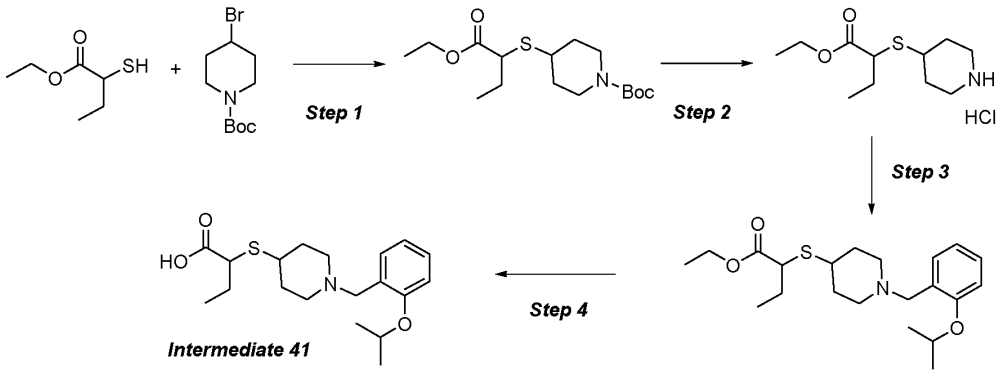
To a solution of ethyl 2-{2-azaspiro[3.3]heptan-6-ylsulfanyl}acetate (756 mg, 0.95 mmol, 1.0 *eq.)* in DCE (7.6 mL) was added Et_3N (529 µL, 3.79 mmol, 4.0 *eq.)*. The resulting mixture was stirred for 5 min. 2-(propan-2-yloxy)benzaldehyde (234 mg, 1.42 mmol, 1.5 *eq.)* was added and the reaction was stirred for another 30 min. Then, STAB (603 mg, 2.84 mol, 3.0 *eq.)* was added and the mixture was stirred at r.t. for 2 h. After completion, it was filtered and concentrated *in vacuo.* Crude product was purified by flash chromatography (silica, 0-5% MeOH in DCM) to afford the *title compound* (226 mg, 47% yield, 72% purity). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 – 7.28 (m, 2H), 7.18 – 7.08 (m, 1H), 7.01 – 6.93 (m, 1H), 4.76 – 4.62 (m, 1H), 4.28 – 4.16 (m, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 4.15 – 3.93 (m, 3H), 3.47 – 3.37 (m, 1H), 3.29 (s, 2H), 2.63 – 2.55 (m, 2H), 2.20 – 2.07 (m, 2H), 1.32 (d, *J* = 6.0 Hz, 6H), 1.29 – 1.22 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H). UPLC (An analogous method to Method 5, ESI) 364.60 $[MH]^+$, RT 2.65 min.

Step 4: *2-[(2-{[2-(propan-2-yloxy)phenyl]methyl}-2-azaspiro[3.3]heptan-6-yl)sulfanyl]acetic acid*

To a stirred solution of ethyl 2-[(2-{[2-(propan-2-yloxy)phenyl]methyl}-2-azaspiro[3.3] heptan-6-yl)sulfanyl]acetate (206 mg, 0.41 mmol, 1 *eq.*) in THF (3.0 mL) at r.t. was added aqueous sodium hydroxide solution (1.2M, 1.0 mL, 1.22 mmol, 3 *eq.*). The resulting mixture was stirred at 60°C for 16 h. After completion, it was concentrated *in vacuo*. Crude product was then diluted with water

and neutralised with 1M aqueous HCl solution till pH = 5. The precipitate was filtered off, washed with excess of ACN and concentrated *in vacuo* to afford the *title compound* (198 mg, 74% purity). UPLC (An analogous method to Method 5, ESI) 336.45 $[MH]^+$, RT 2.18 min.

INTERMEDIATE 41: *2-[(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-4-yl)sulfanyl]butanoic acid*



Step 1: *tert-butyl 4-[(1-ethoxy-1-oxobutan-2-yl)sulfanyl]piperidine-1-carboxylate*

To a solution of *tert*-butyl 4-bromopiperidine-1-carboxylate (500 mg, 1.89 mmol, 1 *eq.*) and anhydrous potassium carbonate (780 mg, 5.68 mmol, 3 *eq.*) in ACN (10.0 mL) was added ethyl 2-sulfanylbutanoate (550 µL, 3.79 mmol, 2 *eq.*) under argon. The reaction mixture was stirred at 70°C for 16 h before filtered and the filtrate was concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 1% MeOH in DCM) to afford the *title compound* (210 mg, 32% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 – 4.13 (m, 2H), 4.05 – 3.81 (m, 2H), 3.23 (dd, *J* = 8.3, 6.8 Hz, 1H), 2.99 – 2.85 (m, 3H), 2.03 – 1.82 (m, 3H), 1.76 – 1.63 (m, 1H), 1.53 – 1.46 (m, 2H), 1.45 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H). UPLC (An analogous method to Method 5, ESI) 231.85 $[MH\text{-}Boc]^+$, RT 3.50 min.

Step 2: *ethyl 2-(piperidin-4-ylsulfanyl)butanoate*

To a solution of *tert*-butyl 4-[(1-ethoxy-1-oxobutan-2-yl)sulfanyl]piperidine-1-carboxylate (210 mg, 0.6 mmol, 1 *eq.*) in DCM (7.0 mL) was added hydrogen chloride in dioxane (4M, 602 µL, 2.4 mmol, 4 *eq.*). The reaction mixture stirred at 50°C for 5 h. After completion, solvent was concentrated *in vacuo* to give the *title compound* (170 mg, quantitative yield, 95% purity), which was used in the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 – 4.13 (m, 2H), 3.51 – 3.27 (m, 2H), 3.21 – 2.99 (m, 4H), 2.38 – 2.19 (m, 2H), 2.06 – 1.83 (m, 3H), 1.74 – 1.69 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.3 Hz, 3H). UPLC (An analogous method to Method 5, ESI) 232.25 $[MH]^+$, RT 1.74 min.

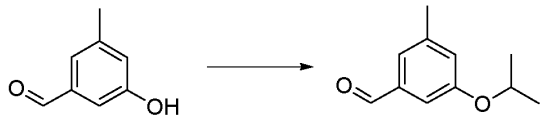
Step 3: *ethyl 2-[(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-4-yl)sulfanyl]butanoate*

To a stirred solution of ethyl 2-(piperidin-4-ylsulfanyl)butanoate hydrochloride (160 mg, 0.54 mmol, 1 *eq.*) in DCE (16.0 mL) under argon was added Et_3N (220 µL, 1.62 mmol, 3 *eq.*). The mixture was stirred for 5 min, then 2-(propan-2-yloxy)benzaldehyde (150 µL, 0.97 mmol, 1.8 *eq.*) was added, followed by STAB (0.46 g, 2.15 mmol, 4 *eq.*). The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was removed *in vacuo* and the crude mixture was dissolved in DCM and washed with saturated aqueous sodium bicarbonate solution. Aqueous layer was extracted with DCM (2x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude was purified by flash chromatography (silica, 20-30% EtOAc in cyclohexane) to afford the *title compound* (200 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 1H), 7.21 – 7.15 (m, 1H), 6.95 – 6.83 (m, 2H), 4.58 – 4.48 (m, 1H), 4.27 – 4.12 (m, 2H), 3.54 (s, 2H), 3.22 (dd, *J* = 8.5, 6.7 Hz, 1H), 2.94 – 2.82 (m, 2H), 2.82 – 2.71 (m, 1H), 2.21 – 2.08 (m, 2H), 2.03 – 1.96 (m, 1H), 1.94 – 1.82 (m, 2H), 1.75 – 1.62 (m, 3H), 1.32 (d, *J* = 6.0 Hz, 6H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H). UPLC (An analogous method to Method 5, ESI) 380.60 $[MH]^+$, RT 2.01 min.

Step 4: *2-[(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-4-yl)sulfanyl]butanoic acid*

To a solution of ethyl 2-[(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-4-yl)sulfanyl] butanoate (200 mg, 0.5 mmol, 1 *eq.*) in MeOH (10.0 mL) was added aqueous sodium hydroxide solution (1M, 2.50 mL, 2.5 mmol, 5 *eq.*). The reaction mixture was stirred at 50°C for 4 h and then at r.t. for another 16 h. After completion, solvent was removed *in vacuo*. Aqueous residue was neutralised with 1M aqueous HCl solution to pH~7 and concentrated *in vacuo*. Residual was washed with ACN, filtered and concentrated *in vacuo* to afford the *title compound* (175 mg, quantitative yield) without any further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.48 (bs, 1H), 7.40 – 7.30 (m, 1H), 7.27 – 7.18 (m, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.89 (t, *J* = 7.3 Hz, 1H), 4.67 – 4.52 (m, 1H), 3.70 – 3.50 (m, 2H), 3.25 – 3.12 (m, 2H), 2.96 – 2.76 (m, 3H), 2.37 – 2.11 (m, 1H), 2.04 – 1.82 (m, 2H), 1.82 – 1.66 (m, 1H), 1.64 – 1.42 (m, 3H), 1.26 (d, *J* = 6.0 Hz, 6H), 0.91 (t, *J* = 7.3 Hz, 3H). UPLC (An analogous method to Method 5, ESI) 352.55 $[MH]^+$, RT 1.85 min.

INTERMEDIATE 42: *3-methyl-5-(propan-2-yloxy)benzaldehyde*

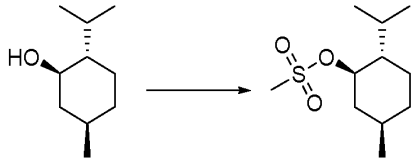


Intermediate 42

To a stirred suspension of 3-hydroxy-5-methylbenzaldehyde (1.00 g, 7.35 mmol, 1 *eq.*) in anhydrous DMF (18.4 mL) was added anhydrous potassium carbonate (3.05 g, 22.04 mmol, 2.0 *eq.*) followed by 2-bromopropane (1.36 g, 11.01 mmol, 1.5 *eq.*). The reaction mixture was stirred

at 85°C for 16 h. An additional amount of 2-bromopropane (0.27 g, 2.20 mmol, 0.3 *eq.*) was added and the mixture was stirred at 90°C for 5 h. Another portion of 2-bromopropane (0.18 g, 1.47 mmol, 0.2 *eq.*) was added and the mixture was stirred at 90°C for another 16 h. The mixture was concentrated *in vacuo*. The residue was re-dissolved in DCM and washed with water. Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude product was purified by flash chromatography (silica, 0-15% EtOAc in hexanes) to afford the *title compound* (0.95 g, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.24 (s, 1H), 7.18 (s, 1H), 6.97 (s, 1H), 4.61 (hept, *J* = 6.0 Hz, 1H), 2.39 (s, 3H), 1.35 (d, *J* = 6.1 Hz, 6H). UPLC (An analogous method to Method 5, ESI) 178.9 $[MH]^+$, RT 2.50 min.

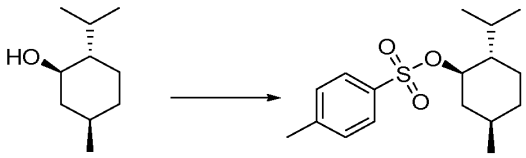
INTERMEDIATE 43: *(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl methanesulfonate*



Intermediate 43

To a solution of *L*-menthol (300 mg, 1.92 mmol, 1.0 *eq.*) in DCM (7.0 mL) was added Et_3N (804 µL, 5.76 mol, 3.0 *eq.*) at 0°C. A solution of methanesulfonyl chloride (178 µL, 2.30 mmol, 1.2 *eq.*) in DCM (0.5 mL) was then added dropwise and the resulting mixture was stirred at r.t. for 16 h. After completion, saturated ammonium chloride solution was added and the layers were separated. Combined organic layers were washed with 1M aqueous HCl solution, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude product was purified by flash chromatography (silica, 0-20% EtOAc in cyclohexane) to afford the *title compound* (350 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (td, *J* = 10.9, 4.6 Hz, 1H), 3.00 (s, 3H), 2.31 – 2.20 (m, 1H), 2.12 – 2.01 (m, 1H), 1.76 – 1.64 (m, 2H), 1.54 – 1.37 (m, 2H), 1.33 – 1.21 (m, 1H), 1.12 – 0.99 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.90 – 0.84 (m, 1H), 0.83 (d, *J* = 6.9 Hz, 3H).

INTERMEDIATE 44: *(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl 4-methylbenzene-1-sulfonate*

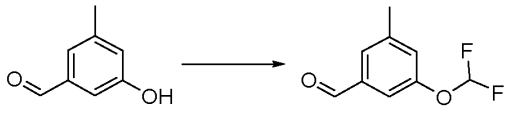


Intermediate 44

To a solution of *L*-menthol (300 mg, 1.92 mmol, 1.0 *eq.*) in DCM (7.0 mL) was added Et_3N (804 µL, 5.76 mol, 3.0 *eq.*) at 0°C. A solution of *p*-toluenesulfonyl chloride (384 mg, 2.02 mmol, 1.1

eq.) in DCM (0.5 mL) was then added dropwise and the resulting mixture was stirred at r.t. for 16 h. After completion, it was washed with 1M aqueous HCl solution. Organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude product was purified by preparative TLC (silica, 20% EtOAc in cyclohexane) to afford the *title compound* (40 mg, 6% yield, 85% purity). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 4.49 – 4.31 (m, 1H), 2.44 (s, 3H), 2.19 – 2.08 (m, 1H), 1.96 – 1.84 (m, 1H), 1.70 – 1.60 (m, 2H), 1.48 – 1.31 (m, 2H), 1.25 – 1.10 (m, 1H), 1.04 – 0.91 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.58 – 0.45 (m, 3H).

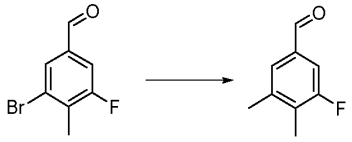
INTERMEDIATE 45: *3-(difluoromethoxy)-5-methylbenzaldehyde*



Intermediate 45

To a stirred solution of 3-hydroxy-5-methylbenzaldehyde (200 mg, 1.47 mmol, 1 *eq.*) and potassium hydroxide (1.65 g, 29.38 mmol, 20 *eq.*) in H_2O (3.7 mL) and ACN (3.7 mL) at 0°C was added bromodifluoromethyl diethylphosphonate (784 mg, 2.94 mmol, 2 *eq.*). The reaction mixture was stirred at 0°C for 30 min, warmed up to r.t. and stirred for 16 h. The mixture was diluted with water and extracted with Et_2O (3x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-20% EtOAc in cyclohexane) to afford the *title compound* (100 mg, 35% yield) as a colourless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.63 (s, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.33 (t, *J* = 73.7 Hz, 1H), 2.42 (s, 3H).

INTERMEDIATE 46: *3-fluoro-4,5-dimethylbenzaldehyde*

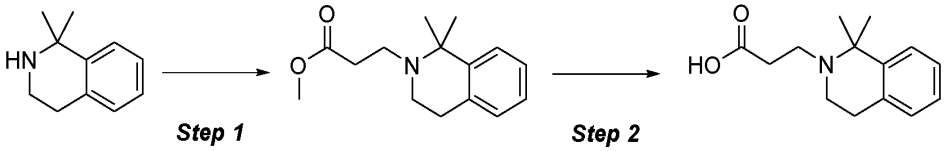


Intermediate 46

A solution of 5-bromo-3-fluoro-4-methylbenzaldehyde (400 mg, 1.84 mmol, 1 *eq.*), potassium methyltrifluoroborate (450 mg, 3.69 mmol, 2.0 *eq.*), potassium carbonate (760 mg, 5.53 mmol, 3.0 *eq.*) in dioxane (16.0 mL) and water (2.0 mL) was purged with argon for 10 min. [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (300 mg, 0.37 mmol, 0.2 *eq.*) was added and the reaction mixture was stirred at 100°C for 16 h. The reaction was diluted with MeOH and distilled. Crude product was collected as a solution of *title compound* (quantitative yield) in MeOH, water and dioxane without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.88 (d, *J* = 1.8 Hz, 1H), 7.57 (s, 1H), 7.46 (d, *J* = 9.5 Hz, 1H), 2.34 (s,

3H), 2.21 (d, *J* = 2.1 Hz, 3H). UPLC (An analogous method to Method 5, ESI) not found $[MH]^+$, RT 3.39 min.

INTERMEDIATE 47: *3-(1,1-dimethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)propanoic acid*



Step 1 ***Step 2*** ***Intermediate 47***

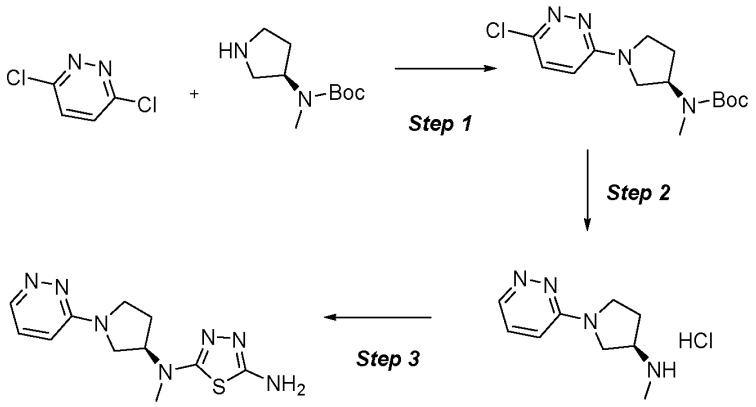
Step 1: *methyl 3-(1,1-dimethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)propanoate*

To a stirred solution of 1,1-dimethyl-1,2,3,4-tetrahydroisoquinoline (30 mg, 1.86 mmol, 1.0 *eq.*) and potassium carbonate (770 mg, 5.58 mmol, 3.0 *eq.*) in DMF (12.0 mL) was added methyl 3-bromopropionate (490 mg, 2.79 mmol, 1.5 *eq.*). The reaction mixture was stirred at 100°C for 5 d. After completion, solvent was removed *in vacuo* and the crude mixture was dissolved in DCM. Water was added and the layers were separated. Aqueous phase was extracted with DCM (2x). Combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-9% MeOH in DCM) to afford the *title compound* (120 mg, 26% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.14 – 6.96 (m, 4H), 3.56 (s, 3H), 2.78 – 2.65 (m, 6H), 2.49 – 2.46 (m, 2H), 1.28 (s, 6H). UPLC (An analogous method to Method 5, ESI) 248.1 $[MH]^+$, RT 1.76 min.

Step 2: *3-(1,1-dimethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)propanoic acid*

To a stirred solution of methyl 3-(1,1-dimethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)propanoate (120 mg, 0.48 mmol, 1 *eq.*) in THF (1.9 mL) was added aqueous sodium hydroxide solution (0.15M, 620 µL, 2.40 mmol, 5 *eq.*) and the solution was stirred at r.t. for 16 h. The mixture was concentrated *in vacuo* to afford the *title compound* (400 mg, quantitative yield) without further purification. UPLC (An analogous method to Method 5, ESI) 234.15 $[MH]^+$, RT 1.44 min.

INTERMEDIATE 48: *N2-methyl-N2-[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]-1,3,4-thiadiazole-2,5-diamine*



Intermediate 48

Step 1: *tert-butyl N-[(3R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl]-N-methylcarbamate*

To a stirred solution of 3,6-dichloropyridazine (0.74 g, 4.99 mmol, 1 *eq.*) and Et_3N (2.09 mL, 14.98 mmol, 3 *eq.*) in ethanol (25.0 mL) was added *tert*-butyl *N*-methyl-*N*-[(3*R*)-pyrrolidin-3-yl]carbamate (1.00 g, 4.99 mmol, 1.0 *eq.*). The reaction mixture was stirred at 70°C for 16 h and the solvent was removed *in vacuo*. Crude mixture was re-dissolved in DCM and saturated aqueous sodium bicarbonate solution was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-10% MeOH in DCM) to afford the *title compound* (0.91 g, 57% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 9.4 Hz, 1H), 6.68 (d, *J* = 9.4 Hz, 1H), 4.99 – 4.80 (m, 1H), 3.84 – 3.68 (m, 2H), 3.60 – 3.38 (m, 2H), 2.82 (s, 3H), 2.27 – 2.13 (m, 2H), 1.48 (s, 9H). UPLC (An analogous method to Method 5, ESI) 312.95 $[MH]^+$, RT 2.36 min.

Step 2: *(3R)-N-methyl-1-(pyridazin-3-yl)pyrrolidin-3-amine hydrochloride*

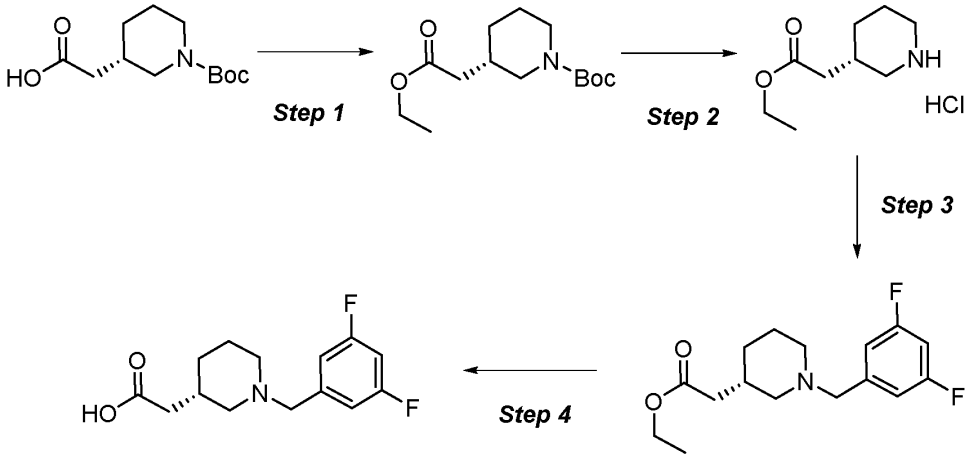
To a stirred solution of *tert*-butyl *N*-[(3*R*)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl]-*N*-methylcarbamate (890 mg, 2.79 mmol, 1.0 *eq.*) in MeOH (27.9 mL) was added palladium on carbon (10% wet. 89 mg, 0.84 mmol, 0.3 *eq.*). The system was evacuated and backfilled with hydrogen three times and stirred under hydrogen atmosphere at r.t. for 16 h. The suspension was filtered through a pad of Celite® and washed with MeOH (20.0 mL). 3M aqueous HCl solution in MeOH (8.36 mL, 25.10 mmol, 9.0 *eq.*) was added and the mixture was stirred at r.t. for 16 h. Solvent was removed *in vacuo* to afford the *title compound* (830 mg, 99% yield, 72% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 9.74 (s, 1H), 8.68 (d, *J* = 4.3 Hz, 1H), 7.97 (dd, *J* = 9.5, 4.4 Hz, 1H), 7.77 (dd, *J* = 9.5, 1.2 Hz, 1H), 4.00 – 3.95 (m, 1H), 3.90 – 3.84 (m,

2H), 3.71 – 3.64 (m, 2H), 2.58 (t, *J* = 5.3 Hz, 3H), 2.45 – 2.37 (m, 2H). UPLC (An analogous method to Method 5, ESI) 178.90 $[MH]^+$, RT 0.61 min.

Step 3: *N2-methyl-N2-[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]-1,3,4-thiadiazole-2,5-diamine*

To a stirred solution of (3*R*)-*N*-methyl-1-(pyridazin-3-yl)pyrrolidin-3-amine hydrochloride (810 mg, 2.70 mmol, 1 *eq.*) in DMF (13.5 mL) was added anhydrous DIPEA (1.88 mL, 10.81 mmol, 4 *eq.*) followed by 2-amino-5-bromo-1,3,4-thiadiazole (970 mg, 5.41 mmol, 2 *eq.*). The reaction mixture was stirred at 60°C for 12 h and the solvent was removed *in vacuo*. Crude mixture was dissolved in DCM and saturated aqueous sodium bicarbonate solution was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with $CHCl_3$:IPA (4:1, 3 x 50mL). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-25% MeOH in DCM) to afford the *title compound* (540 mg, 70% yield) as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.36 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.92 (dd, *J* = 9.1, 1.4 Hz, 1H), 6.46 (s, 2H), 4.53 (p, *J* = 7.2 Hz, 1H), 3.76 – 3.64 (m, 2H), 3.54 – 3.42 (m, 2H), 2.86 (s, 3H), 2.27 – 2.15 (m, 2H). UPLC (An analogous method to Method 5, ESI) 277.85 $[MH]^+$, RT 0.61 min.

INTERMEDIATE 49: *sodium 2-[(3S)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]acetate*



Intermediate 49

Step 1: *tert-butyl (3S)-3-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate*

To a stirred solution of 2-[(3*S*)-1-[(*tert*-butoxy)carbonyl]piperidin-3-yl]acetic acid (0.90 g, 3.70 mmol, 1.0 *eq.*) and potassium carbonate (1.53 g, 11.10 mmol, 3.0 *eq.*) in anhydrous ACN (13.5 mL) under argon was added iodoethane (1.44 g, 9.25 mmol, 2.5 *eq.*). The reaction was stirred at 50°C for 10 h and at r.t. for 5 h. Then, it was filtered and the filtrate was concentrated *in vacuo* to afford the *title compound* (1.30 g, quantitative yield) without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.1 Hz, 2H), 4.00 – 3.65 (m, 1H), 3.83 (dt, *J* = 13.1, 4.0 Hz, 1H), 2.91

– 2.75 (m, 1H), 2.74 – 2.40 (m, 1H), 2.25 (dd, *J* = 15.1, 6.9 Hz, 1H), 2.15 (dd, *J* = 15.1, 7.2 Hz, 1H), 2.03 – 1.90 (m, 1H), 1.88 – 1.78 (m, 1H), 1.67 – 1.57 (m, 1H), 1.52 – 1.38 (m, 10H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.23 – 1.10 (m, 1H). UPLC (An analogous method to Method 5, ESI) 271.85 $[MH]^+$, RT 2.53 min.

Step 2: *ethyl 2-[(3S)-piperidin-3-yl]acetate hydrochloride*

To a solution of *tert*-butyl (3*S*)-3-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (1.30 g, 4.55 mmol, 1 *eq.*) in DCM (40.0 mL) was added HCl solution in dioxane (4M, 0.60 mL, 18.20 mmol, 4 *eq.*). The reaction mixture was stirred at 50°C for 16 h. After completion, solvent was concentrated *in vacuo* to give the *title compound* (0.99 g, quantitative yield) without any further purification. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.46 – 3.34 (m, 2H), 2.91 (td, *J* = 13.2, 3 hz, 1H), 2.75 (t, *J* = 12.2 Hz, 1H), 2.41 (d, *J* = 7.0 Hz, 2H), 2.30 – 2.14 (m, 1H), 1.99 – 1.84 (m, 2H), 1.81 – 1.66 (m, 1H), 1.44 – 1.28 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H). UPLC (An analogous method to Method 5, ESI) 172.00 $[MH]^+$, RT 1.06 min.

Step 3: *ethyl 2-[(3S)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]acetate*

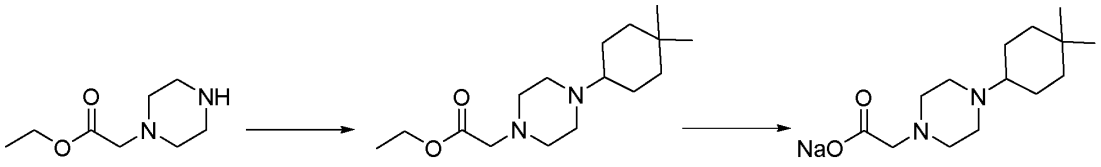
To a stirred solution of ethyl 2-[(3*S*)-piperidin-3-yl]acetate hydrochloride (500 mg, 2.29 mmol, 1.0 *eq.*) and DIPEA (1.59 mL, 9.15 mmol, 4.0 *eq.*) in ACN (22.9 mL) was added 3,5-difluorobenzyl bromide (520 mg, 2.52 mmol, 1.1 *eq.*).The resulting mixture was stirred at r.t. for 16 h and the solvent was removed *in vacuo*. Crude was re-dissolved in DCM and saturated aqueous sodium bicarbonate solution, and the mixture was stirred for 15 min before phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-3% MeOH in DCM) to afford the *title compound* (610 mg, 88% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 – 6.85 (m, 2H), 6.81 – 6.64 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.76 – 3.41 (m, 2H), 3.03 – 2.69 (m, 2H), 2.34 – 2.09 (m, 4H), 1.86 – 1.66 (m, 3H), 1.28 (s, 0H), 1.31 – 1.19 (m, 4H), 1.18 – 1.00 (m, 1H). UPLC (An analogous method to Method 5, ESI) 298.05 $[MH]^+$, RT 1.81 min.

Step 4: *sodium 2-[(3S)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]acetate*

To a stirred solution of ethyl 2-[(3*S*)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]acetate (125 mg, 0.38 mmol, 1 *eq.*) in MeOH (1.9 mL) was added aqueous sodium hydroxide solution (1M, 750 µL, 0.75 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (124 mg, quantitative yield, 82% purity) as a yellow solid without further purification. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.21 – 7.13 (m, 2H), 7.04 (tt, *J* = 9.1, 2.3 Hz, 1H), 4.13 (s, 2H), 3.36 – 3.32 (m, 1H), 3.28 – 3.21 (m, 1H), 2.72 (td, *J* = 12.1, 2.9

Hz, 1H), 2.54 (t, *J* = 11.1 Hz, 1H), 2.32 – 2.17 (m, 3H), 1.94 – 1.85 (m, 2H), 1.84 – 1.71 (m, 1H), 1.29 – 1.17 (m, 1H). UPLC (An analogous method to Method 5, ESI) 270.10 $[MH]^+$, RT 1.28 min.

INTERMEDIATE 50: *sodium 2-[4-(4,4-dimethylcyclohexyl)piperazin-1-yl]acetate*



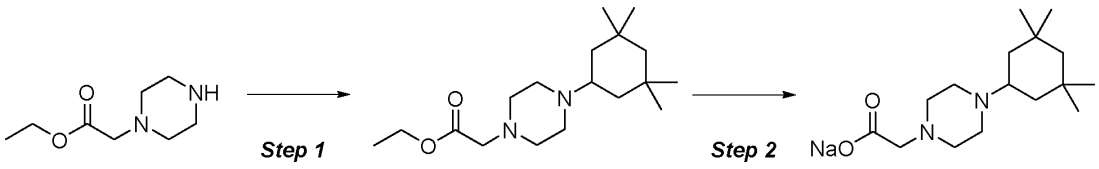
Step 1: *ethyl 2-[4-(4,4-dimethylcyclohexyl)piperazin-1-yl]acetate*

To a stirred solution of 1-(ethoxycarbonylmethyl)piperazine (100 mg, 0.58 mmol, 1.0 *eq.*) and 4,4-dimethylcyclohexanone (81 mg, 0.64 mmol, 1.1 *eq.*) in DCM (5.8 mL) was added STAB (246 mg, 1.16 mmol, 2.0 *eq.*). The reaction mixture was stirred at r.t. for 16 h. MeOH was added to the reaction mixture and the solvents were removed *in vacuo*. Crude was dissolved in DCM and saturated aqueous sodium bicarbonate solution was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the *title compound* (140 mg, 81% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H), 3.47 – 3.40 (m, 2H), 3.29 (s, 2H), 3.25 – 3.15 (m, 2H), 3.11 – 3.02 (m, 3H), 2.97 – 2.86 (m, 1H), 2.12 – 2.04 (m, 2H), 1.86 – 1.72 (m, 2H), 1.61 – 1.57 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.32 – 1.24 (m, 1H), 0.95 (s, 3H), 0.94 (s, 3H). UPLC (An analogous method to Method 5, ESI) 283.30 $[MH]^+$, RT 1.61 min.

Step 2: *sodium 2-[4-(4,4-dimethylcyclohexyl)piperazin-1-yl]acetate*

To a stirred solution of ethyl 2-[4-(4,4-dimethylcyclohexyl)piperazin-1-yl]acetate (140 mg, 0.47 mmol, 1 *eq.*) in MeOH (2.4 mL), was added aqueous sodium hydroxide solution (1M, 940 µL, 0.94 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (170 mg, 70% purity) as a white solid without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.71 (s, 2H), 2.48 – 2.31 (m, 8H), 2.04 – 1.93 (m, 1H), 1.62 – 1.53 (m, 2H), 1.35 – 1.28 (m, 2H), 1.28 – 1.17 (m, 2H), 1.13 – 1.02 (m, 2H), 0.80 (s, 3H), 0.79 (s, 3H). UPLC (An analogous method to Method 5, ESI) 255.10 $[MH]^+$, RT 1.19 min.

INTERMEDIATE 51: *sodium 2-(4-(3,3,5,5-tetramethylcyclohexyl)piperazin-1-yl)acetate*



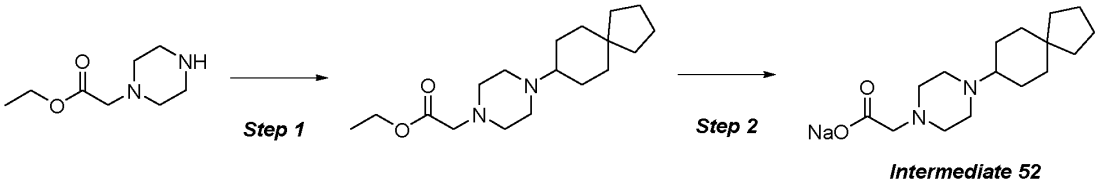
Intermediate 51

Step 1: *ethyl 2-(4-(3,3,5,5-tetramethylcyclohexyl)piperazin-1-yl)acetate*

To a stirred solution of ethyl 2-(piperazin-1-yl)acetate (100 mg, 0.58 mmol, 1.0 *eq.*) and 3,3,5,5-tetramethylcyclohexanone (100 mg, 0.64 mmol, 1.1 *eq.*) in DCM (11.6 mL) was added STAB (246 mg, 1.16 mmol, 2.0 *eq.*). The reaction mixture was stirred at r.t. for 64 h. The mixture was then diluted with DCM and saturated aqueous sodium bicarbonate solution was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the *title compound* (100 mg, 53% yield) as a yellow oil. UPLC (An analogous method to Method 5, ESI) 311.15 $[MH]^+$, RT 1.94 min.

Step 2: *sodium 2-(4-(3,3,5,5-tetramethylcyclohexyl)piperazin-1-yl)acetate* To a stirred solution of ethyl 2-{4-[(3,3,5,5-tetramethylcyclohexyl)methyl]piperazin-1-yl} acetate (100 mg, 0.31 mmol, 1 *eq.*) in MeOH (3.1 mL) was added aqueous sodium hydroxide solution (1M, 610 µL, 0.61 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was removed *in vacuo* to afford the *title compound* (90 mg, quantitative yield) as a yellow solid without further purification. UPLC (An analogous method to Method 5, ESI) 283.15 $[MH]^+$, RT 1.55 min.

INTERMEDIATE 52: *sodium 2-(4-{spiro[4.5]decan-8-yl}piperazin-1-yl)acetate*



Intermediate 52

Step 1: *ethyl 2-(4-{spiro[4.5]decan-8-yl}piperazin-1-yl)acetate*

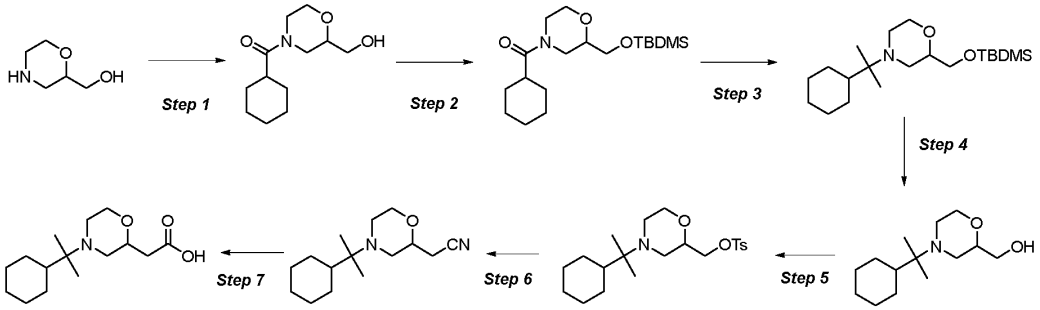
To a stirred solution of ethyl 2-(piperazin-1-yl)acetate (500 mg, 2.90 mmol, 1.0 *eq.*) and spiro[4.5]decan-8-one (490 mg, 3.19 mmol, 1.1 *eq.*) in DCM (29.0 mL) was added STAB (1.23 g, 5.81 mmol, 2.0 *eq.*). The reaction mixture was stirred at r.t. for 64 h. It was then diluted with DCM and saturated aqueous sodium bicarbonate solution was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-10% MeOH in DCM) to afford the *title compound* (690 mg, 76% yield) as a yellow oil. ^1H NMR (300 MHz,

$CDCl_3$) δ 4.19 (q, *J* = 7.2 Hz, 2H), 3.25 (s, 2H), 2.96 (s, 8H), 2.07 – 1.98 (m, 1H), 1.67 – 1.50 (m, 8H), 1.45 – 1.38 (m, 2H), 1.38 – 1.30 (m, 4H), 1.30 – 1.22 (m, 6H). UPLC (An analogous method to Method 5, ESI) 309.30 $[MH]^+$, RT 1.82 min.

Step 2: *sodium 2-(4-{spiro[4.5]decan-8-yl}piperazin-1-yl)acetate*

To a stirred solution of ethyl 2-(4-{spiro[4.5]decan-8-yl}piperazin-1-yl)acetate (690 mg, 2.19 mmol, 1 *eq.*) in MeOH (21.9 mL) was added aqueous sodium hydroxide solution (1M, 4.38 mL, 4.38 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was concentrated *in vacuo* to afford the *title compound* (780 mg, 80% purity) as a yellow solid without further purification. ^1H NMR (300 MHz, Deuterium Oxide) δ 2.99 (s, 2H), 2.85 – 2.36 (m, 8H), 2.26 – 2.14 (m, 1H), 1.84 – 1.75 (m, 2H), 1.63 – 1.46 (m, 6H), 1.45 – 1.37 (m, 2H), 1.35 – 1.21 (m, 6H). UPLC (An analogous method to Method 5, ESI) 281.05 $[MH]^+$, RT 1.59 min.

INTERMEDIATE 53: *2-[4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]acetic acid*



Intermediate 53

Step 1: *(4-cyclohexanecarbonylmorpholin-2-yl)methanol*

To a stirred solution of cyclohexanecarboxylic acid (3.28 g, 25.61 mmol, 1.0 *eq.*) in anhydrous DMF (90.0 mL) were added DIPEA (13.4 mL, 76.8 mmol, 3.0 *eq.*) and HATU (14.61 g, 38.41 mmol, 1.5 *eq.*). The reaction mixture was stirred for 15 min, (morpholin-2-yl)methanol (3.00 g, 25.61 mmol, 1.0 *eq.*) was then added before stirring at r.t. for 16 h. The reaction mixture was diluted with DCM and saturated aqueous sodium bicarbonate solution was added. Stirring was continued for 15 min and phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-10% MeOH in DCM) to give the *title compound* (15.91 g, quantitative yield, 37% purity). UPLC (An analogous method to Method 5, ESI) 227.95 $[MH]^+$, RT 1.88 min.

Step 2: *2-{[(tert-butyldimethylsilyl)oxy]methyl}-4-cyclohexanecarbonylmorpholine*

To a stirred solution of (4-cyclohexanecarbonylmorpholin-2-yl)methanol (1.83 g, 8.03 mmol, 1 *eq.*) in anhydrous DMF (150.0 mL) was added imidazole (3.83 g, 56.20 mmol, 7 *eq.*) followed by

tert-butyldimethylsilyl chloride (3.63 g, 24.09 mmol, 3 *eq.*). The reaction mixture was stirred at r.t. for 16 h. The reaction mixture was diluted with DCM and water was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM (3x). Combined organic phases were dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-50% EtOAc in cyclohexane) to give the *title compound* (1.95 g, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (dd, *J* = 57.3, 13.4 Hz, 1H), 3.98 – 3.85 (m, 2H), 3.78 – 3.59 (m, 2H), 3.57 – 3.17 (m, 3H), 2.98 – 2.73 (m, 1H), 2.56 – 2.39 (m, 1H), 1.85 – 1.77 (m, 2H), 1.76 – 1.65 (m, 3H), 1.58 – 1.47 (m, 2H), 1.31 – 1.18 (m, 3H), 0.92 – 0.87 (m, 9H), 0.09 – 0.04 (m, 6H). UPLC (An analogous method to Method 5, ESI) 342.20 $[MH]^+$, RT 4.63 min.

Step 3: *2-{[(tert-butyldimethylsilyl)oxy]methyl}-4-(2-cyclohexylpropan-2-yl)morpholine*

To a stirred solution of 2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-4-cyclohexanecarbonyl morpholine (920 mg, 2.69 mmol, 1.0 *eq.*) in anhydrous THF (46.0 mL) at -30°C was added $ZnCl_4$ (840 mg, 3.04 mmol, 1.5 *eq.*). The reaction mixture was stirred at -30°C for 30 min and methylmagnesium bromide in Et_2O (3M, 8.98 mL, 26.93 mmol, 10.0 *eq.*) was added dropwise over 15 min. The reaction mixture was stirred at -30°C for 3 h, warmed up to r.t. and stirred for 16 h. It was then quenched with water and diluted with DCM. Phases were separated and the aqueous phase was extracted with DCM (3x). Combined organic phases were washed with water, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-50% EtOAc in cyclohexane) to give the *title compound* (550 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 – 3.81 (m, 1H), 3.71 – 3.64 (m, 1H), 3.58 (td, *J* = 10.9, 2.5 Hz, 1H), 3.54 – 3.45 (m, 2H), 2.93 – 2.87 (m, 1H), 2.67 – 2.61 (m, 1H), 2.33 – 2.25 (m, 1H), 1.98 – 1.91 (m, 1H), 1.85 – 1.73 (m, 4H), 1.69 – 1.62 (m, 1H), 1.45 – 1.39 (m, 1H), 1.35 – 1.24 (m, 1H), 1.20 – 1.09 (m, 3H), 0.98 – 0.92 (m, 1H), 0.90 – 0.86 (m, 15H), 0.06 (s, 6H). UPLC (An analogous method to Method 5, ESI) 356.50 $[MH]^+$, RT 3.63 min.

Step 4: *[4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]methanol*

To a stirred solution of 2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-4-(2-cyclohexylpropan-2-yl)morpholine (550 mg, 1.55 mmol, 1.0 *eq.*) in anhydrous THF (16.5 mL) was added tetrabutylammonium fluoride in THF (1M, 1.85 mL, 1.86 mmol, 1.2 *eq.*). The reaction mixture was stirred at r.t. for 16 h before concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-50% EtOAc in cyclohexane) to give the *title compound* (360 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (dt, *J* = 10.9, 2.8 Hz, 1H), 3.68 – 3.53 (m, 4H), 2.73 – 2.60 (m, 2H), 2.31 (td, *J* = 11.0f, 3.1 Hz, 1H), 2.19 – 2.03 (m, 1H), 1.82 – 1.73 (m, 4H), 1.70 – 1.62 (m, 1H), 1.45 – 1.36 (m, 1H), 1.21 – 1.09 (m, 3H), 0.98 – 0.89 (m, 2H), 0.87 (s, 3H), 0.86 (s, 3H). UPLC (An analogous method to Method 5, ESI) 242.20 $[MH]^+$, RT 1.84 min.

Step 5: *[4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]methyl 4-methylbenzene-1-sulfonate*

To a stirred solution of [4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]methanol (360 mg, 1.50 mmol, 1.0 *eq.*) in anhydrous DCM (15.0 mL) were added Et_3N (63 µL, 4.50 mmol, 3.0 *eq.*) and *p*-toluenesulfonyl chloride (370 mg, 1.95 mmol, 1.3 *eq.*). The reaction mixture was stirred at r.t. for 16 h before concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-20% EtOAc in cyclohexane) to give the *title compound* (530 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.78 (m, 2H), 7.36 – 7.32 (m, 2H), 4.06 – 3.97 (m, 2H), 3.78 (dt, *J* = 10.9, 2.8 Hz, 1H), 3.68 – 3.61 (m, 1H), 3.50 (td, *J* = 10.8, 2.6 Hz, 1H), 2.70 – 2.64 (m, 1H), 2.62 – 2.56 (m, 1H), 2.45 (s, 3H), 2.24 (td, *J* = 11.0, 3.1 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.79 – 1.70 (m, 4H), 1.69 – 1.63 (m, 1H), 1.39 – 1.30 (m, 1H), 1.20 – 1.09 (m, 3H), 0.95 – 0.85 (m, 2H), 0.82 (s, 3H), 0.82 (s, 3H). UPLC (An analogous method to Method 5, ESI) 396.45 $[MH]^+$, RT 2.75 min.

Step 6: *2-[4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]acetonitrile*

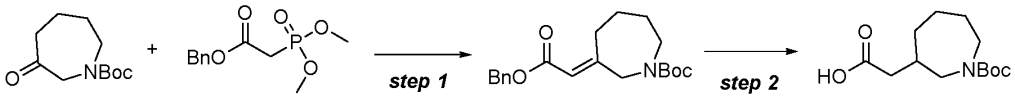
To a stirred solution of [4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]methyl 4-methylbenzene-1-sulfonate (530 mg, 1.34 mmol, 1 *eq.*) in DMSO (26.4 mL) was added potassium cyanide (260 mg, 4.01 mmol, 3 *eq.*). The reaction mixture was stirred at 60°C for 16 h. Then, it was diluted with DCM and water was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM (3x). Combined organic phases were dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-50% EtOAc in cyclohexane) to give the *title compound* (330 mg, 90% purity) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (dt, *J* = 11.0, 2.9 Hz, 1H), 3.78 – 3.70 (m, 1H), 3.60 (td, *J* = 10.7, 2.6 Hz, 1H), 2.86 – 2.79 (m, 1H), 2.69 – 2.62 (m, 1H), 2.55 (d, *J* = 6.1 Hz, 2H), 2.33 (td, *J* = 11.2, 3.1 Hz, 1H), 2.18 – 2.11 (m, 1H), 1.81 – 1.73 (m, 4H), 1.70 – 1.63 (m, 1H), 1.27 – 1.09 (m, 4H), 0.99 – 0.90 (m, 2H), 0.87 (s, 6H). UPLC (An analogous method to Method 5, ESI) 251.15 $[MH]^+$, RT 1.77 min.

Step 7: *2-[4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]acetic acid*

To a stirred solution of 2-[4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]acetonitrile (330 mg, 1.34 mmol, 1 *eq.*) in mixture of ethanol and water (17.0 mL, 1:1) was added potassium hydroxide (0.75 g, 13.363 mmol, 10 *eq.*). The reaction mixture was stirred at 90°C for 16 h. Then, it was neutralised with 1M aqueous HCl and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-10% MeOH in DCM) to give the *title compound* (330 mg, 91% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 – 4.77 (m, 1H), 4.64 (t, *J* = 12.2 Hz, 1H), 4.05 – 3.96 (m, 1H), 3.64 (d, *J* = 11.9 Hz, 1H), 3.35 (d, *J* = 11.8 Hz, 1H), 3.05 – 2.94 (m, 1H), 2.82 (t, *J* = 11.2 Hz, 1H), 2.61 (d, *J* = 6.1 Hz, 2H), 2.05 – 1.91 (m, 2H), 1.91 – 1.80 (m, 2H), 1.74 – 1.60 (m,

2H), 1.40 (s, 3H), 1.39 (s, 3H), 1.28 – 1.12 (m, 5H). UPLC (An analogous method to Method 5, ESI) 270.2 $[MH]^+$, RT 1.69 min.

INTERMEDIATE 54: *2-(1-(tert-butoxycarbonyl)azepan-3-yl)acetic acid*



Intermediate 54

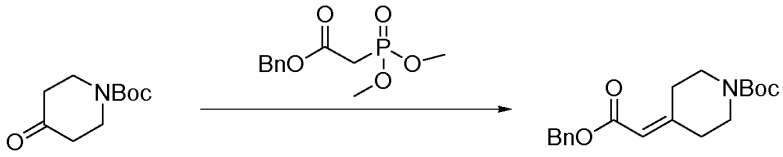
Step 1: *tert-butyl (E)-3-(2-(benzyloxy)-2-oxoethylidene)azepane-1-carboxylate*

To a mixture of benzyl 2-(dimethoxyphosphoryl)acetate (1.16 g, 4.51 mmol, 1.2 *eq.*) in THF (10 mL) was added NaH (225 mg, 5.63 mmol, 1.5 *eq.*) at 0°C. The mixture was stirred at 0°C for 30 min before addition of *tert*-butyl 3-oxoazepane-1-carboxylate (800 mg, 3.76 mmol, 1.0 *eq.*). The reaction mixture was stirred at r.t. for 1 h, then quenched with H_2O (3 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL x 3), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc =10/1) to afford the *title compound* (650 mg, 50 % yield) as a white solid. LCMS (Method 16, ESI) 290.0 $[M+H-56]^+$, RT 1.958 minutes.

Step 2: *2-(1-(tert-butoxycarbonyl)azepan-3-yl)acetic acid*

To a mixture of *tert*-butyl (*E*)-3-(2-(benzyloxy)-2-oxoethylidene)azepane-1-carboxylate (2.60 mg, 0.75 mmol, 1.0 *eq.*) in MeOH (10 mL) was added Pd/C (250 mg, 10% on carbon with ca. 55% water). The reaction mixture was stirred at r.t. under H_2 atmosphere for 1 h and filtered. The filtrate was concentrated *in vacuo* to afford the *title compound* (200 mg, 99.0% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.67-2.93 (m, 5 H), 2.43-2.23 (m, 3H), 1.81-1.69 (m, 3 H), 1.63-1.57 (m, 1 H), 1.48-1.41 (m, 9 H), 1.28-1.21 (m, 1 H). LCMS (Method 15, ESI) 258.1 $[M+H]^+$, RT 1.614 minutes.

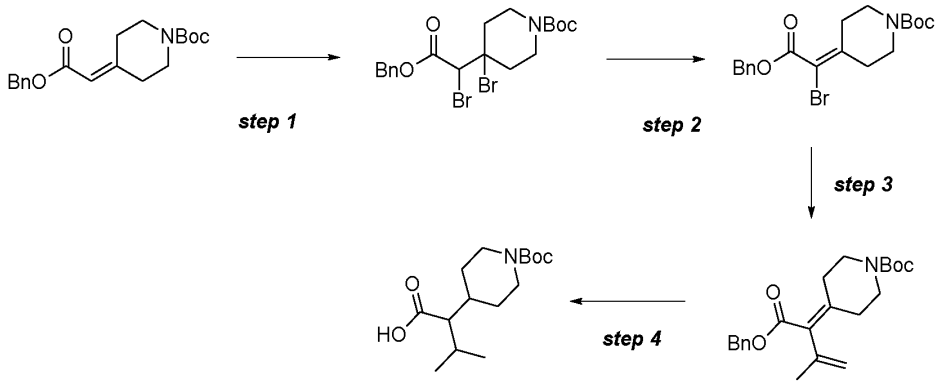
INTERMEDIATE 55: *2-(1-(tert-butoxycarbonyl)piperidin-4-yl)-3-methylbutanoic acid*



Step 1A: *tert-butyl 4-(2-(benzyloxy)-2-oxoethylidene)piperidine-1-carboxylate*

To a mixture of benzyl 2-(dimethoxyphosphoryl)acetate (1.56 g, 6.03 mmol, 1.2 *eq.*) in THF (20 mL) was added NaH (181 mg, 7.54 mmol, 1.5 *eq.*) at 0 °C. The mixture was stirred at 0 °C for 30 min before addition of *tert*-butyl 4-oxopiperidine-1-carboxylate (1.0 g, 5.03 mmol, 1.0 eq.). The reaction mixture was stirred at r.t. for 1 h, then quenched with H_2O (10 mL) and extracted with

EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL x 3), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc =10/1) to afford the *title compound* (1.53 g, 92.2% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.38-7.31 (m, 5 H), 5.83 (s, 2 H), 5.12 (s, 1 H), 3.42-3.37 (m, 4 H), 2.85 (t, *J* = 6.0 Hz, 2 H), 2.27 (t, *J* = 6.0 Hz, 2H), 1.41 (s, 9 H).



Intermediate 55

Step 1B: *tert-butyl 4-(2-(benzyloxy)-1-bromo-2-oxoethyl)-4-bromopiperidine-1-carboxylate*

To a mixture of *tert*-butyl 4-(2-(benzyloxy)-2-oxoethylidene)piperidine-1-carboxylate (2.5 g, 7.55 mmol, 1.0 *eq.*) in DCM (30 mL) was added bromine (0.5 mL, 9.75 mmol, 1.3 *eq.*) at 0 °C. The reaction mixture was stirred at r.t. for 3 h. Upon completion, the mixture was quenched with aqueous saturated $Na_2S_2O_3$ solution and extracted with EtOAc (30 mL×3). The combined organic phase was washed with brine (50 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc =10/1) to afford the *title compound* (2.5 g 67.4 % yield) as a yellow oil.

Step 2: *tert-butyl 4-(2-(benzyloxy)-1-bromo-2-oxoethylidene)piperidine-1-carboxylate*

To a mixture of *tert*-butyl 4-(2-(benzyloxy)-1-bromo-2-oxoethyl)-4-bromopiperidine-1-carboxylate (2.58 g, 5.25 mmol, 1.0 *eq.*), in DCM (30 mL) was added TEA (1.33 g, 13.13 mmol, 2.5 *eq.*) dropwise. The reaction mixture was stirred at r.t. for 1 h, concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc =10/1) to afford the *title compound* (1.9 g, yield 88.2%) as a white solid. LCMS (Method 14, ESI) 311.8 $[M+H-100]^+$, RT 3.73 minutes.

Step 3: *tert-butyl 4-(1-(benzyloxy)-3-methyl-1-oxobut-3-en-2-ylidene)piperidine-1-carboxylate*

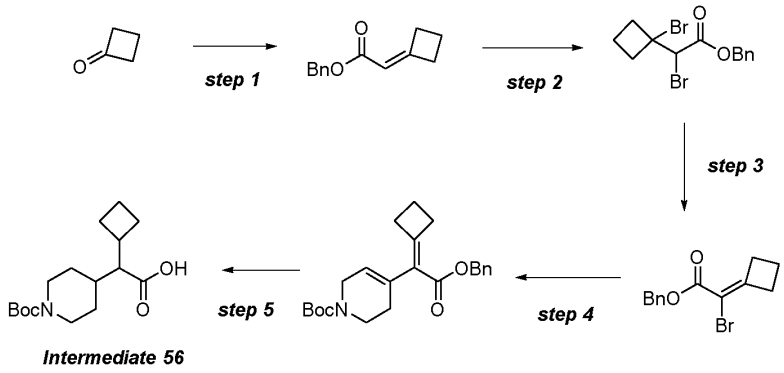
To a mixture of *tert*-butyl 4-(2-(benzyloxy)-1-bromo-2-oxoethylidene)piperidine-1-carboxylate (800 mg, 1.95 mmol, 1.0 *eq.*), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (983 mg, 5.85 mmol, 3.0 *eq.*), $Pd(dppf)Cl_2$ (316 mg, 0.39 mmol, 0.2 *eq.*) in dioxane/H_2O (15mL/1.5mL) was added K_2CO_3 (538 mg, 3.90 mmol, 2.0 *eq.*). The resulting mixture was stirred at 95°C for 16 h in a sealed tube under argon. Upon completion, the reaction mixture was filtered and

concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc =10/1) to afford the *title compound* (510 mg, yield 70.4 %) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38-7.33 (m, 5H), 5.15 (s, 2H), 5.12-5.11 (m, 1H), 4.76-4.75 (m, 1H), 3.37-3.34 (m, 4H), 2.54-2.52 (m, 3H), 2.31 (t, *J* =5.6Hz, 2H), 1.78 (s, 2H), 1.40(s, 9H). LCMS (Method 14, ESI) 271.9 [M+H-100]$^+$, RT 3.81 minutes.

Step 4: *2-(1-(tert-butoxycarbonyl)piperidin-4-yl)-3-methylbutanoic acid*

To a mixture of *tert*-butyl 4-(1-(benzyloxy)-3-methyl-1-oxobut-3-en-2-ylidene)piperidine-1-carboxylate (460 mg, 1.24 mmol, 1.0 *eq.*) in MeOH (10 mL) was added Pd/C (500 mg, 10% on carbon with ca. 55% water). The reaction mixture was stirred at 50 °C under H_2 atmosphere for 3 h, then filtered. The filtrate was concentrated *in vacuo* to afford the *title compound* (320 mg, yield 90.6%) as a colourless oil. LCMS (Method 16, ESI) 230.0 [M+H-56]$^+$, RT 1.042 minutes.

INTERMEDIATE 56: *2-(1-(tert-butoxycarbonyl)piperidin-4-yl)-2-cyclobutylacetic acid*



Intermediate 56

Step 1: *benzyl 2-cyclobutylideneacetate*

To a mixture of benzyl 2-(dimethoxyphosphoryl)acetate (5.75 g, 22.26 mmol, 1.2 *eq.*) in THF (350.0 mL) was added NaH (4.11 g, 27.83 mmol, 1.5 *eq.*) at 0°C. The mixture was stirred at 0°C for 30 min. Cyclobutanone (5.75 g, 22.26 mmol, 1.2 *eq.*) in THF (5.0 mL) was added at 0°C and the resulting mixture was stirred at r.t. for 1.5 h before quenched by saturated ammonium chloride solution (150 mL), extracted with EtOAc (200 mL x 3). The combined organic phase was washed with brine (200 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc = 30/1) to afford the *title compound* (3.0 g, yield 70%) as a colourless oil. LCMS (Method 15, ESI) 244.2 [M+41+H]$^+$, RT 1.988 minutes.

Step 2: *benzyl 2-bromo-2-(1-bromocyclobutyl)acetate*

To a mixture of benzyl 2-cyclobutylideneacetate (2.68 g, 13.27 mmol, 1.0 *eq.*) in anhydrous DCM (20.0 mL) was added Br_2 (2.54 g, 15.92 mmol, 1.2 *eq.*) dropwise at 0°C. The mixture was stirred at r.t. for 40 min before quenched with saturated NaS_2O_3 solution (20 mL) and extracted with DCM

(30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc = 97/3) to afford the *title compound* (4.5 g, yield 84%) as a colourless oil.

Step 3: *benzyl 2-bromo-2-cyclobutylideneacetate*

To a mixture of benzyl 2-bromo-2-(1-bromocyclobutyl)acetate (4.2 g, 11.67 mmol, 1.0 *eq.*) in DCM (40.0 mL) was added TEA (3.53 g, 34.00 mmol, 3.0 *eq.*) at r.t., and the mixture was stirred at r.t. for 1 h. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (silica, PE/EtOAc = 95/5) to afford the *title compound* (3.0 g, yield 86%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4–7.28 (m, 5 H), 5.22 (s, 2 H), 3.1–3.01 (m, 2 H), 2.84–2.76 (m, 2 H), 2.09–1.95 (m, 2 H).

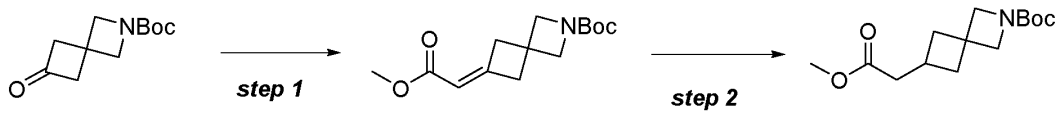
Step 4: *tert-butyl 4-(2-(benzyloxy)-1-cyclobutylidene-2-oxoethyl)-3,6-dihydropyridine-1(2H)-carboxylate*

A mixture of benzyl 2-bromo-2-cyclobutylideneacetate (2.7 g, 9.64 mmol, 1.0 *eq.*), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.98 g, 9.64 mmol, 1.0 *eq.*), $Pd(dppf)Cl_2 \cdot DCM$ (704.68 mg, 0.96 mmol, 0.1 *eq.*) and K_2CO_3 (3.99 g, 28.92 mmol, 3.0 *eq.*) in dioxane (50.0 mL) and H_2O (5.0 mL) was stirred at 90°C for 3 h under N_2. The reaction mixture was diluted with H_2O (60 mL), extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine (50 mL x 2), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc = 95/5) to afford the *title compound* (1.56 g, yield 42%) as a yellow oil. LCMS (Method 22, ESI) 284.2 $[M-100+H]^+$, RT 1.663 minutes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 5.46 (s, 1 H), 5.15 (s, 2 H), 3.95-3.93 (m, 2 H), 3.56–3.44 (m, 2 H), 3.10 (t, *J* = 7.6 Hz, 2 H), 2.81 (t, *J* = 8.0 Hz, 2 H), 2.20 (d, *J* = 1.6 Hz, 2 H), 2.06 – 1.94 (m, 2 H), 1.47-1.46 (m, 9 H).

Step 5: *2-(1-(tert-butoxycarbonyl)piperidin-4-yl)-2-cyclobutylacetic acid*

To a mixture of *tert*-butyl 4-(2-(benzyloxy)-1-cyclobutylidene-2-oxoethyl)-3,6-dihydro pyridine-1(2H)-carboxylate (300 mg, 0.78 mmol, 1.0 *eq.*) in MeOH (4.0 mL) was added Pd (300 mg, 10% on carbon with ca. 55% water) at r.t.. The mixture was stirred at r.t. for 1 h under H_2 (1 atm). The reaction mixture was then filtered and the filtrate was concentrated *in vacuo* to afford the *title compound* (330 mg, crude) as a yellow oil which was used directly without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (s, 1H), 2.95-2.98 (m, 1H), 2.70–2.54 (m, 2H), 2.30–2.20 (m, 1H), 2.12–1.54 (m, 7H), 1.44 (s, 9H), 1.28-1.23 (m, 5H). LCMS (Method 15, ESI) 198.3 $[M-100+H]^+$, RT 1.824 minutes.

INTERMEDIATE 57: *tert-butyl 6-(2-methoxy-2-oxoethyl)-2-azaspiro[3.3]heptane-2-carboxylate*



Intermediate 57

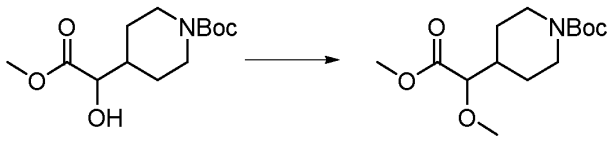
Step 1: *tert-butyl 6-(2-methoxy-2-oxoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate*

To a mixture of methyl 2-(dimethoxyphosphoryl)acetate (1.55 g, 8.53 mmol, 1.2 *eq.*) in THF (30.0 mL) was added NaH (426.00 mg, 10.65 mmol, 1.5 *eq.*) at 0°C, and the mixture was stirred at 0°C for 30 min. *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (1.5 g, 7.10 mmol, 1.0 *eq.*) in THF (10.0 mL) was added at 0°C. The resulting mixture was stirred at r.t. for 30 min before quenched by saturated ammonium chloride solution (40 mL), extracted with EtOAc (40 mL x 3). The combined organic phase was washed with brine (40 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc = 3/1) to afford the *title compound* (1.8 g, yield 95%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (s, 1 H), 4.06 – 3.86 (m, 4 H), 3.69 (s, 3 H), 3.29 (s, 2 H), 3.01 (s, 2 H), 1.44 (s, 9 H).

Step 2: *tert-butyl 6-(2-methoxy-2-oxoethyl)-2-azaspiro[3.3]heptane-2-carboxylate*

To a mixture of *tert*-butyl 6-(2-methoxy-2-oxoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate (1.8 g, 6.69 mmol, 1.0 *eq.*) in MeOH (20.0 mL) was added Pd (200 mg, 10% on carbon with ca. 55% water) at r.t.. The mixture was stirred at r.t. for 1 h under H_2. The reaction mixture was filtered and concentrated *in vacuo* to afford the *title compound* (1.71 g, yield 94.5%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 2 H), 3.80 (s, 2 H), 3.65 (s, 3 H), 2.56-2.47 (m, 1 H), 2.42-2.27 (m, 4 H), 1.90-1.77 (m, 2 H), 1.43 (s, 9 H).

INTERMEDIATE 58: *tert-butyl 4-(1,2-dimethoxy-2-oxoethyl)piperidine-1-carboxylate*

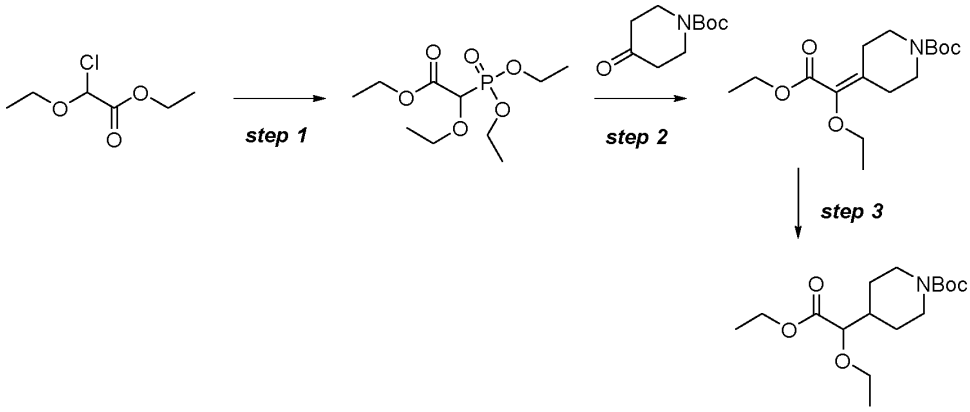


Intermediate 58

To a mixture of *tert*-butyl 4-(1-hydroxy-2-methoxy-2-oxoethyl)piperidine-1-carboxylate (400 mg, 1.47 mmol, 1.0 *eq.*), methyl iodide (416 mg, 2.93 mmol, 2.0 *eq.*) in THF (10 mL) was added *t*-BuOK (2.2 mL, 2.21 mmol, 1.5 *eq.*).The resulting mixture was stirred at r.t. for 2 h, then quenched with saturated ammonium chloride solution (10 mL) and extracted with EtOA (20 mL×3). The combined organic phase was washed with brine (30 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc = 3/1) to afford the *title compound* (330 mg, 78.6 % yield) as a colourless oil. LCMS (Method 23,

ESI)188.1 [M+H-100]$^+$, RT 0.73 minutes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14-4.11 (m, 2H), 3.77 (s, 3H), 4.47 (d, *J* =6.0Hz, 1H), 3.35 (s, 3H), 2.70-2.61 (m, 2H), 1.90-1.82 (m, 1H), 1.71-1.67 (m, 1H), 1.60-1.54 (m, 1H), 1.45 (s, 9H), 1.39-1.26 (m, 2H).

INTERMEDIATE 59: *tert-butyl 4-(1,2-diethoxy-2-oxoethyl)piperidine-1-carboxylate*



Intermediate 59

Step 1: *ethyl 2-(diethoxyphosphoryl)-2-ethoxyacetate*

A mixture of ethyl 2-chloro-2-ethoxyacetate (1.0 g, 6.02 mmol, 1.0 *eq.*) and triethyl phosphite (1.10 g, 6.62 mmol, 1.1 *eq.*) was stirred at 130°C for 5 h under argon. The reaction mixture was concentrated *in vacuo* to afford the *title compound* (1.5 g, crude, 92.9 % yield) as a colourless oil. LCMS (Method 15, ESI) 269.1 [M+H]$^+$, RT 1.457 minutes.

Step 2: *tert-butyl 4-(1,2-diethoxy-2-oxoethylidene)piperidine-1-carboxylate*

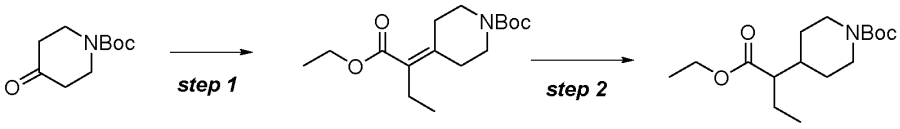
To a mixture of ethyl 2-(diethoxyphosphoryl)-2-ethoxyacetate (1.40 g, 5.26 mmol, 1.2 *eq.*) in THF (20 mL) was added NaH (263 mg, 6.57 mmol, 1.5 *eq.*) at 0°C. The mixture was stirred at 0°C for 0.5 h, added with *tert*-butyl 4-oxopiperidine-1-carboxylate (872 mg, 4.38 mmol, 1.0 *eq.*) and stirred at r.t. for 2 h under argon. The reaction mixture was quenched with NH_4Cl (5mL) and extracted with EtOA (20 mL×3). The combined organic phase was washed with brine (30 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc = 10/1) to afford the *title compound* (470 mg, yield 34.3%) as a colourless oil. LCMS (Method 16, ESI) 214.2 [M+H-100]$^+$, RT 1.948 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.19-4.14 (m, 2H), 3.68-3.63 (m, 2H), 3.37-3.32 (m, 4H), 2.61 (t, *J* = 5.6Hz, 2H), 2.37 (t, *J* = 5.6Hz, 2H), 1.40 (s, 9H), 1.24 (t, *J* =7.2Hz, 3H), 1.17 (t, *J* = 6.8Hz, 3H).

Step 3: *tert-butyl 4-(1,2-diethoxy-2-oxoethyl)piperidine-1-carboxylate*

To a mixture of *tert*-butyl 4-(1,2-diethoxy-2-oxoethylidene)piperidine-1-carboxylate (420 mg, 1.34 mmol, 1.0 *eq.*) in MeOH (10 mL) with added Pd/C (300 mg, 10% on carbon with ca. 55% water), and it was stirred at r.t. under H_2 atmosphere for 2 h. The reaction mixture was then filtered and

the filtrate was concentrated *in vacuo* to afford the *title compound* (402 mg, yield 95.0 %) as a colourless oil. LCMS (Method 15, ESI) 216.2 $[M+H-100]^+$, RT 1.037 minutes.

INTERMEDIATE 60: *tert-butyl 4-(1-ethoxy-1-oxobutan-2-yl)piperidine-1-carboxylate*



Intermediate 60

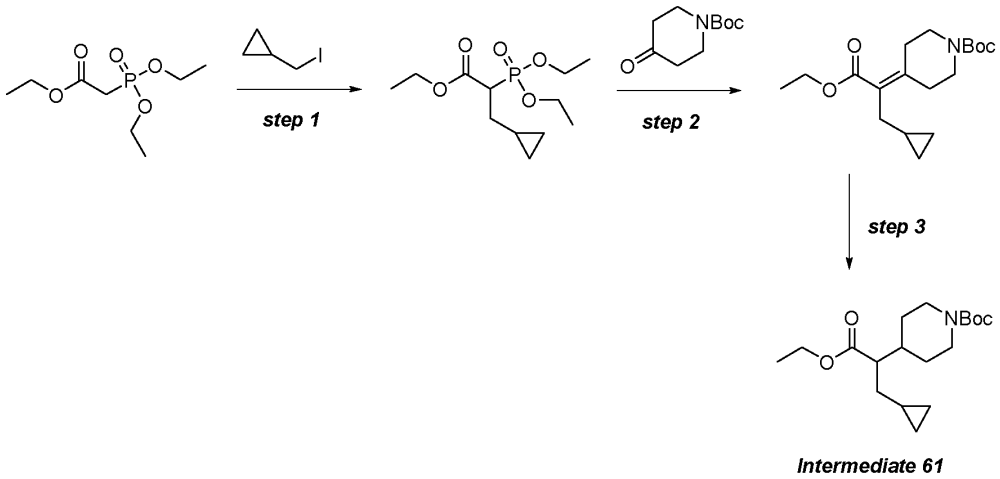
Step 1: *tert-butyl 4-(1-ethoxy-1-oxobutan-2-ylidene)piperidine-1-carboxylate*

To a mixture of ethyl 2-(diethoxyphosphoryl)butanoate (1.0 g, 6.03 mmol, 1.2 *eq.*) in THF (20.0 mL) was added NaH (119 mg, 4.95 mmol, 1.5 *eq.*) at 0°C, and the mixture was stirred at 0°C for 30 min. *tert*-butyl 4-oxopiperidine-1-carboxylate (657 mg, 3.3 mmol, 1.0 *eq.*) in THF (5.0 mL) was added at 0°C. The resulting mixture was stirred at r.t. for 1.5 h before quenched by saturated ammonium chloride solution (20 mL), extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (PE/EtOAc =94%/6%) to afford the *title compound* (630 mg, yield 64%) as a colourless oil. LCMS (Method 19, ESI) 198.2 $[M+H-100]^+$, RT 2.036 minutes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.2 Hz, 2 H), 3.54–3.36 (m, 4 H), 2.54 (t, *J* = 5.6 Hz, 2 H), 2.35-2.29 (m, 4 H), 1.47 (s, 9 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.01 (t, *J* = 7.6 Hz, 3 H).

Step 2: *tert-butyl 4-(1-ethoxy-1-oxobutan-2-yl)piperidine-1-carboxylate*

To a mixture of *tert*-butyl 4-(1-ethoxy-1-oxobutan-2-ylidene)piperidine-1-carboxylate (530 mg, 1.78 mmol, 1.0 *eq.*) in MeOH (10.0 mL) was added Pd/C (350 mg, 10% on carbon with ca. 55% water) at r.t., and the mixture was stirred for 1 h under H_2. The reaction mixture was then filtered and the filtrate was concentrated *in vacuo* to afford the *title compound* (510 mg, yield 96%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18–4.06 (m, 4 H), 2.65 (t, *J* = 12.8 Hz, 2 H), 2.12–2.06 (m, 1 H), 1.74-1.53 (m, 6 H), 1.52 (s, 9 H), 1.27 (t, *J* = 7.6 Hz, 3 H), 1.28-1.23 (m, 1 H), 0.88 (t, *J* = 7.6 Hz, 3 H).

INTERMEDIATE 61: *tert-butyl 4-(3-cyclopropyl-1-ethoxy-1-oxopropan-2-yl)piperidine-1-carboxylate*



Intermediate 61

Step 1: *ethyl 3-cyclopropyl-2-(diethoxyphosphoryl)propanoate*

To a mixture of ethyl 2-(diethoxyphosphoryl)acetate (800 mg, 3.57 mmol, 1.0 *eq.*) in DMSO (10.0 mL) was added *t*-BuOK (1M, 4.64 mL, 1.3 *eq.*) at 0°C, and the mixture was stirred at r.t. for 15 min. Then (iodomethyl)cyclopropane (974.99 mg, 5.36 mmol, 1.5 *eq.*) was added at r.t., and the resulting mixture was stirred at 60°C for 3 h. The reaction mixture was diluted with H_2O (40 mL), extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (30 mL x 2), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (silica, PE/EA = 1/1) to afford the *title compound* (880 mg, yield 89%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36–4.01 (m, 6 H), 3.11-3.02 (m, 1 H), 2.06–1.91 (m, 1 H), 1.72–1.63 (m, 1 H), 1.37-1.28 (m, 9 H), 0.80-0.69 (m, 1 H), 0.51–0.38 (m, 2 H), 0.18–0.01 (m, 2 H).

Step 2: *tert-butyl 4-(3-cyclopropyl-1-ethoxy-1-oxopropan-2-ylidene)piperidine-1-carboxylate*

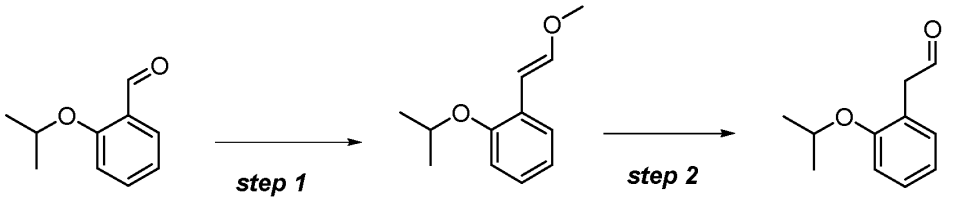
To a mixture of ethyl 3-cyclopropyl-2-(diethoxyphosphoryl)propanoate (386.55 mg, 1.94 mmol, 1.2 *eq.*) in THF (10.0 mL) was added NaH (58.32 mg, 2.43 mmol, 1.5 *eq.*) at 0 °C. The mixture was stirred at 0 °C for 30 min. *tert*-butyl 4-oxopiperidine-1-carboxylate (450 mg, 1.62 mmol, 1.0 *eq.*) in THF (2.0 mL) was added at 0 °C. The resulting mixture was stirred at r.t. for 1.5 h before quenched by saturated ammonium chloride solution (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc = 92/8) to afford the *title compound* (140 mg, yield 27%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, *J* = 7.2 Hz, 2 H), 3.50-3.45 (m, 4 H), 2.55–2.52 (m, 2 H), 2.38–2.35 (m, 2 H), 2.28 (d, *J* = 6.8 Hz, 2 H), 1.48 (s, 9 H), 1.33 (t, *J* = 7.2 Hz, 3 H), 0.79-0.72 (m, 1 H),

0.47–0.42 (m, 2 H), 0.13-0.10 (m, 2 H). LCMS (Method 15, ESI) 224.2 $[M+H-100]^+$, RT 2.116 minutes.

Step 3: *tert-butyl 4-(3-cyclopropyl-1-ethoxy-1-oxopropan-2-yl)piperidine-1-carboxylate*

To a mixture of *tert*-butyl 4-(3-cyclopropyl-1-ethoxy-1-oxopropan-2-ylidene)piperidine-1-carboxylate (220 mg, 0.62 mmol, 1.0 *eq.*) in MeOH (5.0 mL) was added Pd/C (100 mg, 10% on carbon with ca. 55% water) at r.t. The mixture was stirred at r.t. for 1 h under H_2. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to afford the *title compound* (190 mg, crude) as a colourless oil. LCMS (Method 15, ESI) 270.2 $[M+H-56]^+$, RT 2.128 minutes.

INTERMEDIATE 62: *2-(2-isopropoxyphenyl)acetaldehyde*



Intermediate 62

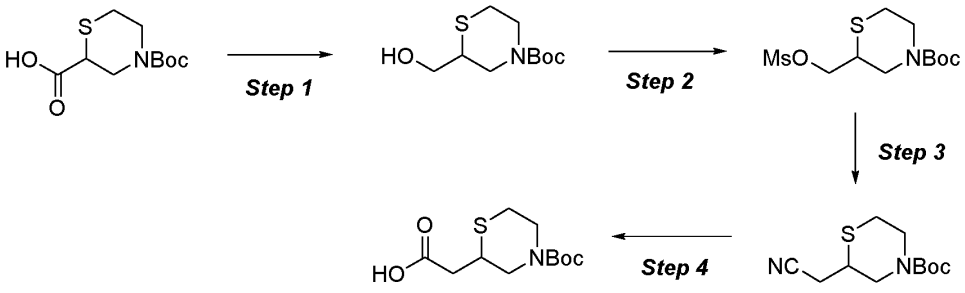
Step 1: *(E)-1-isopropoxy-2-(2-methoxyvinyl)benzene*

To a mixture of (methoxymethyl)triphenylphosphonium chloride (13.92 g, 42.87 mmol, 2.0 *eq.*) in THF (160.0 mL) was added LiHMDS (1 M, 42.87 mL, 2.0 *eq.*) at -70 °C. The mixture was warmed slowly to 0 °C and stirred for 2 h. Then the mixture was cooled to -70 °C and 2-isopropoxybenzaldehyde (3.52 g, 21.44 mmol, 1.0 *eq.*) was added. The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was quenched by saturated ammonium chloride solution (300 mL), extracted with EtOAc (300 mL x 3). The combined organic phase was washed with brine (300 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (PE/EtOAc = 97/3) to afford the *title compound* (2.16 g, yield 52%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO) δ 7.31–7.18 (m, 1 H), 7.13–7.02 (m, 1 H), 7.00–6.89 (m, 1 H), 6.83 (m, 1 H), 6.33–5.41 (m, 2 H), 4.59-4.52 (m, 1 H), 3.67 (s, 3 H), 1.28-1.23 (m, 6 H). LCMS (Method 22, ESI) 193.2 $[M+H]^+$, RT 1.448 minutes.

Step 2: *2-(2-isopropoxyphenyl)acetaldehyde*

A mixture of (E)-1-isopropoxy-2-(2-methoxyvinyl)benzene (2.16 g, 11.25 mmol, 1.0 *eq.*) in formic acid (25.0 mL) was stirred at r.t. for 2 h. The reaction mixture was then concentrated *in vacuo* and the residue purified by flash chromatography (PE/EtOAc = 30/1) to afford the *title compound* (720 mg, yield 36%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO) δ 9.59 (s, 1 H), 7.33–7.12 (m, 2 H), 7.02 (d, J = 8.4 Hz, 1 H), 6.89 (t, J = 7.6 Hz, 1 H), 4.64-4.58 (m, 1 H), 3.59 (s, 2 H), 1.22 (d, J = 6.0 Hz, 6 H).

INTERMEDIATE 63: *2-(4-(tert-butoxycarbonyl)thiomorpholin-2-yl)acetic acid*



Intermediate 63

Step 1: *tert-butyl 2-(hydroxymethyl)thiomorpholine-4-carboxylate*

To a solution of 4-(*tert*-butoxycarbonyl)thiomorpholine-2-carboxylic acid (1 g, 4.05 mmol, 1.0 *eq.*) in anhydrous THF (20 mL) was added a solution of BH_3 in THF (1 M, 16.2 mL, 4.0 *eq.*) slowly at 0° C. The reaction mixture was stirred at r.t. for 16 h then quenched with saturated aqueous sodium carbonate solution (50 mL). The aqueous layer was extracted with EtOAc (2×50 mL). The combined organic layers were washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the *title compound* (1.06 g, crude) as a colourless oil, which was used without further purification. LCMS (Method 15, ESI): 256.4 $[M+Na]^+$, RT 1.633 minutes.

Step 2: *tert-butyl 2-(((methylsulfonyl)oxy)methyl)thiomorpholine-4-carboxylate*

To a solution of *tert*-butyl 2-(hydroxymethyl)thiomorpholine-4-carboxylate (1.06 g, 4.55 mmol, 1.0 *eq.*) and methanesulfonyl chloride (1.04 g, 9.1 mmol, 2.0 *eq.*) in DCM (10 mL) was added TEA (1.38 g, 13.65 mmol, 3.0 *eq.*) slowly. After stirring for 3 h at 0 °C the mixture was diluted with water (100 mL), the organic phase separated was dried over sodium sulfate and concentrated *in vacuo* to afford the *title compound* (825 mg, yield 58.93%). No mass signal was detected by LCMS.

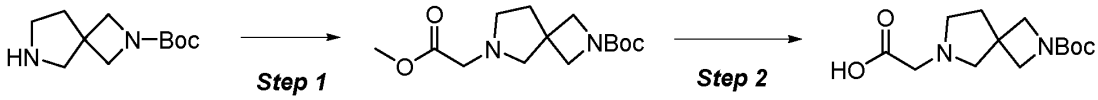
Step 3: *tert-butyl 2-(cyanomethyl)thiomorpholine-4-carboxylate*

A mixture of the *tert*-butyl 2-(((methylsulfonyl)oxy)methyl)thiomorpholine-4-carboxylate (825 mg, 2.65 mmol, 1.0 *eq.*) in DMSO(10 ml) was added KCN (516.75 mg, 7.95 mmol, 3.0 *eq.*). The resulting mixture was stirred at 80 °C for 2 h under argon. The reaction mixture was quenched with saturated aqueous ammonium chloride, extracted with EtOAc (x3). The combined organic phase was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0-5% MeOH in DCM) to afford the *title compound* (243 mg, yield 37.91%). No mass signal was detected by LCMS.

Step 4: *2-(4-(tert-butoxycarbonyl)thiomorpholin-2-yl)acetic acid*

To a stirred solution of the *tert*-butyl 2-(cyanomethyl)thiomorpholine-4-carboxylate (243 mg, 1.0 mmol, 1.0 *eq.*) in EtOH/ Water (1/1) was added KOH (112.46 mg, 2.01 mmol, 2.0 *eq.*). The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was concentrated *in vacuo* to afford the *title compound* (275 mg, crude) without further purification. ^{1}H NMR (400 MHz, DMSO) δ 4.23 – 3.66 (m, 2H), 3.28 – 3.09 (m, 1H), 3.06 – 2.85 (m, 2H), 2.84 – 2.55 (m, 2H), 2.47 – 2.04 (m, 1H), 1.96 – 1.79 (m, 1H), 1.39 (d, *J* = 1.4 Hz, 9H). LCMS (Method 15, ESI): 261.9 $[M+H]^+$, RT 1.438 minutes.

INTERMEDIATE 64: *Preparation of 2-(2-(tert-butoxycarbonyl)-2,6-diazaspiro[3.4]octan-6-yl)acetic acid*



Intermediate 64

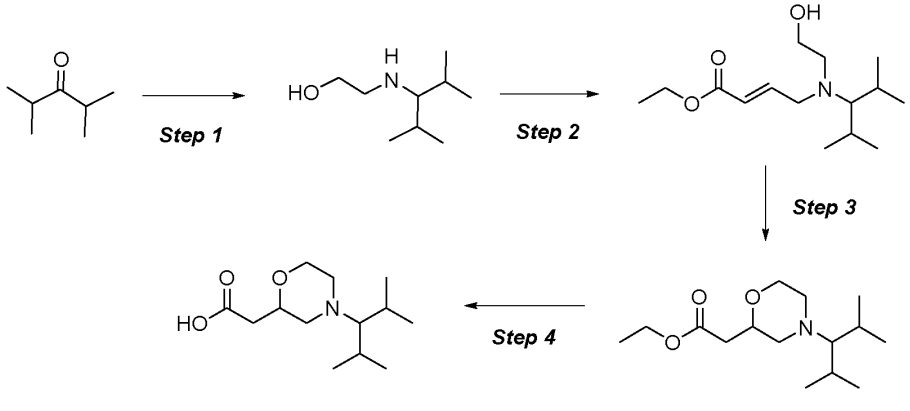
Step 1: *tert-butyl 6-(2-methoxy-2-oxoethyl)-2,6-diazaspiro[3.4]octane-2-carboxylate*

To a mixture of *tert*-butyl 2,6-diazaspiro[3.4]octane-2-carboxylate (1 g, 4.72 mmol, 1.0 *eq.*) in ACN (10 mL) were added *methyl 2-bromoacetate* (1.08 g, 7.08 mmol, 1.5 *eq.*) and DIPEA (1.22 g, 9.44 mmol, 2.0 *eq.*) The resulting mixture was stirred at 40°C for 2 h, then quenched with saturated aqueous ammonium chloride, extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to afford the *title compound* (630 mg, yield 47.01%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.76 (d, *J* = 21.8 Hz, 4H), 3.60 (s, 3H), 3.31 (s, 2H), 2.76 (s, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 1.99 – 1.92 (m, 2H), 1.37 (s, 9H).

Step 2: *Preparation of 2-(2-(tert-butoxycarbonyl)-2,6-diazaspiro[3.4]octan-6-yl)acetic acid*

To a stirred solution of the *tert*-butyl 6-(2-methoxy-2-oxoethyl)-2,6-diazaspiro[3.4]octane-2-carboxylate (630 mg, 2.22 mmol, 1.0 *eq.*) in MeOH/THF/Water (1/1/1) was added LiOH (186.48 mg, 4.44 mmol, 2.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h and concentrated *in vacuo* to afford the *title compound* (530 mg, yield 88.5%) without purification. No mass signal was detected by LCMS.

INTERMEDIATE 65: *2-(4-(2,4-dimethylpentan-3-yl)morpholin-2-yl)acetic acid*



Intermediate 65

Step 1: *2-((2,4-dimethylpentan-3-yl)amino)ethan-1-ol*

To a mixture of 2,4-dimethylpentan-3-one (2 g, 17.51 mmol, 1.0 *eq.*) in MeOH (20 mL) were added 2-aminoethan-1-ol (5.35 g, 87.57 mmol, 5.0 *eq.*) and $Ti(Oi\text{-}Pr)_4$ (14.93 g, 52.54 mmol, 3.0 *eq.*) . The resulting mixture was heated in a microwave reactor at 100°C for 2 h. Then $NaBH_3CN$ (3.3 g, 52.54 mmol, 3.0 *eq.*) was added, and the reaction mixture was heated in a microwave reactor at 100°C for another 2 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (silica, DCM/MeOH = 20/1) to afford the *title compound* (2.1 g, 75.3% yield) as a yellow oil. LCMS (Method 21, ESI): 160.1$[M+H]^+$, RT 1.178 minutes.

Step 2: *ethyl (E)-4-((2,4-dimethylpentan-3-yl)(2-hydroxyethyl)amino)but-2-enoate*

To a stirred solution of 2-((2,4-dimethylpentan-3-yl)amino)ethan-1-ol (2.1 g, 13.18 mmol, 1.0 *eq.*) in THF (20 mL) was added ethyl (*E*)-4-bromobut-2-enoate (3.82 g, 19.78 mmol, 1.5 *eq.*) and K_2CO_3 (5.47 g, 39.55 mmol, 3.0 *eq.*). The resulting mixture was stirred at 25°C for 16 h before the reaction mixture was concentrated *in vacuo.* The residue was purified by reverse flash chromatography (0-90% ACN in H_2O) to afford the *title compound* (186 mg, 7.5% yield) as a yellow oil. LCMS (Method 21, ESI): 272.1$[M+H]^+$, RT 2.021 minutes.

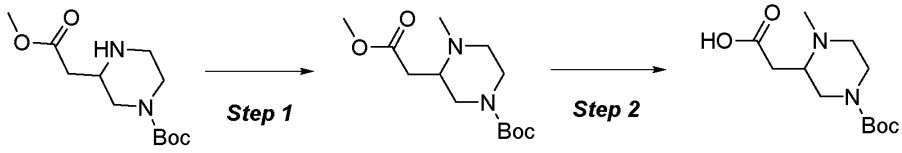
Step 3: *ethyl 2-(4-(2,4-dimethylpentan-3-yl)morpholin-2-yl)acetate*

To a stirred solution of ethyl (*E*)-4-((2,4-dimethylpentan-3-yl)(2-hydroxyethyl)amino)but-2-enoate (263 mg, 0.969 mmol, 1.0 *eq.*) in toluene (2 mL) was added DBU (148 mg, 0.969 mmol, 1.0 *eq.*). The resulting mixture was stirred at 100°C for 16 h before concentrated *in vacuo.* The residue was purified by Prep-TLC (DCM/MeOH = 20/1) to afford the *title compound* (186 mg, 70.7% yield). LCMS (An analogous method to Method 15, ESI): 272.3$[M+H]^+$, RT 0.983 minutes.

Step 4: *2-(4-(2,4-dimethylpentan-3-yl)morpholin-2-yl)acetic acid*

To a stirred solution of ethyl 2-(4-(2,4-dimethylpentan-3-yl)morpholin-2-yl)acetate (186 mg, 0.685 mmol, 1.0 *eq.*) in THF/Water (5 mL/1 mL) was added LiOH (25 mg, 1.03 mmol, 1.5 *eq.*). The resulting mixture was stirred at 60°C for 16 h. The reaction mixture was concentrated *in vacuo* to afford the *title compound* (210 mg crude, 50% purity) without further purification. LCMS (Method 18, ESI): 244.2 $[M+H]^+$, RT 1.051 minutes.

INTERMEDIATE 66: *2-(4-(tert-butoxycarbonyl)-1-methylpiperazin-2-yl)acetic acid*



Intermediate 66

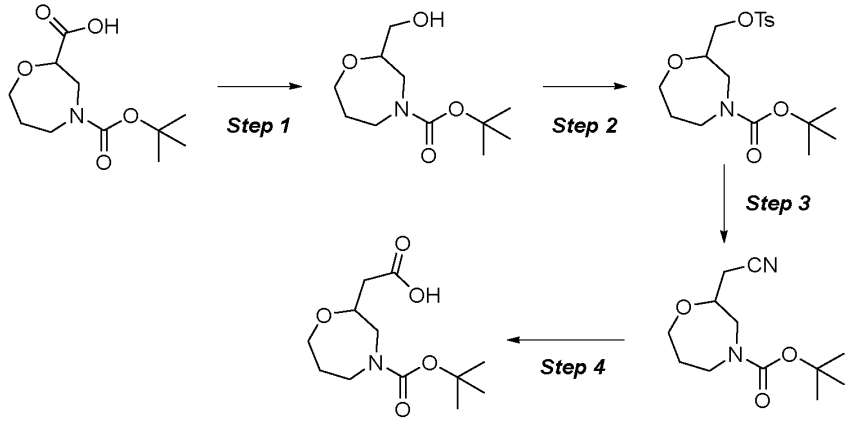
Step 1: *tert-butyl 3-(2-methoxy-2-oxoethyl)-4-methylpiperazine-1-carboxylate*

To a mixture of *tert*-butyl 3-(2-methoxy-2-oxoethyl)piperazine-1-carboxylate (1 g, 3.87 mmol, 1.0 *eq.*) in ACN (10 mL) were added *methyl iodide* (0.24 mL, 3.87 mmol, 1.0 *eq.*) and potassium carbonate (1.61 g, 11.61 mmol, 3.0 *eq.*). The resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica, MeOH: DCM= 0 - 5%) to afford the *title compound* (953 mg, yield: 91.4%) as a yellow oil. LCMS (Method 15, ESI): 273.3 $[M+H]^+$, RT 0.373 minutes.

Step 2: *2-(4-(tert-butoxycarbonyl)-1-methylpiperazin-2-yl)acetic acid*

To a stirred mixture of *tert*-butyl 3-(2-methoxy-2-oxoethyl)-4-methylpiperazine-1-carboxylate (853 mg, 3.13 mmol, 1.0 *eq.*) in THF/Water (10 mL/2 mL) was added LiOH (113 mg, 4.70 mmol, 2.0 *eq.*). The resulting mixture was stirred at 60 °C. for 2 h. The reaction mixture was concentrated *in vacuo* to afford the *title compound* (960 mg, crude) without further purification. LCMS (Method 15, ESI): 259.2 $[M+H]^+$, RT 1.095 minutes.

INTERMEDIATE 67: *2-{4-[(tert-butoxy)carbonyl]-1,4-oxazepan-2-yl}acetic acid*



Intermediate 67

Step 1: *tert-butyl 2-(hydroxymethyl)-1,4-oxazepane-4-carboxylate*

To a stirred solution of 4-[(*tert*-butoxy)carbonyl]-1,4-oxazepane-2-carboxylic acid (1.25 g, 5.10 mmol, 1 *eq.*) in anhydrous THF (25.5 ml) under argon at 0°C was added a solution of borane tetrahydrofuran complex (1M, 10.20 mL, 10.20 mmol, 2 *eq.*) dropwise over 30 min. The reaction mixture was stirred at r.t. for 16 h. Crude material was quenched with saturated aqueous sodium bicarbonate solution and extracted with EtOAc (2x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-50% EtOAc in cyclohexane) to afford the *title compound* (900 mg, 73% yield) as an yellow oil. UPLC (An analogous method to Method 5, ESI) 231.95 $[MH]^+$, RT 2.20 min.

Step 2: *tert-butyl 2-{[(4-methylbenzenesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate*

To a stirred solution of *tert*-butyl 2-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (0.88 g, 3.61 mmol, 1.0 *eq.*) and triethylamine (1.51 ml, 10.84 mmol, 3.0 *eq.*) in anhydrous DCM (36.1 ml) under argon was added p-toluenesulfonyl chloride (0.90 g, 4.70 mmol, 1.3 *eq.*) and the reaction mixture was stirred at r.t. for 16 h. The reaction mixture was concentrated *in vacuo* and the crude was purified by flash chromatography (silica, 0-20% EtOAc in cyclohexane) to afford the *title compound* (1.38 g, 88% yield, 89% purity). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 4.05 – 3.92 (m, 3H), 3.84 – 3.57 (m, 3H), 3.46 – 3.34 (m, 1H), 3.33 – 3.18 (m, 1H), 3.10 – 2.92 (m, 1H), 2.45 (s, 3H), 1.92 – 1.78 (m, 2H), 1.44 (s, 9H).

Step 3: *tert-butyl 2-(cyanomethyl)-1,4-oxazepane-4-carboxylate*

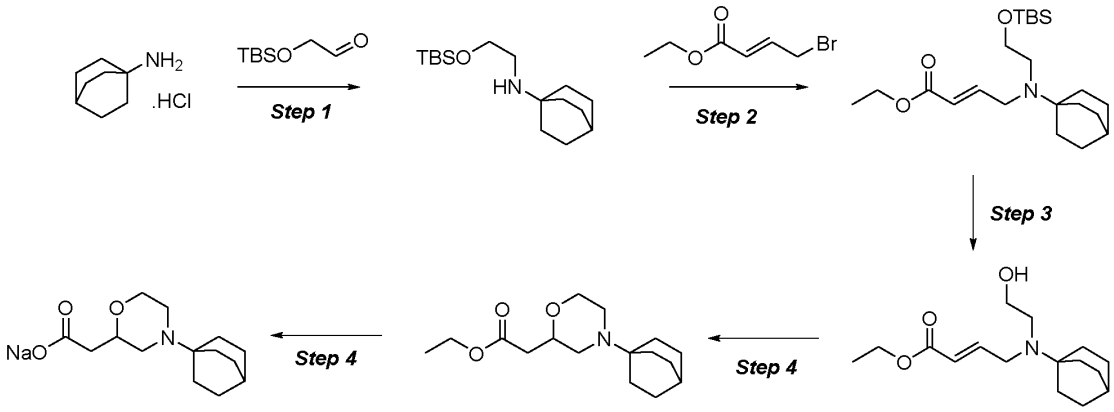
To a stirred solution of *tert*-butyl 2-{[(4-methylbenzenesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate (1.33 g, 3.07 mmol, 1 *eq.*) in DMSO (40.0 mL) was added potassium cyanide (0.60 g, 9.21 mmol, 3 *eq.*). The reaction mixture was stirred at 55°C for 5 h before diluted with DCM and

water was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM (3x). Combined organic phases were dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-50% EtOAc in cyclohexane). Obtained fraction was lyophilised twice with water to afford the *title compound* (668 mg, 86% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.03 – 3.89 (m, 1H), 3.81 – 3.63 (m, 2H), 3.58 – 3.49 (m, 1H), 3.49 – 3.38 (m, 1H), 3.29 – 3.19 (m, 1H), 3.15 – 2.97 (m, 1H), 2.82 – 2.72 (m, 1H), 2.72 – 2.63 (m, 1H), 1.84 – 1.70 (m, 2H), 1.41 (s, 9H).

Step 4: *2-{4-[(tert-butoxy)carbonyl]-1,4-oxazepan-2-yl}acetic acid*

To a stirred solution of *tert*-butyl 2-(cyanomethyl)-1,4-oxazepane-4-carboxylate (638 mg, 2.52 mmol, 1 *eq.*) in a mixture of ethanol and water (32.0 mL, 1:1) was added potassium hydroxide (1.42 g, 25.23 mmol, 10 *eq.*). The reaction mixture was stirred at 85°C for 16 h before it was neutralized with 1M aqueous HCl. Crude material was extracted with DCM (5x). Combined organic phases were dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the *title compound* (238 mg, 20% yield, 55% purity) as an yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.13 – 4.02 (m, 1H), 3.99 – 3.91 (m, 1H), 3.84 – 3.61 (m, 2H), 3.56 – 3.49 (m, 1H), 3.33 – 3.22 (m, 1H), 3.07 – 2.93 (m, 1H), 2.56 – 2.47 (m, 2H), 1.98 – 1.84 (m, 2H), 1.47 (s, 9H). UPLC (An analogous method to Method 5, ESI) 159.95 [MH-Boc]$^+$, RT 2.67 min

INTERMEDIATE 68: *sodium 2-(4-{bicyclo[2.2.2]octan-1-yl}morpholin-2-yl)acetate*



Intermediate 68

Step 1: *N-(2-((tert-butyldimethylsilyl)oxy)ethyl)bicyclo[2.2.2]octan-1-amine*

To a mixture of bicyclo[2.2.2]octan-1-amine hydrochloride (644 mg, 4.0 mmol, 1.0 *eq.*) in MeOH (20 mL) was added 2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde (696 mg, 4 mmol, 1.0 *eq.*), KOAc (491 mg, 5.0 mmol, 1.25 *eq.*) and $NaBH_3CN$ at 25 °C. The reaction mixture was stirred at 25 °C for 16 h before quenched with water and extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine (50 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc =2/1) to afford the

title compound (603 mg, 53.2% yield) as a colourless oil. LCMS (Method 21, ESI) 284.1 $[M+H]^+$, RT 1.774 minutes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (t, *J* = 5.2 Hz, 2 H), 2.69 (t, *J* = 6.8 Hz, 2 H), 1.96 (s, 8 H), 1.65-1.61 (m, 6 H), 0.89 (s, 9 H), 0.065 (s, 6 H).

Step 2: *ethyl (E)-4-(bicyclo[2.2.2]octan-1-yl(2-((tert-butyldimethylsilyl)oxy)ethyl)amino)but-2-enoate*

To a mixture of *N*-(2-((tert-butyldimethylsilyl)oxy)ethyl)bicyclo[2.2.2]octan-1-amine (603 mg, 2.13 mmol, 1.0 *eq.*) in THF (20 mL) was added ethyl (*E*)-4-bromobut-2-enoate (1.23 g, 6.39 mmol, 3.0 *eq.*) and K_2CO_3 (588 mg, 4.26 mmol, 2.0 *eq.*). The reaction was stirred at 65 °C for 16 h under nitrogen. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc = 50/1) to afford the *title compound* (409 mg, yield 48.6%) as a colourless oil. LCMS (Method 15, ESI) 396.2 $[M+H]^+$, RT 0.930 minutes.

Step 3: *ethyl (E)-4-(bicyclo[2.2.2]octan-1-yl(2-hydroxyethyl)amino)but-2-enoate*

To a solution of ethyl (*E*)-4-(bicyclo[2.2.2]octan-1-yl(2-((tert-butyldimethylsilyl)oxy) ethyl)amino)but-2-enoate (409 mg, 1.03 mmol, 1.0 *eq.*) in DCM (10 mL) was added TFA (10 mL), and the resulting mixture was stirred at 40 °C for 16 h under argon. Upon completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc = 50/1) to afford the *title compound* (280 mg, 96.2% yield) as a colourless oil. LCMS (Method 15, ESI) 282.1$[M+H]^+$, RT 0.814 minutes.

Step 4: *ethyl 2-(4-(bicyclo[2.2.2]octan-1-yl)morpholin-2-yl)acetate*

To a mixture of ethyl (*E*)-4-(bicyclo[2.2.2]octan-1-yl(2-hydroxyethyl)amino)but-2-enoate (280 mg, 1.00 mmol, 1.0 *eq.*) in toluene (30 mL) was added DBU (609 mg, 4.00 mmol, 4.0 *eq.*). The reaction mixture was stirred at 110 °C for 16 h then concentrated *in vacuo*. The residue was purified by Prep HPLC to afford the *title compound* (203 mg, 72.5% yield) as a white solid. LCMS (Method 15, ESI) 282.1 $[M+H]^+$, RT 0.803 minutes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18-4.05 (m, 3 H), 4.00-3.86 (m, 2H), 3.49-3.35 (m, 2 H), 2.81-2.70 (m, 2 H), 2.48-2.47 (m, 2 H), 1.77-1.76 (m, 6 H), 1.68-1.65 (m, 7 H), 1.18 (t, *J* = 6.8 Hz, 3 H).

Step 5: *sodium 2-(4-{bicyclo[2.2.2]octan-1-yl}morpholin-2-yl)acetate*

To a stirred solution of ethyl 2-(4-{bicyclo[2.2.2]octan-1-yl}morpholin-2-yl)acetate (200 mg, 0.74 mmol, 1.0 *eq.*) in MeOH (7.4 mL) was added aqueous sodium hydroxide solution (1M, 1.50 mL, 1.50 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 16 h. After completion, solvent was evaporated *in vacuo* to afford the *title compound* (200 mg, quantitative yield, 95% purity) without further purification. UPLC (Method 5, ESI) 253.9 $[MH]^+$, RT 1.56 min.

In the following general procedures, all variables are as defined herein and PG/PG^2 are respectively suitable nitrogen/carboxylic acid protecting groups as understood by one skilled in the art, and more specifically, as defined above.

One skilled in the art will appreciate that the compounds of formula (I) may be synthesised by one or more of the following general procedures. The comments regarding ring A above in the Process and Intermediate sections are equally applicable here i.e. in any one of the following General Procedures, where PG is attached to ring A, PG is attached to a nitrogen ring atom of ring A.

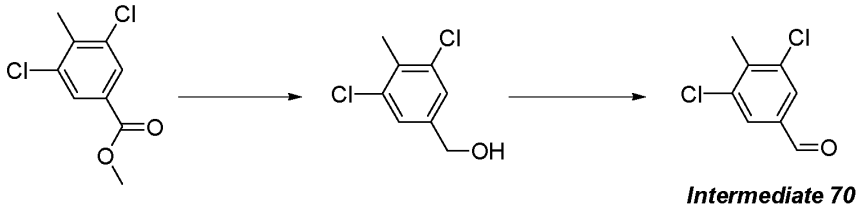
INTERMEDIATE 69: *3-(difluoromethoxy)-4-methylbenzaldehyde*



Intermediate 69

Potassium hydroxide (4.94 g, 88.1 mmol) was suspended in a solution of acetonitrile (10 mL) and water (10 mL) and cooled to -20 °C. 3-hydroxy-4-methylbenzaldehyde (600.0 mg, 4.4 mmol) was dissolved in acetonitrile (10 mL) and was added dropwise, followed by bromodifluoromethyl diethylphosphonate (2.35 g, 8.81 mmol) over 15 min. Then the mixture was allowed to warm to r.t. over 1 h. The mixture was extracted with EtOAc (3 × 30 mL), the combined organic layers were washed with brine (2 × 30 mL) and dried over sodium sulphate, filtered, and the filtrate was concentrated *in vacuo*. Crude material was purified by flash chromatography (silica, 0-20% EtOAc in PE) to afford the *title compound* (402.3 g, 49% yield) as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6), d 9.97 (s, 1H), 7.74 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.64 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 73.8 Hz, 1H), 2.32 (s, 3H).

INTERMEDIATE 70: *3,5-dichloro-4-methylbenzaldehyde*



Intermediate 70

Step 1: *(3,5-dichloro-4-methylphenyl)methanol*

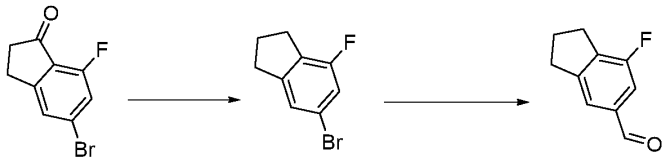
To a stirring solution of methyl 3,5-dichloro-4-methylbenzoate (500.0 mg, 2.28 mmol) in THF (20 mL) was added lithium aluminum hydride (2.5 M in THF, 1.8 mL, 4.5 mmol). Then the reaction mixture was stirred at r.t. for 16 h. The reaction mixture was quenched with methanol and

concentrated *in vacuo* to give the residue, which was purified by flash chromatography (silica, 0-50% EtOAc in PE) to afford the *title compound* (300.0 mg, 68.8% yield) as a colourless oil.

Step 2: *3,5-dichloro-4-methylbenzaldehyde*

To a stirring solution of (3,5-dichloro-4-methylphenyl)methanol (300.0 mg, 1.57 mmol) in DCM (15 mL) was added DMP (1.33 g, 3.14 mmol). Then the reaction mixture was stirred at r.t. for 16 h. The reaction mixture was concentrated *in vacuo* and re-dissolved in DCM and washed with H_2O. The mixture was extracted with DCM (20 mL) three times. The combined organic phases were washed with H_2O and brine, dried over anhydrous sodium sulphate, filtered, and the filtrate was concentrated *in vacuo.* The residue was purified by flash chromatography (silica, 0-50% EtOAc in PE) to give the *title compound* (150.1 mg, 30.3% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 7.87 (s, 2H), 2.55 (s, 3H).

INTERMEDIATE 71: *7-fluoro-2,3-dihydro-1H-indene-5-carbaldehyde*



Intermediate 71

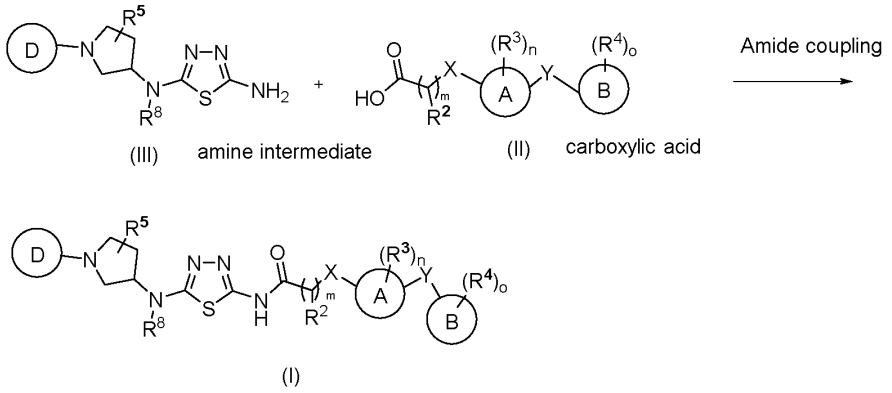
Step 1: *6-bromo-4-fluoro-2,3-dihydro-1H-indene*

A solution of 5-bromo-7-fluoro-2,3-dihydro-1H-inden-1-one (500.0 mg, 2.18 mmol), triethylsilane (5 mL) and trifluoroacetic acid (10 mL) was stirred at 50° C for 16 h before concentrated *in vacuo*. The residue was extracted with EtOAc (50 mL), washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo.* Crude material was purified by flash chromatography (silica, 0-5% EtOAc in PE) to afford the *title compound* (350.0 mg, 75.6% yield) as a colourless oil.

Step 2: *7-fluoro-2,3-dihydro-1H-indene-5-carbaldehyde*

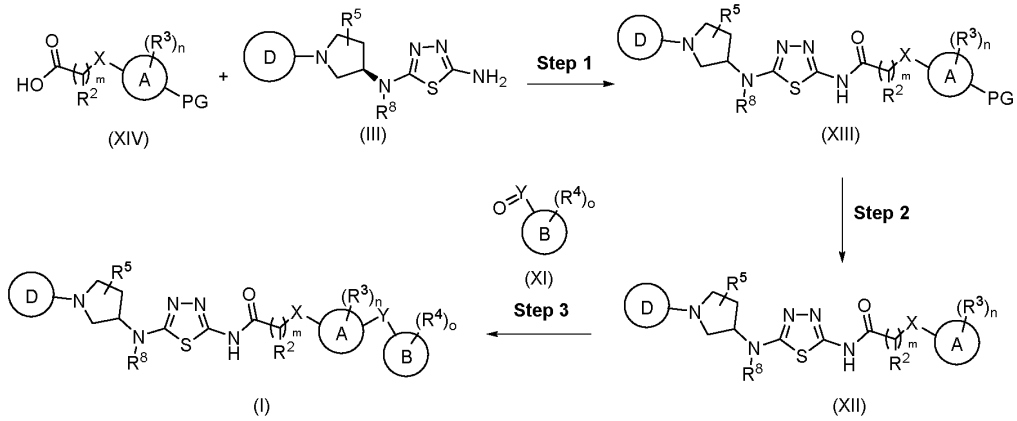
To a solution of 6-bromo-4-fluoro-2,3-dihydro-1H-indene (350 mg, 1.63 mmol) in THF (10 mL) was added *n*-butyl lithium (2.5 M in hexane, 1.3 mL, 3.25 mmol) dropwise slowly at -78°C under nitrogen. After the addition, the mixture was stirred for 1 h, and *N*, *N*-dimethyl formamide (1 mL) was added dropwise. The mixture was stirred at -78°C for 1 h. The reaction solution was then quenched with water, extracted with EtOAc (30 mL x 3), and the combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Crude material was purified by flash chromatography (silica, 0-20% EtOAc in PE) to afford the *title compound* (180.5 mg, 67.4% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (d, J = 1.6 Hz, 1H), 7.59 (s, 1H), 7.37 (d, J = 8.8 Hz, 1H), 3.05-2.97 (m, 4H), 2.22-2.15 (m, 2H).

General Procedure 1



To a stirring solution of the *acid intermediate* (1.0 *eq.*) and DIPEA (3.0 *eq.*) in DMF was added the *amine intermediate* (1.2 *eq.*) and the *coupling reagent* (HATU, T3P or PyBOP, 1.5 *eq.*). The reaction mixture was stirred at r.t. for 16 h. The reaction mixture was diluted with DCM and saturated aqueous sodium bicarbonate solution was added. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM (2x). Combined organic phases were washed with water and brine, dried over sodium sulphate, filtered and concentrated *in vacuo.* The crude material was purified either by flash chromatography (silica, DCM: MeOH= 10:1), preparative HPLC (H_2O/ACN + 0.5% NH_3) or preparative HPLC (H_2O/ACN + 0.5% FA) to give the *compound of formula (I)*.

General Procedure 2A



Step 1:

To a stirring solution of *acid* (1.0 *eq.*) in DMF was added (*R*)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine (1.0 *eq.*) and the *coupling reagent* (HATU, T3P or PyBOP, 1.5 *eq.*). Then the DIPEA (3 *eq.*) was dropwise added. The reaction mixture was stirred at r.t. for 2 h before added ice water and extracted with EA. The organics were combined, washed with brine and

concentrated *in vacuo*. The crude was purified by flash chromatography (silica, DCM: MeOH= 10:1), followed by trituration three times with PE and PE:EA=10:1 to afford *amide*.

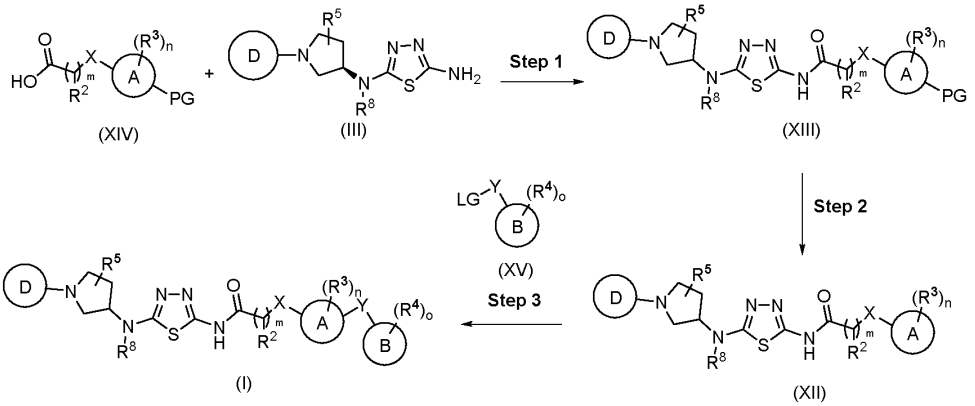
Step 2:

To a stirring solution of *amide* (1.0 *eq.*) in MeOH was added HCl in 1,4-dioxane (185 mL, 736.5 mmol, 15 *eq.*). The reaction mixture was stirred at r.t. for 4 h before concentrated *in vacuo* to afford *amine*.

Step 3:

To a stirring solution of *amine* (1.0 *eq.*) in DCE was added TEA (5 *eq.*) and *aldehyde* (2.0 *eq.*). The reaction mixture was stirred at r.t. for 30 min followed by addition of STAB (8 *eq.*). The reaction mixture was stirred at r.t. for 16 h and LCMS showed the reaction was completed. Reaction mixture was concentrated *in vacuo* and the residue was dissolved in DCM and 1:1 mixture of H_2O and saturated aqueous $NaHCO_3$ solution. The mixture was stirred for 15 min and phases were separated. Aqueous phase was extracted with DCM. Combined organic phases were washed with H_2O and brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. Trituration three times with Et_2O to afford the *compound of formula (I)*.

General Procedure 2B

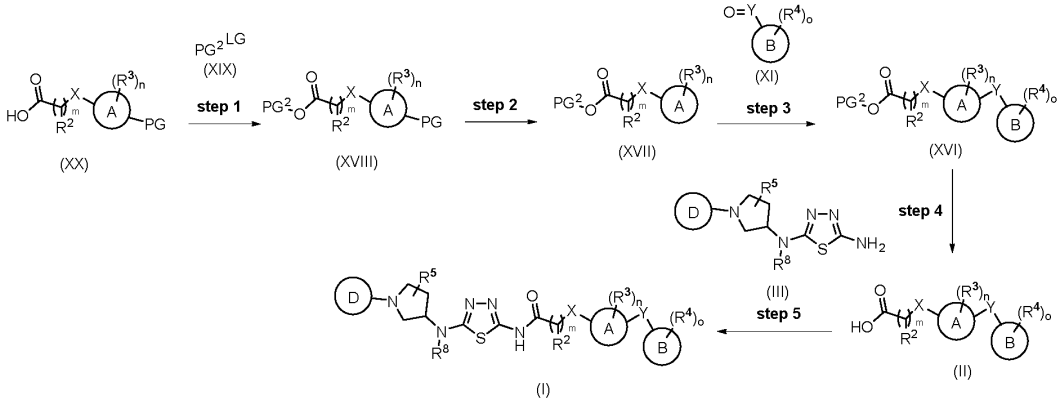


Steps 1 and **2** are identical as described in General Procedure 2A.

Step 3:

To a stirring solution of *amine* (1.0 *eq.*) in ACN were added TEA (21.0 *eq.*) and alkyl/benzyl bromide (1.3 *eq.*). The reaction mixture was stirred at r.t. for 16 h and LCMS showed the reaction was completed. Reaction mixture was concentrated *in vacuo* and the crude obtained was purified by either flash chromatography, or/and preparative TLC, or/and preparative HPLC (mobile phases: ACN, H_2O + 0.05% NH_3) followed by lyophilisation with ACN/H_2O to afford *the compound of formula (I)*.

General Procedure 3A and/or 3C



General Procedure A starts from a compound of formula (XVIII) wherein PG^2 is methyl (i.e. Step 1 is not needed). General Procedure C starts from a compound of formula (XX) wherein PG^2 is benzyl. Steps 2, 3 and 5 are the same in both procedures. Step 4 is different for General Procedures A and C, see Steps 4A and 4C below.

Step 1C:

To a mixture of *compounds of formula (XX), benzyl bromide* (2.0 *eq.*) in DMF was added K_2CO_3 (2.0 *eq.*). The mixture stirred at 85 °C for 16 h until the reaction was completed. The reaction mixture was diluted with water and extracted with EtOAc. The extracts were dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, EA:PE=1:8) to afford *compounds of formula (XVIII)* wherein PG^2 is benzyl.

Step 2:

To a solution of *compounds of formula (XVIII)* wherein PG^2 is methyl or benzyl in dioxane was added HCl in dioxane and the mixture was stirred at r.t. until PG removal (e.g. Boc group deprotection) was completed. The mixture was concentrated *in vacuo* to afford *amine hydrochloride*.

Step 3:

To a mixture of *amine hydrochloride* (1.5 *eq.*) and *aldehyde* (1.0 *eq.*) in DCE was added Et_3N (1.5 *eq.*) and glacial acetic acid (4 *eq.*). The mixture was stirred at r.t. for 5-10 min and then with *STAB* (3 *eq.*) was added. The resulting mixture was stirred at r.t. for 3 h before concentrated *in vacuo*. The residue was purified by reversed-phase chromatography (10-50% ACN/H_2O with 0.05% $NH_3 \cdot H_2O$) to afford *compounds of formula (XVI).*

Step 4A:

To a solution of *compounds of formula (XVI)* wherein PG^2 is methyl in MeOH/H2O was added LiOH (5 eq.). The mixture was stirred at r.t. for several h until the completion of hydrolysis, then adjusted to pH=5~6, extracted with MeOH/DCM. The extracts were evaporated to dryness to afford *compounds of formula (II)*.

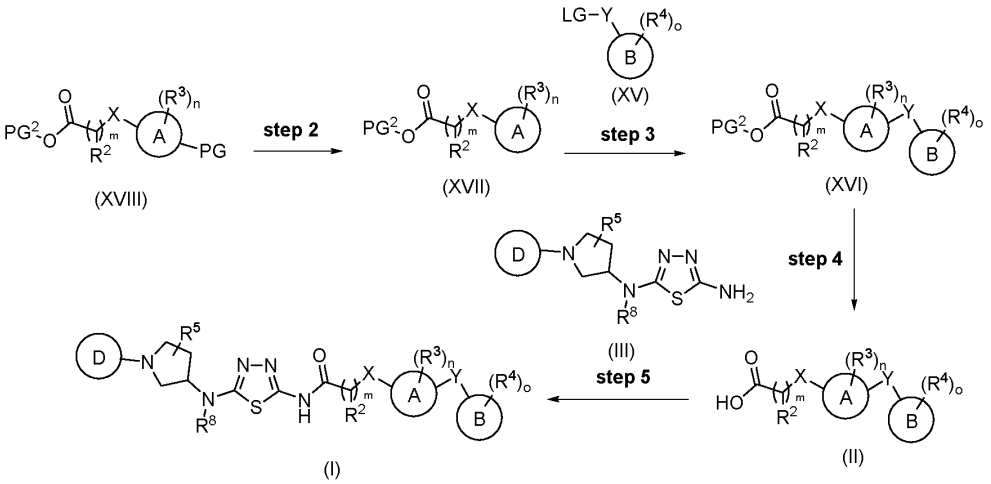
Step 4C:

To a solution of *compounds of formula (XVI)* wherein PG^2 is benzyl in MeOH was added Pd/C (1 *eq.*). The mixture was stirred at r.t. under H_2 atmosphere for 16 h before filtered. The filtrate was concentrated *in vacuo* to afford *compounds of formula (II)*.

Step 5:

A solution of *compounds of formula (II)* (1.0 *eq.*), *amine intermediate* (1.1 *eq.*) in anhydrous DMF was added the coupling reagent (HATU, T3P or PyBOP, 2.0 *eq.*) and DIPEA (3.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h. Reaction mixture was concentrated *in vacuo* and the crude obtained was purified by either flash chromatography, or/and preparative TLC, or/and preparative HPLC (mobile phases: ACN, H_2O + 0.05% NH_3) followed by lyophilisation with ACN/H_2O to afford *the compound of formula (I).*

General Procedure 3B

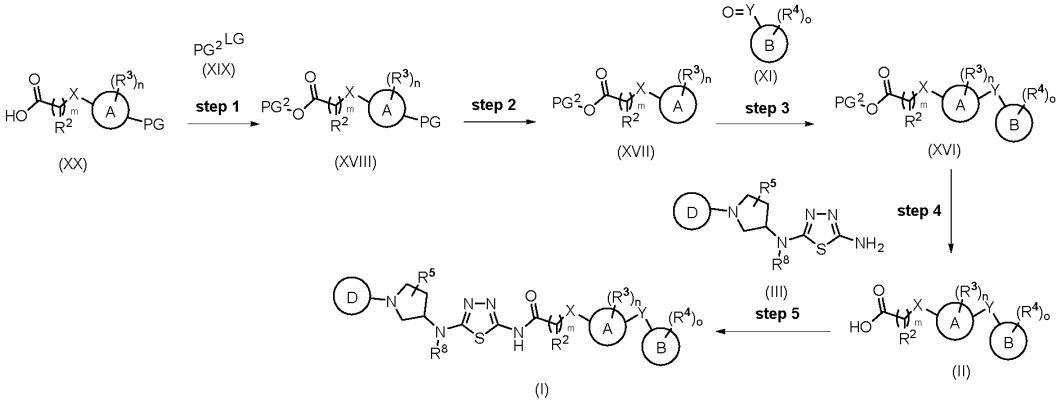


Steps 2, 4 and 5 are identical as described in General Procedure 3A.

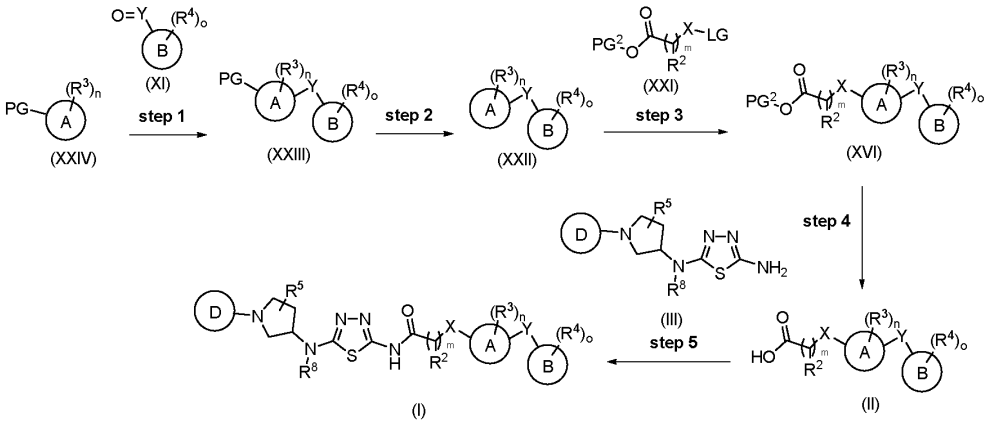
Step 3:

To a mixture of *amine hydrochloride* (1.5 *eq.*) in DMF was added Et_3N (3.0 *eq.*) and *alkyl halide* (1.0 *eq.*). The mixture was stirred at 40 °C for 3 h before diluted with water and extracted with MeOH/DCM (10:1). The extracts were dried over sodium sulphate, filtered and concentrated *in*

vacuo. The residue was purified by flash chromatography (silica, EA:PE=2:1) to afford *N-alkylation methyl ester.*



General Procedure 4



Step 1:

To a stirring solution of *amine* (1.0 *eq.*) in DCM was added AcOH (3 *eq.*) and aldehyde (1.0 *eq.*). Then the reaction mixture was stirred at r.t. for 30 min and then STAB (3 *eq.*) was added. The resulting mixture was stirred at r.t. for 2 h before LCMS showed the reaction was completed. The reaction mixture was added to ice cold water, extracted with EA, washed three times with brine, concentrated *in vacuo*. The crude was purified by flash chromatography (silica, PE: EA= 4:1) followed by trituration three times with PE and PE:EA=10:1 to afford *tertiary amine*.

Step 2:

To a stirring solution of *tertiary amine* (1.0 *eq.*) in DCM was added TFA. The reaction mixture was stirred at r.t. for 2 h before concentrated *in vacuo* to afford *amine*.

Step 3:

To a stirring solution of *amine* (1.0 *eq.*) in ACN was added DIPEA (5 *eq.*) and methyl bromoacetate (1.0 *eq.*). Then the reaction mixture was stirred at 40 °C for 4 h. The reaction mixture was added to ice cold water, extracted with EA, washed three times with brine, concentrated, purified by flash chromatography (silica, DCM: MeOH= 20:1) to afford *amine with methyl acetate*.

Step 4:

To a stirring solution of *amine with methyl acetate* (1.0 *eq.*) in MeOH/THF/Water (1/1/1) was added LiOH (2 *eq.*). Then the reaction mixture was stirred at r.t. for 2 h until the reaction was completed. Reaction mixture was concentrated *in vacuo* and purified by reversed-phase chromatography (ACN/H_2O with 0.05% HCl) afford *acid*.

Step 5:

To a stirring solution of the *acid* (1.0 *eq.*) in DMF was added the *amine intermediate* (1.0 *eq.*) and PyBOP (1.5 *eq.*). Then the DIPEA (3 *eq.*) was dropwise added. The reaction mixture was stirred at r.t. for 2 h until reaction was completed. Reaction mixture was concentrated *in vacuo* and the crude obtained was purified by either flash chromatography, or/and preparative TLC, or/and preparative HPLC (mobile phases: ACN, H_2O + 0.05% NH_3) followed by lyophilisation with ACN/H_2O to afford *the compound of formula (I).*

General Procedure 5 – SFC chiral separation

General Procedure 5A

Chiral-Chromatography purification conditions: DAICELCHIRALCEL®OD: 250*25 mm 10 μm; Mobile Phase A: n-Hexane; Mobile Phase B: EtOH (+0.1% 7.0 mol/L Ammonia in MeOH); Flow rate: 40 ml/min.

General Procedure 5B

Chiral-Chromatography purification conditions: DAICELCHIRALPAK®IG: 250*25 mm 10 μm; Mobile Phase A: n-Hexane; Mobile Phase B: EtOH (+0.1% 7.0 mol/L Ammonia in MEOH); Flow rate: 60 ml/min.

General Procedure 5C

Chiral-Chromatography purification conditions: Column: DALCELCHIRALCEL®AS: 250*25 mm 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (+0.1% 7.0 mol/L ammonia in MeOH); Flow rate:80 ml/min.

General Procedure 5D

Chiral-Chromatography purification conditions: DAICELCHIRALCEL®OD: 250*25 mm 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (+0.1% 7.0 mol/L ammonia in MeOH); Flow rate: 70 ml/min.

General Procedure 5E

Chiral-Chromatography purification conditions: Column: DAICELCHIRALCEL®OJ: 250*25 mm 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (+0.1% 7.0 mol/L ammonia in MeOH); Flow rate: 100 ml/min.

General Procedure 5F

Chiral-Chromatography purification conditions: Column: DAICELCHIRALPAK®AD: 250*25 mm 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: IPA (+0.1% 7.0 mol/L Ammonia in MeOH); Flow rate: 100 ml/min.

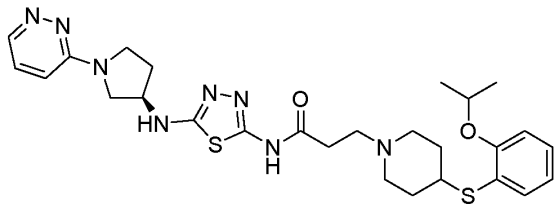
General Procedure 5G

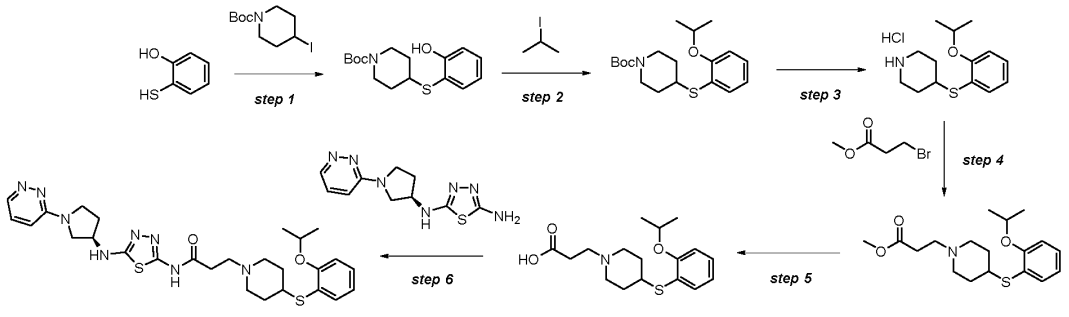
Chiral-Chromatography purification conditions: DAICELCHIRALPAK®AS: 250*25 mm 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (+0.1% 7.0 mol/L ammonia in MeOH); Flow rate: 120 ml/min.

Synthesis of Examples

In the Examples that follow, Intermediate compounds may have been prepared in a plurality of batches and the batch used in subsequent steps described herein may not be the same batch as that exemplified.

EXAMPLE 1: *(R)-3-(4-((2-isopropoxyphenyl)thio)piperidin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide*





Step 1: *tert-butyl 4-((2-hydroxyphenyl)thio)piperidine-1-carboxylate*

To a mixture of 2-mercaptophenol (1.0 g, 7.94 mmol, 1.0 *eq.*) in DMA (30.0 mL) was added *tert*-butyl 4-iodopiperidine-1-carboxylate (2.47 g, 7.94 mmol, 1.0 *eq.*) and Cs_2CO_3 (6.47 g, 19.85 mmol, 2.5 *eq.*) at r.t., and the resulting mixture was stirred at 30 °C for 2 h. The reaction mixture was then diluted with H_2O (60 mL), extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine (50 mL x 2), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc =10:1) to afford the *title compound* (1.7 g, yield 69%) as a yellow oil. LCMS (Method 16, ESI) 295.1 $[M-56+41+H]^+$, RT 1.890 minutes.

Step 2: *tert-butyl 4-((2-isopropoxyphenyl)thio)piperidine-1-carboxylate*

To a mixture of 4-((2-hydroxyphenyl)thio)piperidine-1-carboxylate (500 mg, 1.61 mmol, 1.0 *eq.*) in DMF (10.0 mL) was added 2-iodopropane (821 mg, 4.83 mmol, 3.0 *eq.*), K_2CO_3 (444 mg, 3.22 mmol, 2.0 *eq.*) and DIPEA (415 mg, 3.22 mmol, 2.0 *eq.*) at r.t.. The mixture was stirred at 45 °C for 3 h. The reaction mixture was diluted with H_2O (30 mL), extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (30 mL x 2), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc=95%/5%) to afford the *title compound* (500 mg, yield 84%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.24–7.13 (m, 1 H), 6.89 –6.86 (m, 2 H), 4.62-4.56 (m, 1 H), 3.97-3.92 (m, 2 H), 3.42–3.29 (m, 1 H), 2.95 (m, 2 H), 1.97– 1.83 (m, 2 H), 1.66-1.47 (m, 2 H), 1.45 (s, 9 H), 1.38 (d, *J* = 6.0 Hz, 6 H). LCMS (Method 16, ESI) 296.1 $[M-56+H]^+$, RT 2.067 minutes.

Step 3: *4-((2-isopropoxyphenyl)thio)piperidine hydrochloride*

To a mixture of *tert*-butyl 4-((2-isopropoxyphenyl)thio)piperidine-1-carboxylate (500 mg, 1.42 mmol, 1.0 *eq.*) in dioxane (3.0 mL) was added HCl in dioxane (2 M, 3 mL) at r.t.. The mixture was stirred at 30 °C for 2 h before concentrated *in vacuo* to afford the *title compound* (530 mg, crude) as a yellow oil. LCMS (Method 15, ESI) 252.2 $[M+H]^+$, RT 1.235 minutes.

Step 4: *methyl 3-(4-((2-isopropoxyphenyl)thio)piperidin-1-yl)propanoate*

To a mixture of 4-((2-isopropoxyphenyl)thio)piperidine hydrochloride (356 mg, 14.2 mmol, 1.0 *eq.*) in ACN (10.0 mL) were added DIPEA (1.10 g, 8.52 mmol, 6.0 *eq.*) and methyl 3-bromopropanoatestirred (356 mg, 2.13 mmol, 1.5 *eq.*) at r.t.. The mixture was stirred at 50 °C for 2 h. The reaction mixture was diluted with H_2O (30 mL), extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (30 mL x 2), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc = 97%/3%) to afford the *title compound* (470 mg, yield 98%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.18 (td, *J* = 8.0, 1.6 Hz, 1 H), 6.89-6.86 (m, 2 H), 4.62-4.55 (m, 1 H), 3.67 (s, 3 H), 3.23 (s, 1H), 2.93–2.80 (m, 2 H), 2.71 (t, *J* = 7.2 Hz, 2 H), 2.53 (t, *J* = 7.2 Hz, 2 H), 2.16 (s, 2 H), 1.97 (d, *J* = 11.6 Hz, 2 H), 1.70-1.61 (m, 2 H), 1.37 (d, *J* = 6.1 Hz, 6 H). LCMS (Method 16, ESI) 338.1 $[M+H]^+$, RT 1.792 minutes.

Step 5: *3-(4-((2-isopropoxyphenyl)thio)piperidin-1-yl)propanoic acid*

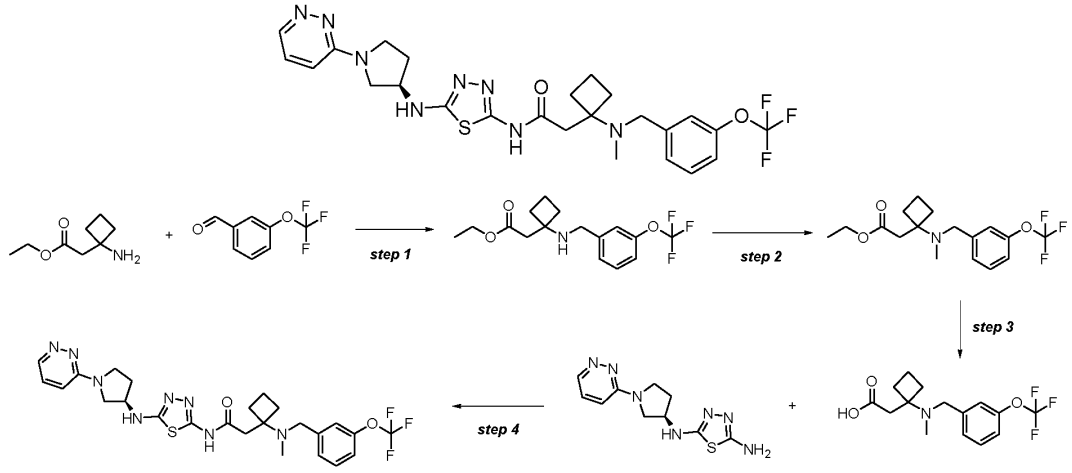
To a mixture of methyl 3-(4-((2-isopropoxyphenyl)thio)piperidin-1-yl)propanoate (200 mg, 0.59 mmol, 1.0 *eq.*) in MeOH (3.0 mL) and H_2O (1.0 mL) was added LiOH (71 mg, 2.95 mmol, 5.0 *eq.*) at r.t.. The mixture was stirred at r.t. for 3 h. The reaction mixture was quenched with 1M aqueous HCl solution, extracted with DCM/MeOH (10/1) (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the *title compound* (200 mg, crude) as a white solid. LCMS (Method 16, ESI) 324.0 $[M+H]^+$, RT 1.075 minutes.

Step 6: *(R)-3-(4-((2-isopropoxyphenyl)thio)piperidin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidine-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide)*

To a mixture of 3-(4-((2-isopropoxyphenyl)thio)piperidin-1-yl)propanoic acid (116 mg, 0.36 mmol, 1.2 *eq.*) in DMF (4 mL) were added DIPEA (91 mg, 0.90 mmol, 3.0 *eq.*), PyBOP (234 mg, 0.45 mmol, 1.5 *eq.*) and (*R*)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine (80 g, 0.3 mmol, 1.0 *eq.*) at r.t.. The mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with H_2O (20 mL), extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL x 2), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, DCM/MeOH =93%/7%) to afford crude product which was further purified by reversed-phase flash chromatography (C-25 g, MeCN%=46%, +0.1% $NH_3 \cdot H_2O$) to afford the *title compound* (80.03 mg, yield 39 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1 H), 8.48 (dd, *J* = 4.4 Hz, 1.2 Hz, 1 H), 7.62 (d, *J* = 5.6 Hz, 1 H), 7.28-7.35 (m, 2 H), 7.16-7.20 (m, 1 H), 6.99 (d, *J* = 8.0 Hz, 1 H), 6.86-6.90 (m, 2 H), 4.60-4.66 (m, 1 H), 4.35-4.41 (m, 1 H), 3.73-3.77 (m, 1 H), 3.48-3.60 (m, 3 H), 3.21-3.27 (m, 1 H), 2.77-2.85

(m, 2 H), 2.52-2.61 (m, 4 H), 2.25-2.33 (m, 1 H), 2.04-2.13 (m, 3 H), 1.84-1.87 (m, 2 H), 1.43-1.52 (m, 2 H), 1.27 (d, *J* = 6.0 Hz, 6 H). LCMS (Method 16, ESI): 569.0 $[M+H]^+$, RT 1.546 minutes.

EXAMPLE 2: *(R)-2-(1-(methyl(3-(trifluoromethoxy)benzyl)amino)cyclobutyl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*



Step 1: *ethyl 2-(1-((3-(trifluoromethoxy)benzyl)amino)cyclobutyl)acetate*

To a mixture of ethyl 2-(1-aminocyclobutyl)acetate (300 mg, 1.91 mmol, 1.0 *eq.*) in DCE (7.0 mL) was added TEA (385.82 mg, 3.82 mmol, 2.0 *eq.*), 3-(trifluoromethoxy)benzaldehyde (399.08 mg, 2.10 mmol, 1.1 *eq.*) and AcOH (458.4 mg, 7.64 mmol, 4.0 *eq.*) at r.t.. The mixture was stirred at r.t. for 3 min before the addition of STAB (809.84 g, 3.82 mmol, 2.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was quenched with saturated aqueous sodium carbonate (10 mL), extracted with DCM/MeOH (10/1) (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc =5/1) to afford the *title compound* (600 mg, yield 81%) as a colourless oil. LCMS LCMS (Method 14, ESI) 332.1 $[M+H]^+$, RT 1.382 minutes.

Step 2: *ethyl 2-(1-(methyl(3-(trifluoromethoxy)benzyl)amino)cyclobutyl)acetate*

To a mixture of ethyl 2-(1-((3-(trifluoromethoxy)benzyl)amino)cyclobutyl)acetate (250 mg, 0.75 mmol, 1.0 *eq.*) in anhydrous DCE (10.0 mL) was added TEA (151.5 g, 1.5 mmol, 2.0 *eq.*), paraformaldehyde (1.02 g, 11.33 mmol, 15.0 *eq.*) and AcOH (180 mg, 3.0 mmol, 4.0 *eq.*) at r.t.. The mixture was stirred at r.t. for 3 min. STAB (318 mg, 1.50 mmol, 2.0 *eq.*) was then added at r.t., and the resulting mixture was stirred at 40 °C for 16 h. The reaction mixture was quenched with saturated aqueous sodium carbonate (10 mL), extracted with DCM/MeOH (10/1) (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over sodium sulphate,

filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, PE/EtOAc =93%/7%) to afford the *title compound* (180 mg, yield 58%) as a colourless oil. LCMS (Method 15, ESI) 346.1 $[M+H]^+$, RT 1.428 minutes.

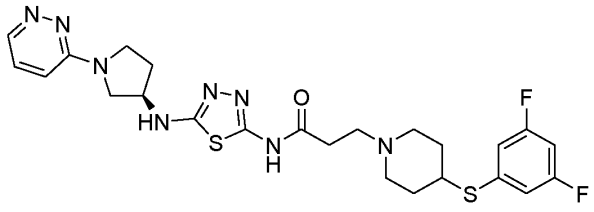
Step 3: *2-(1-(methyl(3-(trifluoromethoxy)benzyl)amino)cyclobutyl)acetic acid*

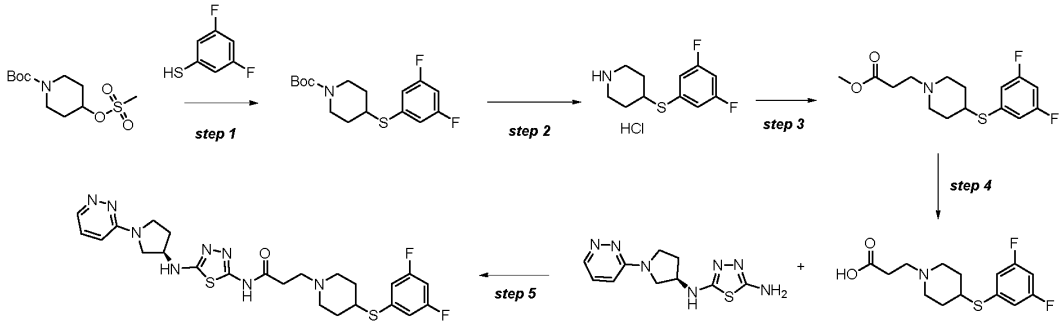
To a mixture of ethyl 2-(1-(methyl(3-(trifluoromethoxy)benzyl)amino)cyclobutyl)acetate (150 mg, 0.43 mmol, 1.0 *eq.*) in MeOH (6.0 mL) was added NaOH (2M, 4.35 mL, 20.0 *eq.*) at r.t.. The mixture was stirred at 50 °C for 16 h before quenched with 1M HCl solution and extracted with DCM/MeOH (10/1) (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the *title compound* (300 mg, crude) as a yellow oil. LCMS (Method 15, ESI) 318.3 $[M+H]^+$, RT 1.317 minutes.

Step 4: *(R)-2-(1-(methyl(3-(trifluoromethoxy)benzyl)amino)cyclobutyl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*

To a mixture of 2-(1-(methyl(3-(trifluoromethoxy)benzyl)amino)cyclobutyl)acetic acid (250 mg, 0.79 mmol, 1.0 *eq.*) in DMF (4 mL) was added DIPEA (79.98 mg, 0.62 mmol, 2.0 *eq.*), PyBOP (322.40 mg, 0.62 mmol, 2.0 *eq.*) and (*R*)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine (81.53 g, 0.31 mmol, 1.0 *eq.*) at r.t., and the mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with H_2O (20 mL), extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL x 2), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, DCM/MeOH =97%/3%) followed by reversed-phase flash chromatography (C-25 g, MeCN%=30%, +0.1% $NH_3.H_2O$) to afford the *title compound* (126.22 mg, yield 73 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.13 (s, 1 H), 8.48 (d, *J* =4.8 Hz, 1 H), 7.63 (d, *J* =6.0 Hz, 1 H), 7.46-7.42 (m, 1 H), 7.36-7.31 (m, 2 H), 7.26-7.23 (m, 1 H), 7.22-7.20 (m, 1 H), 6.87(d, *J* =9.2 Hz, 1 H), 4.44-4.35 (m, 1 H), 3.79-3.75 (m, 1 H), 3.62-3.46 (m, 5 H), 2.65 (s, 2 H), 2.36-2.31 (m, 2 H), 2.19-2.04 (m, 3 H), 2.02-1.99 (m, 3 H), 1.76-1.65 (m, 1 H), 1.62-1.56 (m, 1 H). LCMS (Method 13, ESI): 563.3 $[M+H]^+$, RT 5.987 minutes.

EXAMPLE 3: *(R)-3-(4-((3,5-difluorophenyl)thio)piperidin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide*





Step 1: *tert-butyl 4-((3,5-difluorophenyl)thio)piperidine-1-carboxylate*

To a stirred solution of *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (954 mg, 3.42 mmol, 1.0 *eq.*) in ACN (10 mL) was added 3,5-difluorobenzenethiol (500 mg, 3.42 mmol, 1.0 *eq.*) and K_2CO_3 (708 mg, 5.13 mmol, 1.5 *eq.*). The resulting mixture was stirred at 80 °C for 3 h. Upon completion, the reaction mixture was cooled to r.t. and diluted with water (100 mL), extracted with EtOAc (3 x 30 mL). The combine organic phase was washed with brine (2 x 100 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0-6% EtOAc in PE) to afford the *title compound* (860 mg, 2.61 mmol, 76.43 % yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.16–7.04 (m, 3 H), 3.82 (d, J = 13.6 Hz, 2 H), 3.70-3.63 (m, 1 H), 2.98 (s, 2 H), 1.94-1.89 (m, 2 H), 1.44–1.37 (m, 11 H).

Step 2: *4-((3,5-difluorophenyl)thio)piperidine hydrochloride*

A solution of *tert*-butyl 4-((3,5-difluorophenyl)thio)piperidine-1-carboxylate (300 mg, 0.91 mmol) in HCl/dioxane (4M, 3 mL) was stirred at r.t. for 1 h. The solvent was concentrated *in vacuo* to give the *title compound* (250 mg, crude) as a yellow oil. LCMS (Method 15, ESI) 230.1 $[M+H]^+$, RT 1.223 minutes.

Step 3: *methyl 3-(4-((3,5-difluorophenyl)thio)piperidin-1-yl)propanoate*

To a stirred solution of 4-((3,5-difluorophenyl)thio)piperidine hydrochloride (245 mg , 0.91 mmol, 1.0 *eq.*) in ACN (5.0 mL) was added DIPEA (551 mg, 5.46 mmol, 6 *eq.*) and methyl 3-bromopropanoate (299 mg, 1.37 mmol, 1.5 *eq.*). The resulting mixture was stirred at 50 °C for 3 h. Upon completion, the reaction was cooled to r.t. and diluted with water (30 mL), extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with brine (2 x 100 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0-15% EtOAc in PE) to afford the *title compound* (290 mg, crude) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.17–6.97 (m, 3 H), 3.58 (s, 3 H), 3.52–3.41 (m, 1 H), 2.81–2.70 (m, 2 H), 2.56-2.51 (m, 2 H), 2.49-2.45 (m, 2 H), 2.16-2.14 (m, 2 H), 1.92-1.88 (m, 2 H), 1.52-1.42 (m, 2 H). LCMS (Method 15, ESI) 316.2 $[M+H]^+$, RT 1.288 minutes.

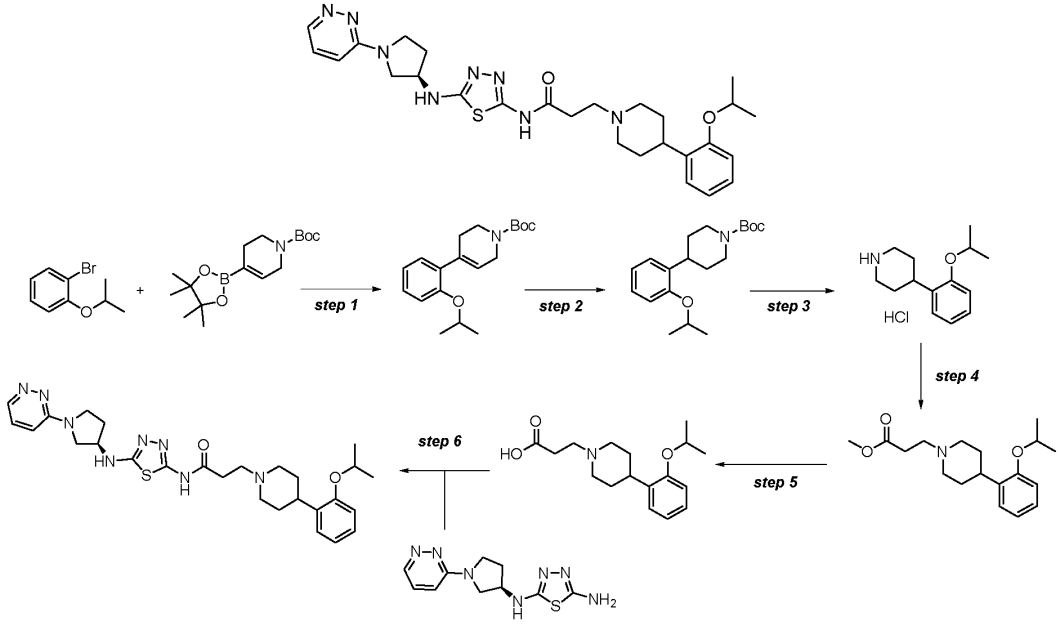
Step 4: *3-(4-((3,5-difluorophenyl)thio)piperidin-1-yl)propanoic acid*

To a solution of 3-(4-((3,5-difluorophenyl)thio)piperidin-1-yl)propanoate (290 mg , crude, 0.92 mmol, 1.0 *eq.*) in MeOH/H_2O (6 mL/2 mL) was added LiOH (110 mg, 4.60 mmol, 5.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h. Upon completion, the reaction was diluted with water (20 mL), adjusted to pH to pH<7 with 1M HCl and extracted with EtOAc (30 mL). The combined organic phase was washed with brine (50 mL), dried over sodium sulphate filtered and concentrated *in vacuo* to afford the *title compound* (200 mg, 0.66 mmol, yield 72.18 %) as a white solid. LCMS (Method 15, ESI) 302.2 $[M+H]^+$, RT 1.276 minutes.

Step 5: *(R)-3-(4-((3,5-difluorophenyl)thio)piperidin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidine-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide*

To a solution of 2-(3-bromo-5-methylphenyl)acetic acid (70 mg, 0.23 mmol, 1.2 *eq.*) in anhydrous DMF (3.0 mL) was added PyBOP (151 mg, 0.29 mmol, 1.5 *eq.*) and DIPEA (58 mg, 0.57 mmol, 3.0 *eq.*) and (*R*)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine (50 mg, 0.19 mmol, 1.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h under argon. Upon completion, the reaction mixture was purified by reversed-phase column (0% to 41.0% MeCN/water with 0.1% NH_4OH) to afford the *title compound* (60.55 mg, 0.163 mmol, 45.2 % yield) as a white solid. LCMS (Method 16, ESI): 547.1 $[M+H]^+$, RT 1.417 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 12.02 (s, 1 H), 8.49-8.48 (m, 1 H), 7.62 (d, *J* =6.4 Hz, 1 H), 7.35-7.32 (m, 1 H), 7.12-7.04 (m, 3 H), 6.88-6.86 (m, 1 H), 4.39-4.38 (m, 1 H), 3.78-3.74 (m, 1 H), 3.59-3.48 (m, 4 H), 2.80-2.78 (m, 2 H), 2.63-2.60 (m, 2 H), 2.55-2.51 (m, 2 H), 2.30-2.27 (m, 1 H), 2.20-2.17 (m, 2 H), 2.14-2.07 (m, 1 H), 1.94-1.91 (m, 2 H), 1.51-1.48 (m, 2 H).

EXAMPLE 4: *(R)-3-(4-(2-isopropoxyphenyl)piperidin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide*



Step 1*: tert-butyl 4-(2-isopropoxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate*

To a stirred solution of 1-bromo-2-isopropoxybenzene (2 g, 9.30 mmol, 1.0 *eq.*) in dioxane (50 mL) and H_2O (5 mL) was added *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (5.75 g, 18.6 mmol, 2.0 *eq.*), K_2CO_3(5.75 g, 18.6 mmol, 2.0 *eq.*), Pd(dppf)Cl_2·CH_2Cl_2(754 mg, 0.93 mmol, 0.1 *eq.*). The resulting mixture was stirred at 95 °C for 3 h under argon. Upon completion, the reaction was cooled to r.t. and diluted with water (100 mL), extracted with EtOAc (3 x 100 mL). The combine organic phase was washed with brine (2 x 100 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0%-10% EtOAc in PE) to afford the *title compound* (2.2 g, 6.93 mmol, 74.54 % yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.27–7.15 (m, 1 H), 7.11 (dd, *J* = 7.6, 1.6 Hz, 1 H), 6.97 (d, *J* = 8.01 Hz, 1 H), 6.88 (dt, *J* = 7.6, 3.6 Hz, 1 H), 5.71 (s, 1 H), 4.63–4.47 (m, 1 H), 3.94 (s, 2 H), 3.47 (t, *J* = 5.6 Hz, 2 H), 2.41 (d, *J* = 1.6 Hz, 2 H), 1.41 (d, *J* = 12.8 Hz, 10 H), 1.24 (d, *J* = 6.0 Hz, 6 H).

Step 2: *preparation of tert-butyl 4-(2-isopropoxyphenyl)piperidine-1-carboxylate*

To a stirred solution of *tert*-butyl 4-(2-isopropoxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate (0.5 g, 1.58 mmol, 1.0 *eq.*) in MeOH (15 mL) was added Pd/C (300 mg, 10% on carbon with ca. 55% water). The resulting mixture was stirred at r.t. for 2 h under H_2. Upon completion, the mixture was filtered and the filtrate was concentrated *in vacuo* to afford the *title compound* (460 mg, 1.44 mmol, yield 91.44%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.20–7.04 (m, 2H), 6.95 (d,

J = 8.4 Hz, 1H), 6.85 (t, *J* = 7.0 Hz, 1H), 4.59-4.56 (m, 1H), 4.08-4.05 (m, 2H), 3.02-2.92 (m, 1H), 2.78 (s, 2H), 1.69-1.59 (d, *J* = 12.4 Hz, 2H), 1.58–1.36 (m, 11H), 1.26 (t, *J* = 8.0 Hz, 6H).

Step 3: *preparation of 4-(2-isopropoxyphenyl)piperidine hydrochloride*

A solution of *tert*-butyl 4-(2-isopropoxyphenyl)piperidine-1-carboxylate (480 mg, 1.50 mmol) in HCl/dioxane (4 M, 3 mL) was stirred at r.t. for 2 h. The solvent was concentrated *in vacuo* to give the *title compound* (330 mg, crude) as a yellow oil. LCMS (Method 15, ESI) 220.2 $[M+H]^+$, RT 1.229 minutes.

Step 4: *preparation of methyl 3-(4-(2-isopropoxyphenyl)piperidin-1-yl)propanoate*

To a stirred solution of 4-(2-isopropoxyphenyl)piperidine hydrochloride (330 mg , 1.50 mmol, 1.0 *eq.*) in ACN (10.0 mL) was added DIPEA (909 mg, 2.25 mmol, 6 *eq.*) and methyl 3-bromopropanoate (376 mg, 2.25 mmol, 1.5 *eq.*). The resulting mixture was stirred at 50 °C for 3 h. Upon completion, the reaction was cooled to r.t. and diluted with water (30 mL), extracted with EtOAc (3 x 30 mL). The combine organic phase was washed with brine (2 x 100 mL), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0-15% EtOAc in PE) to afford the *title compound* (280 mg, 0.92 mmol, 60.93 % yield) as a yellow oil. LCMS (Method 15, ESI) 306.6 $[M+H]^+$, RT 1.328 minutes.

Step 5: *preparation of methyl 3-(4-(2-isopropoxyphenyl)piperidin-1-yl)propanoic acid*

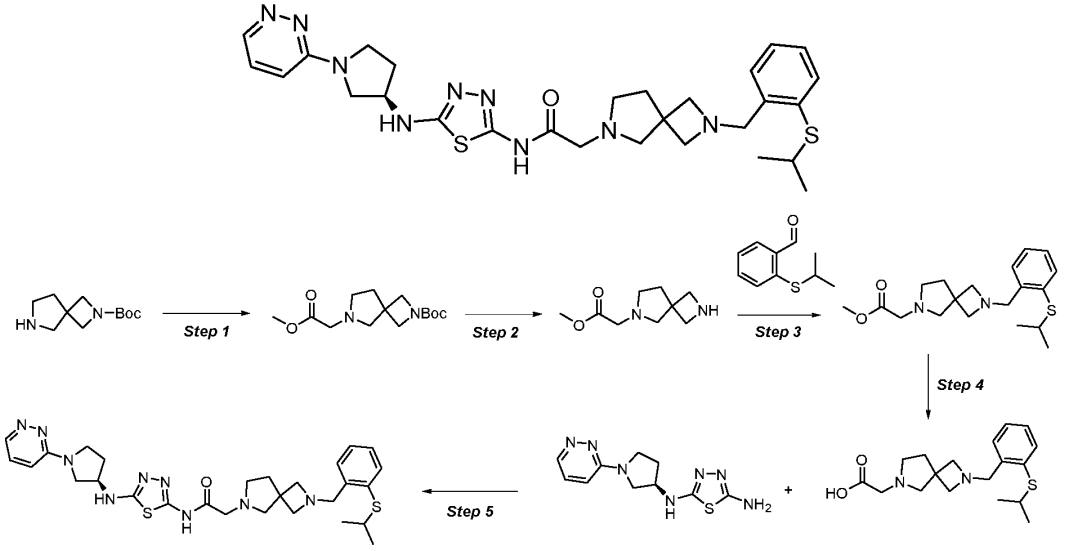
To a solution of methyl 3-(4-(2-isopropoxyphenyl)piperidin-1-yl)propanoate (280 mg , 0.92 mmol, 1.0 *eq.*) in MeOH/H_2O (6 mL/ 2 mL) was added LiOH (110 mg, 4.60 mmol, 5.0). The resulting mixture was stirred at r.t. for 2 h. Upon completion, the reaction was diluted with H_2O (20 mL), adjusted to pH<7 with 1M HCl, extracted with EtOAc (30 mL). The organic layer was washed with brine (50 mL), dried over sodium sulphate filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0-15% MeOH in DCM) to afford the *title compound* (240 mg, 0.82 mmol, 89.84 % yield) as a yellow solid. LCMS (Method 15, ESI) 292.3 $[M+H]^+$, RT 1.270 minutes.

Step 6: *preparation of (R)-3-(4-(2-isopropoxyphenyl)piperidin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide*

To a solution of 3-(4-(2-isopropoxyphenyl)piperidin-1-yl)propanoic acid (120 mg, 0.41 mmol, 1.2 *eq.*) in anhydrous DMF (3.0 mL) was added PyBOP (265 mg, 0.51 mmol, 1.5 *eq.*) and DIPEA (103 mg, 1.02 mmol, 3.0 *eq.*) and (*R*)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine (90 mg, 0.34 mmol, 1.0 *eq.*) . The resulting mixture was stirred at r.t. for 2 h under argon. Upon completion, the reaction mixture was purified by reversed-phase column (0-40% MeCN in water with 0.1% NH_4OH) to afford the *title compound* (60.20 mg, 27.24 % yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.12 (s, 1 H), 8.48 (d, *J* =4.8 Hz, 1 H), 7.63 (d, *J* =6.4 Hz, 1 H), 7.35-7.31 (m, 1 H), 7.15-7.10 (m, 2 H), 6.95-6.93 (m, 1 H), 6.88-6.84 (m, 2 H), 4.61-4.54 (m, 1 H), 4.42-4.36 (m, 1 H), 3.78-3.74 (m, 1 H), 3.59-3.50 (m, 3 H), 3.30-2.97 (m, 2 H), 2.87-2.78 (m, 1 H), 2.67-2.56 (m, 4 H), 2.34-2.26 (m, 1 H), 2.12-2.01 (m, 3 H), 1.70-1.53 (m, 4 H), 1.26-1.25 (m, 6 H).
LCMS (Method 19, ESI): 537.1 [M+H]$^+$, RT 1.188 minutes.

EXAMPLE 5: *(R)-2-(2-(2-(isopropylthio)benzyl)-2,6-diazaspiro[3.4]octan-6-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*



Step 1: *Preparation of tert-butyl 6-(2-methoxy-2-oxoethyl)-2,6-diazaspiro[3.4]octane-2-carboxylate*

To a mixture of *tert*-butyl 2,6-diazaspiro[3.4]octane-2-carboxylate (1 g, 4.72 mmol, 1.0 *eq.*) in ACN (10 mL) were added methyl 2-bromoacetate (789 mg, 5.19 mmol, 1.1 *eq.*) and DIPEA (1.83 g, 14.16 mmol, 3.0 *eq.*) The resulting mixture was stirred at 40°C for 2 h before quenched with saturated aqueous ammonium chloride, extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to afford the *title compound* (1.1 g, yield 82.15%) as a white oil. No mass signal was detected by LCMS.

Step 2: *Preparation of methyl 2-(2,6-diazaspiro[3.4]octan-6-yl)acetate*

To a solution of the *tert*-butyl 6-(2-methoxy-2-oxoethyl)-2,6-diazaspiro[3.4]octane-2-carboxylate (1.1 g , 1.0 *eq.*) in DCM (5 mL) was added TFA (5 mL), and the resulting mixture was stirred at r.t. for 2 h. The reaction mixture was concentrated *in vacuo* to afford the *title compound* (2.5 g, crude) without further purification. LCMS (Method 15, ESI): 185.2 [M+H]$^+$, RT 0.587 minutes.

Step 3: *Preparation of methyl 2-(2-(2-(isopropylthio)benzyl)-2,6-diazaspiro[3.4]octan-6-yl)acetate*

A mixture of the methyl 2-(2,6-diazaspiro[3.4]octan-6-yl)acetate (2.5 g, 13.59 mmol, 1.0 *eq.*) and TEA (4.12 g, 40.77 mmol, 3.0 *eq.*) in DCM was added 2-(isopropylthio)benzaldehyde (1.22 g, 6.80 mmol, 0.5 *eq.*). The resulting mixture was stirred at r.t. for 2 h under argon. To the mixture was added $NaBH(OAc)_3$ (14.4 g, 67.95 mmol, 5.0 *eq.*). The resulting mixture was stirred at r.t. for 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride, extracted with EtOAc (x3). The combined organic phase was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0-5% MeOH in DCM) to afford the *title compound* (1.2 g, yield 25.53%) as a yellow oil. LCMS (Method 15, ESI): 349.1 $[M+H]^+$, RT 0.933 minutes.

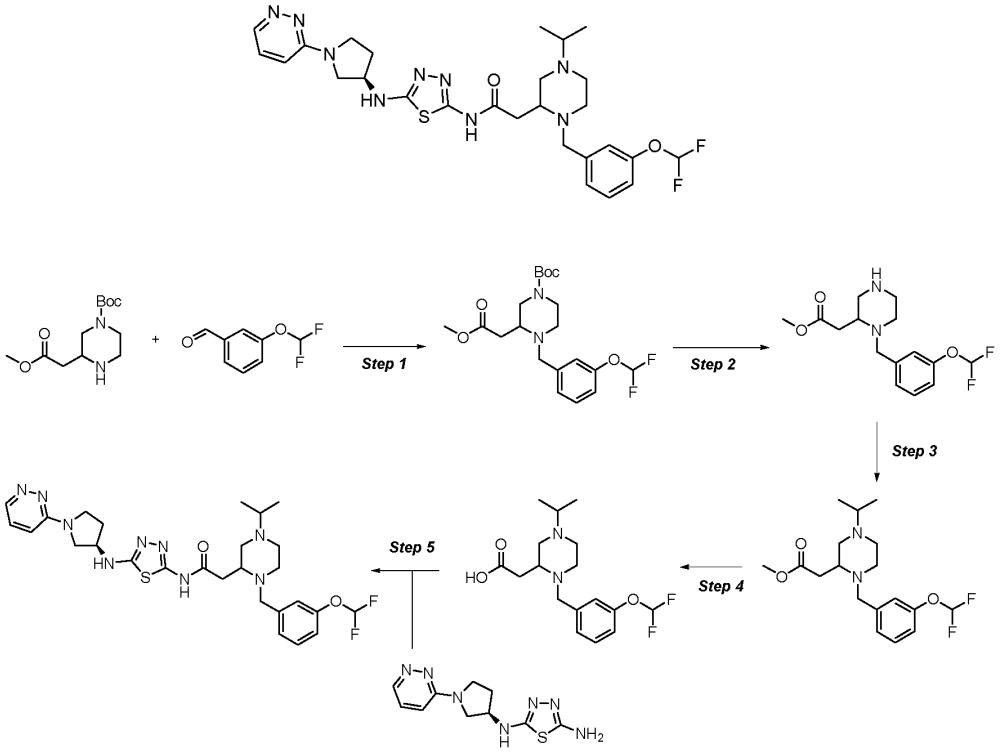
Step 4: *Preparation of 2-(2-(2-(isopropylthio)benzyl)-2,6-diazaspiro[3.4]octan-6-yl)acetic acid*

To a stirred solution of the methyl 2-(2-(2-(isopropylthio)benzyl)-2,6-diazaspiro[3.4]octan-6-yl)acetate (1.2 g, 3.45 mmol, 1.0 *eq.*) in MeOH/THF/Water (1/1/1) was added LiOH (289.8 mg, 6.90 mmol, 2.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h before concentrated *in vacuo* to afford the *title compound* (1.9 g, crude) as a yellow oil without purification LCMS (Method 15, ESI): 335.1 $[M+H]^+$, RT 0.986 minutes.

Step 5: *Preparation of (R)-2-(2-(2-(isopropylthio)benzyl)-2,6-diazaspiro[3.4]octan-6-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*

A solution of 2-(2-(2-(isopropylthio)benzyl)-2,6-diazaspiro[3.4]octan-6-yl)acetic acid (200 mg, 0.60 mmol, 1.0 *eq.*), (R)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine (prepared according to the procedure of *Intermediate 1*) (236.7 mg, 0.90 mmol, 1.5 *eq.*) in anhydrous DMF was added PyBOP (780.59 mg, 1.50 mmol, 2.5 *eq.*) and DIPEA (232.2 mg, 1.80 mmol, 3.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was purified by reversed phase chromatography (30% ACN/H_2O with 0.1% FA) to afford the crude product, which was further purified by reversed-phase chromatography (30% ACN/H_2O with $NH_3.H_2O$) and lyophilised with CH_3CN/H_2O to afford the *title compound* (38.03 mg, yield 21.9%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 11.67 (s, 1H), 8.52 – 8.43 (m, 1H), 7.65 (d, *J* = 6.1 Hz, 1H), 7.41 – 7.31 (m, 3H), 7.25 – 7.18 (m, 2H), 6.87 (dd, *J* = 9.1, 1.1 Hz, 1H), 4.39 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.63 – 3.53 (m, 4H), 3.51 – 3.40 (m, 2H), 3.40 – 3.34 (m, 2H), 3.11 (dd, *J* = 30.7, 6.7 Hz, 4H), 2.76 (s, 2H), 2.57 (t, *J* = 6.9 Hz, 2H), 2.30 (td, *J* = 13.5, 7.8 Hz, 1H), 2.08 (td, *J* = 11.9, 5.0 Hz, 1H), 1.92 (t, *J* = 6.9 Hz, 2H), 1.22 (d, *J* = 6.6 Hz, 6H). LCMS (Method 15, ESI) 580.3 $[M+H]^+$, RT 0.744 minutes.

EXAMPLE 6: *2-(1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*



Step 1: *Preparation of tert-butyl 4-(3-(difluoromethoxy)benzyl)-3-(2-methoxy-2-oxoethyl)piperazine-1-carboxylate*

To a stirring solution of *tert*-butyl 3-(2-methoxy-2-oxoethyl)piperazine-1-carboxylate (800 mg, 3.10 mmol, 1.0 *eq.*) in DCM (20 mL) was added AcOH (559 mg, 9.30 mmol, 3.0 *eq.*) and 3-(difluoromethoxy)benzaldehyde (534 mg, 3.10 mmol, 1.0 *eq.*). Then the reaction mixture was stirred at r.t. for 30 min followed by addition of STAB (1.97 g, 9.30 mmol, 3.0 *eq.*). The reaction mixture was stirred at r.t. for 16 h before concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0-30% EtOAc in PE) to afford the *title compound* (1.2 g, yield 93.7 %). LCMS (Method 13, ESI): 415.3 $[M+H]^+$, RT 1.435 minutes.

Step 2: *Preparation of methyl 2-(1-(3-(difluoromethoxy)benzyl)piperazin-2-yl)acetate*

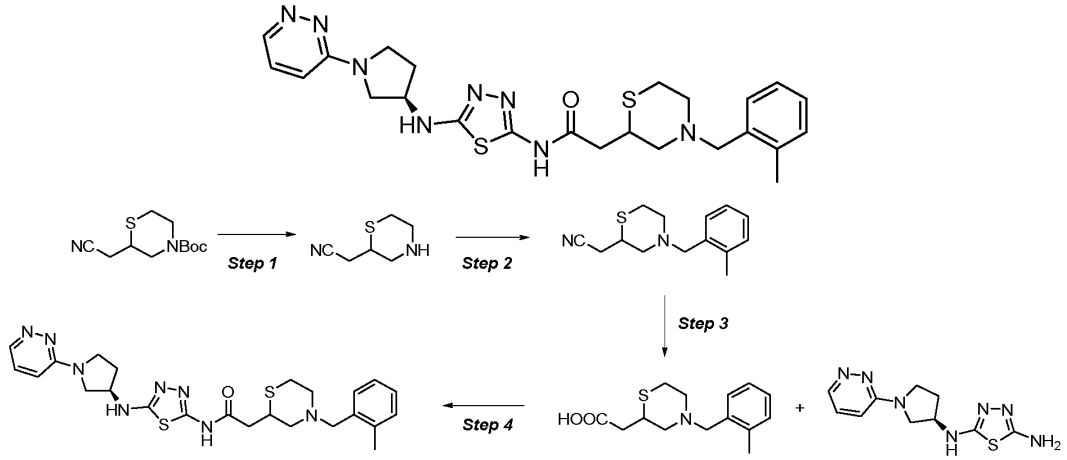
To a solution of *tert*-butyl 4-(3-(difluoromethoxy)benzyl)-3-(2-methoxy-2-oxoethyl)piperazine-1-carboxylate (1.2 g, 2.89 mmol, 1.0 *eq.*) in DCM (6 mL) was added TFA (2 mL). The reaction mixture was stirred at r.t. for 2 h before concentrated *in vacuo* to afford the *title compound* (911 mg, crude), which was used without further purification. LCMS (Method 13, ESI): 315.3 $[M+H]^+$, RT 1.219 minutes.

Step 3: *Preparation of methyl 2-(1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)acetate*
To a stirring solution of methyl 2-(1-(3-(difluoromethoxy)benzyl)piperazin-2-yl)acetate (911 mg, 2.90 mmol, 1.0 *eq.*) in DCM (20 mL) was added TEA (880 mg, 8.69 mmol, 3.0 *eq.*) and acetone (1.68 g, 28.98 mmol, 10.0 *eq.*). Then the reaction mixture was stirred at r.t. for 2 h followed by addition of STAB (1.84 g, 8.69 mmol, 3.0 *eq.*). The reaction mixture was stirred at r.t. for 16 h before concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0-5% MeOH in DCM) to afford the *title compound* (1.2 g, crude) as a colourless oil. LCMS (Method 13, ESI): 357.3 $[M+H]^+$, RT 1.283 minutes.

Step 4: *Preparation of 2-(1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)acetic acid*
To a stirring solution of methyl 2-(1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)acetate (1.2 g, 3.37 mmol, 1.0 *eq.*) in MeOH/THF/Water (1/1/1) (5 mL/5 mL/5 mL) was added LiOH (283 mg, 6.73 mmol, 2.0 *eq.*). Then the reaction mixture was stirred at r.t. for 2 h before concentrated *in vacuo* and purified by reversed-phase chromatography (ACN/H_2O with 0.05% HCl to afford the *title compound* (450 mg, yield 38.8 %) as white solid. LCMS (Method 13, ESI): 343.3 $[M+H]^+$, RT 1.202 minutes.

Step 5: *Preparation of 2-(1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*
To a stirring solution of 2-(1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)acetic acid (131 mg, 0.38 mmol, 1.0 *eq.*) in DMF (2 mL) was added *(R)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine (prepared according to the procedure of Intermediate 1)* (100 mg, 0.38 mmol, 1.0 *eq.*) and PyBOP (295 mg, 0.57 mmol, 1.5 *eq.*). Then the DIPEA (147 mg, 1.13 mmol, 3.0 *eq.*) was added dropwise. The reaction mixture was stirred at r.t. for 2 h. LCMS showed the reaction was completed. Reaction mixture was concentrated *in vacuo* and purified by reversed-phase chromatography (ACN/H_2O with 0.06% $NH_3.H_2O$) to afford the *title compound* as a white solid (120 mg, yield 35.9 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.01 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.38-7.31 (m, 2H), 7.20-7.01 (m, 4H), 6.87 (dd, *J* = 9.2, 0.8 Hz, 1H), 4.41-4.34 (m, 1H), 3.80-3.73 (m, 2H), 3.57-3.36 (m, 4H), 3.02-2.93 (m, 1H), 2.77-2.62 (m, 5H), 2.33-2.25 (m, 5H), 2.08-2.07 (m, 1H), 0.92 (d, *J* = 12.0 Hz, 6H). LCMS (Method 15, ESI): 588.0 $[M+H]^+$, RT 0.908 minutes.

EXAMPLE 7: *2-(4-(2-methylbenzyl)thiomorpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*



Step 1: *Preparation of 2-(thiomorpholin-2-yl)acetonitrile*

To a solution of *tert*-butyl 2-(cyanomethyl)thiomorpholine-4-carboxylate (220 mg, 0.91 mmol, 1.0 *eq.*) in anhydrous DCM (3 mL) was added HCl/Dioxane (4M, 3 mL, 12.0 mmol). The reaction mixture was stirred at r.t. for 2 h before concentrated *in vacuo* to afford the *title compound* (180 mg, crude), which was used without further purification. LCMS (Method 19, ESI): 143.2 $[M+H]^+$, RT 0.453 minutes.

Step 2: *Preparation of 2-(4-(2-methylbenzyl)thiomorpholin-2-yl)acetonitrile*

To a solution of 2-(thiomorpholin-2-yl)acetonitrile (180 mg, 1.26 mmol, 1.0 *eq.*) and DIPEA (818 mg, 6.33 mmol, 5.0 *eq.*) in DMF (5 mL) was added 1-(bromomethyl)-2-methylbenzene (352 mg, 1.89 mmol, 1.5 *eq.*). The reaction mixture was stirred at 40 °C for 2 h before quenched with saturated aqueous ammonium chloride, extracted with EtOAc (x3). The combined organic phase was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0-40% EtOAc in PE) to afford the *title compound* (170 mg, yield 54.5 %). LCMS (Method 19, ESI): 247.1 $[M+H]^+$, RT 1.317 minutes. ^1H NMR (400 MHz, DMSO-*d6)* δ 7.21 (d, *J* = 6.4 Hz, 1H), 7.13 (m, 3H), 3.47-3.39 (m, 2H), 3.13-3.08 (m, 1H), 2.90-2.86 (m, 2H), 2.80-2.74 (m, 2H), 2.59-2.53 (m, 4H), 2.30 (s, 3H).

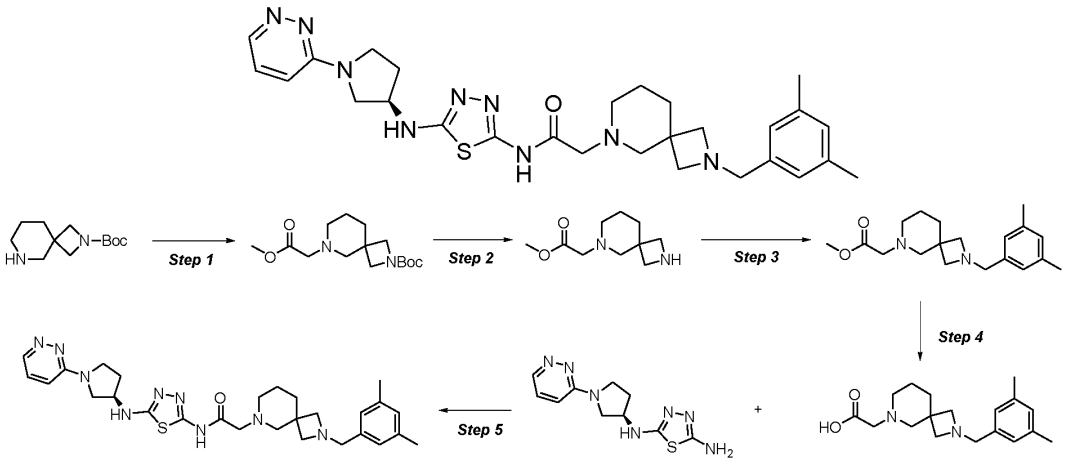
Step 3: *Preparation of 2-(4-(2-methylbenzyl)thiomorpholin-2-yl)acetic acid*

To a mixture of 2-(4-(2-methylbenzyl)thiomorpholin-2-yl)acetonitrile (170 mg, 0.69 mmol, 1.0 *eq.*) in EtOH (3 mL) and H_2O (3 mL) was added KOH (39 mg, 1.38 mmol, 2.0 *eq.*). The resulting mixture was stirred at 100 °C for 16 h before concentrated in vacuo and purified by reversed-phase chromatography (ACN/H_2O with 0.01% HCl) to afford the *title compound* (100 mg, yield 54.6 %) as a white solid. LCMS (Method 19, ESI): 266.1 $[M+H]^+$, RT 1.043 minutes..

Step 4: *Preparation of 2-(4-(2-methylbenzyl)thiomorpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*

To a stirring solution of 2-(4-(2-methylbenzyl)thiomorpholin-2-yl)acetic acid (100 mg, 0.38 mmol, 1.0 *eq.*) in DMF (3 mL) was added *(R)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine (prepared according to the procedure of Intermediate 1)* (100 mg, 0.38 mmol, 1.0 *eq.*) and PyBOP (295 mg, 0.57 mmol, 1.5 *eq.*). Then the DIPEA (147 mg, 1.13 mmol, 3.0 *eq.*) was added dropwise, and the reaction mixture was stirred at r.t. for 2 h. Reaction mixture was concentrated in vacuo and purified by reversed-phase chromatography (ACN/H_2O with 0.06% $NH_3.H_2O$) to afford the *title compound* (24.26 mg, yield 12.6 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 8.48 (d, *J* =4.4 Hz, 1H), 7.62 (d, *J* =6.0 Hz, 1H), 7.33 (dd, *J* =8.8, 4.0 Hz, 1H), 7.21-7.20 (m, 1H), 7.12-7.08 (m, 3H), 6.87 (d, *J* =8.8 Hz, 1H), 4.40-4.37 (m, 1H), 3.78-3.73 (m, 1H), 3.59-3.49 (m, 3H), 3.42 (s, 2H), 3.20-3.19 (m, 1H), 2.80-2.67 (m, 3H), 2.62-2.54 (m, 4H), 2.46-2.42 (m, 1H), 2.32-2.27 (m, 4H), 2.11-2.04 (m, 1H). LCMS (Method 13, ESI): 511.3 $[M+H]^+$, RT 1.043 minutes.

EXAMPLE 8: *(R)-2-(2-(3,5-dimethylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*



Step 1: *Preparation of tert-butyl 6-(2-methoxy-2-oxoethyl)-2,6-diazaspiro[3.5]nonane-2-carboxylate*

To a mixture of *tert*-butyl 2,6-diazaspiro[3.5]nonane-2-carboxylate (200 mg, 0.88 mmol, 1.0 *eq.*) and DIPEA (229 mg,1.77 mmol, 2.0 *eq.*) in anhydrous ACN (4 mL) was added methyl 2-bromoacetate (203 mg, 1.33 mmol, 1.5 *eq.*) at 0 °C. The resulting mixture was stirred at 40 °C for 2 h under argon and then quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography

(silica, 0-30% EtOAc in PE) to afford the *title compound* (250 mg, yield 95.4%) as a yellow oil. No mass signal was detected by LCMS.

Step 2: *Preparation of methyl 2-(2,6-diazaspiro[3.5]nonan-6-yl)acetate*

To a solution of *tert*-butyl 6-(2-methoxy-2-oxoethyl)-2,6-diazaspiro[3.5]nonane-2-carboxylate (250 mg, 0.84 mmol, 1.0 *eq.*) in DCM was added TFA ((3 mL). The resulting mixture was stirred at r.t. for 2 h under argon. The reaction mixture was concentrated *in vacuo* to afford the *title compound* (167 mg, yield 100%) without further purification. No mass signal was detected by LCMS.

Step 3: *Preparation of methyl 2-(2-(3,5-dimethylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)acetate*

To a mixture of methyl 2-(2,6-diazaspiro[3.5]nonan-6-yl)acetate (167 mg, 0.84 mmol, 1.0 *eq.*) and TEA (255 mg, 2.53 mmol, 3.0 *eq.*) in DCM was added 3,5-dimethylbenzaldehyde (169 mg, 1.26 mmol, 1.5 *eq.*), and the resulting mixture was stirred at r.t. for 2 h under argon. STAB (533 mg, 2.53 mmol, 3.0 *eq.*) was then added, and the resulting mixture was stirred at r.t. for 2 h. The reaction mixture was quenched with saturated aqueous ammonium chloride at 0°C and extracted with EtOAc (x3). The combined organic phase was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0-5% MeOH in DCM) to afford the *title compound* (310 mg, yield 99.9%) as light yellow solid. LCMS (Method 13, ESI): 317.2 $[M+H]^+$, RT 1.083 minutes.

Step 4: *Preparation of 2-(2-(3,5-dimethylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)acetic acid*

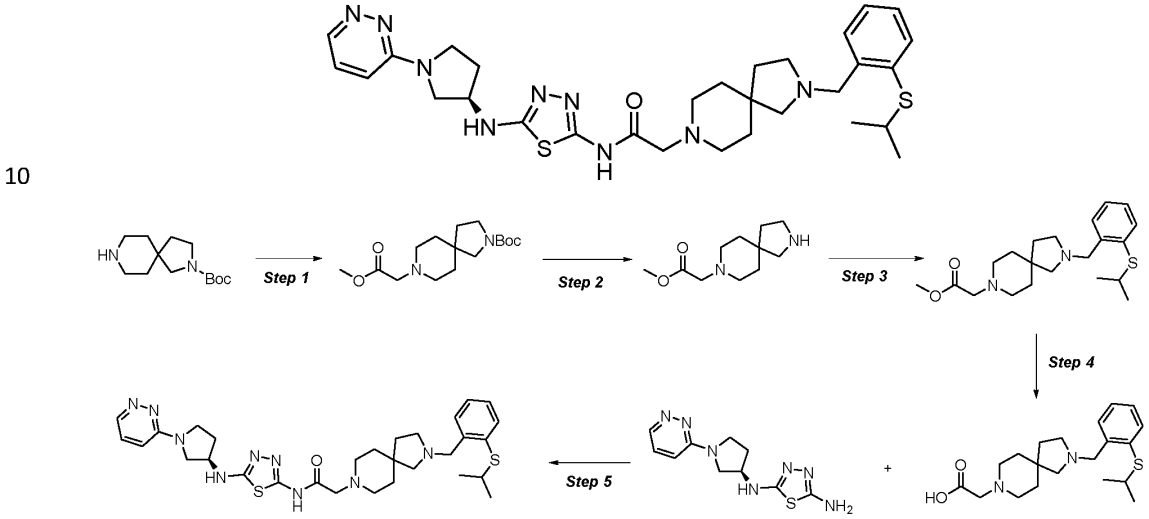
To a stirred solution of methyl 2-(2-(3,5-dimethylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)acetate (310 mg, 0.98 mmol, 1.0 *eq.*) in MeOH/THF/Water (1/1/1) was added LiOH (83 mg, 1.96 mmol, 2.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was purified by reversed-phase chromatography (30% ACN/H_2O with 0.01% HCl) to afford the *title compound* (200 mg, yield 67.3%) as a yellow oil. LCMS (Method 13, ESI): 303.3 $[M+H]^+$, RT 1.044 minutes.

Step 5: *Preparation of (R)-2-(2-(3,5-dimethylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*

A solution of 2-(2-(3,5-dimethylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)acetic acid (69 mg, 0.23 mmol, 1.0 *eq.*), *(R)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine (Intermediate 1)* (66 mg, 0.25 mmol, 1.1 *eq.*) in anhydrous DMF was added PyBOP (238 mg, 0.45 mmol, 2.0 *eq.*) and DIPEA (89 mg, 0.68 mmol, 3.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h before purified by reversed phase chromatography (30% ACN/H_2O with 0.01% FA) to afford the crude product, which was further purified by reversed phase chromatography (50% ACN/H_2O with 0.1% $NH_3.H_2O$) and lyophilised with CH_3CN/H_2O to afford the *title compound*

(18.12 mg, yield 14.5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.67 (d, *J* = 5.6 Hz, 1H), 7.33 (dd, *J* = 9.6, 5.6 Hz, 1H), 6.88-6.83 (m, 4H), 4.40-4.38 (m, 1H), 3.78-3.74 (m, 1H), 3.59-3.56 (m, 2H), 3.52-3.49 (m, 1H), 3.47 (s, 2H), 3.22 (s, 2H), 2.98 (d, *J* = 6.8 Hz, 2H), 2.80 (d, *J* = 6.8 Hz, 2H), 2.53 (s, 2H), 2.38 (s, 2H), 2.32-2.25 (m, 1H), 2.22 (s, 6H), 2.09-2.08 (m, 1H), 1.47 (d, *J* = 8.4 Hz, 4H). LCMS (Method 21, ESI): 548.2 $[M+H]^+$, RT 1.567 minutes.

EXAMPLE 9: (*R*)-2-(2-(2-(isopropylthio)benzyl)-2,8-diazaspiro[4.5]decan-8-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide



Step 1: *Preparation of tert-butyl 8-(2-methoxy-2-oxoethyl)-2,8-diazaspiro[4.5]decane-2-carboxylate*

To a mixture of *tert*-butyl 2,6-diazaspiro[3.5]nonane-2-carboxylate (300 mg, 1.25 mmol, 1.0 *eq.*) and DIPEA (323 mg, 2.50 mmol, 2.0 *eq.*) in anhydrous ACN was added methyl 2-bromoacetate (287 mg, 1.87 mmol, 1.5 *eq.*) at 0 °C. The resulting mixture was stirred at 40 °C for 2 h under argon and then quenched with saturated aqueous ammonium chloride, extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0-30% EtOAc in PE) to afford the *title compound* (220 mg, yield 52.3%) as a yellow oil. No mass signal was detected by LCMS.

Step 2: *Preparation of methyl 2-(2,8-diazaspiro[4.5]decan-8-yl)acetate*

To a solution of *tert*-butyl 6-(2-methoxy-2-oxoethyl)-2,6-diazaspiro[3.5]nonane-2-carboxylate (220 mg, 0.70 mmol, 1.0 *eq.*) in DCM was added TFA (3 mL). The resulting mixture was stirred at r.t. for 2 h under argon. The reaction mixture was concentrated *in vacuo* to afford the *title*

compound (150 mg, yield 100%) as yellow oil without further purification. No mass signal was detected by LCMS.

Step 3: *Preparation of methyl 2-(2-(2-(isopropylthio)benzyl)-2,8-diazaspiro[4.5]decan-8-yl)acetate*

A mixture of methyl 2-(2,6-diazaspiro[3.5]nonan-6-yl)acetate (150 mg, 0.71 mmol, 1.0 *eq.*) and TEA (215 mg, 2.12 mmol, 3.0 *eq.*) in DCM was added 3,5-dimethylbenzaldehyde (190 mg, 0.71 mmol, 1.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h under argon before the addition of STAB (450 mg, 2.12 mmol, 3.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h and then quenched with saturated aqueous ammonium chloride at 0°C, extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 0-5% MeOH in DCM) to afford the *title compound* (320 mg, yield 99.5%) as a light yellow solid. LCMS (Method 13, ESI): 378.2 $[M+H]^+$, RT 1.108 minutes.

Step 4: *Preparation of 2-(2-(2-(isopropylthio)benzyl)-2,8-diazaspiro[4.5]decan-8-yl)acetic acid*

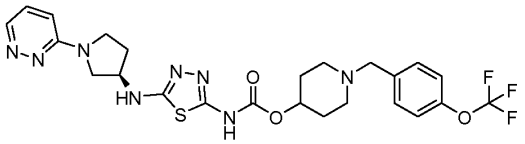
To a stirred solution of the *methyl 2-(2-(3,5-dimethylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)acetate* (320 mg, 0.85 mmol, 1.0 *eq.*) in MeOH/THF/Water (1/1/1) was added lithium hydroxide (72 mg, 1.70 mmol, 2.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was purified by reversed-phase flash chromatography (C-120 g, ACN%=30%, +0.1% HCl) to afford the *title compound* (200 mg, yield 64.7%) as white solid. LCMS (Method 13, ESI): 363.3 $[M+H]^+$, RT 1.091 minutes.

Step 5: *Preparation of (R)-2-(2-(2-(isopropylthio)benzyl)-2,8-diazaspiro[4.5]decan-8-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*

A solution of 2-(2-(3,5-dimethylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)acetic acid (83 mg, 0.23 mmol, 1.0 *eq.*), (R)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine *(prepared according to the procedure of Intermediate 1)* (66 mg, 0.25 mmol, 1.1 *eq.*) in anhydrous DMF was added PyBOP (238 mg, 0.45 mmol, 2.0 *eq.*) and DIPEA (89 mg, 0.68 mmol, 3.0 *eq.*). The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was purified by reversed phase chromatography (30% ACN/H_2O with 0.1% FA) to afford the crude product, which was further purified by reversed-phase chromatography (50% ACN/H_2O with 0.1% HCl) and lyophilised with CH_3CN/H_2O to afford the *title compound*. (35.21 mg, yield 25 %) as a white solid. ^1H NMR (400 MHz, DMSO-d6) δ 11.37 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.43-7.38 (m, 2H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.24-7.19 (m, 2H), 6.87 (dd, *J* = 8.4, 1.2 Hz, 1H), 4.39-4.38 (m, 1H), 3.77-3.73 (m, 1H), 3.63 (s, 2H), 3.58-3.55 (m, 2H), 3.52-3.45 (m, 3H), 3.18 (s,

2H), 2.43-2.37 (m, 4H), 2.32-2.27 (m, 4H), 2.11-2.04 (m, 1H), 1.55-1.47 (m, 6H), 1.21 (d, *J* = 6.4 Hz, 6H). LCMS (Method 13, ESI): 608.4 $[M+H]^+$, RT 1.056 minutes.

EXAMPLE 10: *1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidine-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamate*



To a stirred solution of 4-nitrophenyl 1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl carbonate *(*prepared according to the procedure of *Intermediate 14)* (110 mg, 0.18 mmol, 1 *eq.*) in DMF (4.2 mL), was added (R)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine *(*prepared according to the procedure of *Intermediate 1)* (52 mg, 0.19 mmol, 1.1 *eq.*) followed by DIPEA (60 µL, 0.35 mmol, 2 *eq.*). The reaction mixture was stirred at r.t. for 48 h. The mixture was concentrated *in vacuo* and purified by preparative HPLC (mobile phases: ACN, H_2O + 0.05% NH_3) to afford the *title compound* (10 mg, 10% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.49 (bs, 1H), 8.47 (d, *J* = 4.2 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.46 – 7.38 (m, 2H), 7.37 – 7.27 (m, 3H), 6.86 (d, *J* = 9.1 Hz, 1H), 4.72 – 4.61 (m, 1H), 4.40 – 4.29 (m, 1H), 3.73 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61 – 3.45 (m, 5H), 2.69 – 2.60 (m, 2H), 2.29 – 2.15 (m, 3H), 2.11 – 2.00 (m, 1H), 1.93 – 1.82 (m, 2H), 1.68 – 1.53 (m, 2H). LCMS (An analogous method to Method 7, ESI) 254 nm: 565.30 $[MH]^+$, RT 2.83 min; 205 nm: 565.20 $[MH]^+$, RT 2.83 min.

Example 11 was prepared from *Intermediate 1 and Intermediate 5* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 12 was prepared from *Intermediate 1, Intermediate 6* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 15 was prepared from *Intermediate 1, Intermediate 7* in accordance with *General Procedure 1 with T3P as the amide coupling reagent.*

Example 16 was prepared from *Intermediate 1, Intermediate 8* in accordance with *General Procedure 1 with T3P as the amide coupling reagent.*

Example 17 was prepared from *Intermediate 1, (3R)-1-Boc-piperidine-3-carboxylic acid* and *4-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 18 was prepared from *Intermediate 1, (3S)-1-Boc-piperidine-3-carboxylic acid* and *4-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 19 was prepared from *Intermediate 1, (3S)-1-Boc-piperidine-3-carboxylic acid* and *3-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 20 was prepared from *Intermediate 1, (3R)-1-Boc-piperidine-3-carboxylic acid* and *3-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 21 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *3-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 22 was prepared from *Intermediate 1, 2-[1-(tert-butoxycarbonyl)piperidin-4-yl]propanoic acid* and *4-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 23 *and* **Example 24** were prepared from **Example 22** with Chiral-Chromatography purification conditions: Column: REGIS (S,S)WHELK-O1: 250*25 mm 10 μm; Mobile Phase A: n-Hexane; Mobile Phase B: EtOH (+0.1% 7.0 mol/L ammonia in MeOH); Flow rate: 40 ml/min.

Example 25 was prepared from *Intermediate 1, (R)-(N-Boc-piperidin-3-yl)acetic acid* and *4-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 26 was prepared from *Intermediate 1, (R)-(N-Boc-piperidin-3-yl)acetic acid* and *3-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 27 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *4-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 28 was prepared from *Intermediate 1, 2-[1-(tert-butoxycarbonyl)piperidin-4-yl]propanoic acid* and *3-(bromomethyl)-5-(trifluoromethyl) pyridine* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 29 was prepared from *Intermediate 1, Intermediate 10* and *4-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 30 was prepared from *Intermediate 1, 2-{4-[(tert-butoxy)carbonyl]-1,4-diazepan-1-yl}acetic acid and 4-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 31 was prepared from *Intermediate 1* and *Intermediate 11* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 32 was prepared from *Intermediate 1* and *Intermediate 12* in accordance with *General Procedure 1 with T3P as the amide coupling reagent.*

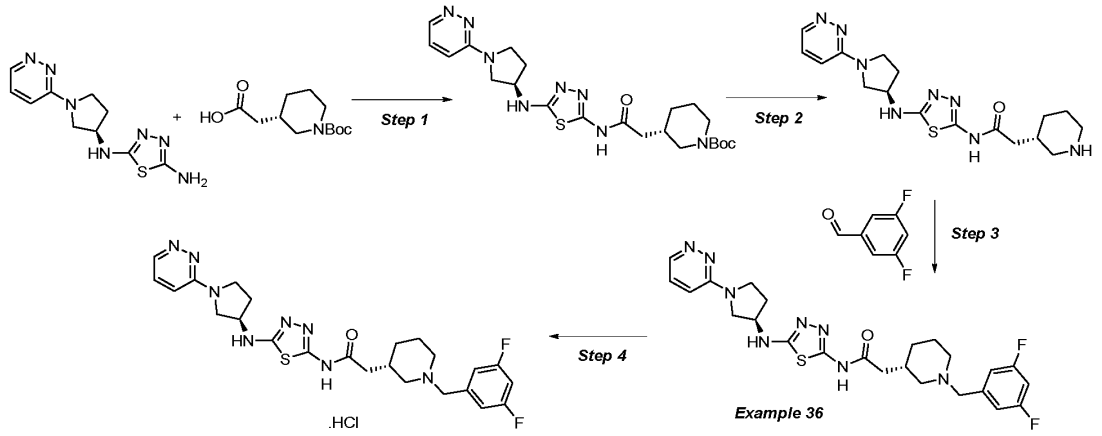
Example 33 was prepared from *Intermediate 1* and *Intermediate 13* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 34 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *2-(chloromethyl)-6-methyl-4-(trifluoromethyl) pyridine* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 35 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *3,5-dimethylbenzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 36 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid and 3,5-difluorobenzyl bromide* in accordance with *General Procedure 2B with HATU as the amide coupling reagent.*

The HCl salt of *Example 36* was synthesised in the following route:



Step 1: *tert-butyl (S)-3-(2-oxo-2-((5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)piperidine-1-carboxylate*

To a stirred solution of (*S*)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid (12.0 g, 49.3 mmol, 1.0 *eq.*) in DMF (240 mL) was added (R)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine (prepared according to the procedure of *Intermediate 1)* (12.9 g, 49.3 mmol, 1.0 *eq.*) and PyBOP (38.4 g, 73.9 mmol, 1.5 *eq.*). Then the DIPEA (28.1 g, 147.9 mmol, 3 *eq.*) was dropwise added. The reaction mixture was stirred at r.t. for 2 h before the reaction was completed. The reaction mixture was added to iced water, extracted with EtOAC and washed with brine. The organic was concentrated *in vacuo* and purified by flash chromatography (silica, DCM: MeOH= 10:1, V/V). The resulting compound was then recrystallised three times with PE and PE:EA=10:1 to afford the *title compound* (24.0 g, 49.1 mmol, 99.4% yield) as a purple solid.

LCMS (ESI): 489.3[M+H]$^+$, RT 1.417 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.48 (d, *J* = 4.0 Hz, 1H), 7.63 (d, *J* = 5.5 Hz, 1H), 7.35 (dd, *J* = 9.0, 4.3 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 4.39 (s, 1H), 3.78-3.73 (m, 1H), 3.60 – 3.49 (m, 3H), 3.01 (d, *J* = 3.7 Hz, 1H), 2.82 (s, 1H), 2.29 (d, *J* = 11.0 Hz, 4H), 2.08 (d, *J* = 5.4 Hz, 1H), 1.85 (s, 1H), 1.73 (s, 3H), 1.56 (s, 1H), 1.36 (s, 9H), 1.17 (s, 1H).

Step 2: *2-((S)-piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*

To a stirred solution of *tert*-butyl (*S*)-3-(2-oxo-2-((5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)piperidine-1-carboxylate (24.0 g, 49.1 mmol, 1.0 *eq.*) in MeOH (1 L) was added HCl/Dioxane (185 mL, 736.5 mmol, 15 *eq.*). The reaction mixture was stirred at r.t. for 4 h before the reaction was completed. The reaction mixture was concentrated in vacuo to afford the *title compound* (19.0 g, 48.8 mmol, 99.5% yield) as a brown solid. LCMS (ESI): 389.2 [M+H]$^+$, RT 1.055 minutes.

Step 3: *2-((S)-1-(3,5-difluorobenzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide* ***(Example 36)***

To a stirred solution of 2-((*S*)-piperidin-3-yl)-N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide (8.5 g, 21.8 mmol, 1.0 *eq.*) in DCE (300 mL) was added TEA (11.0 g, 109 mmol, 5 *eq.*) and 3,5-difluorobenzaldehyde (6.2 g, 43.6 mmol, 2.0 *eq.*). Then the reaction mixture was stirred at r.t. for 30 min followed by addition of STAB (40.0 g, 174.4 mmol, 8 *eq.*). The reaction mixture was stirred at r.t. for 16 h before the reaction was completed. Reaction mixture was concentrated *in vacuo* and then re-dissolved in DCM and 1:1 mixture of H_2O and saturated sodium bicarbonate solution. The mixture was stirred for 15 min and phases were separated, and the aqueous phase was extracted with DCM. Combined organic phases were washed with H_2O and brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. Recrystallisation three times with Et_2O afforded the *title compound* (6.0 g, 11.6 mmol, 53.4% yield) as a yellow solid. LCMS (ESI): 515.4 [M+H]$^+$, RT 5.209 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.48 (dd, *J* = 4.4, 1.1 Hz, 1H), 7.62 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.09-6.97 (m, 3H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.42-4.35 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61-3.53 (m, 2H), 3.48 (ddd, *J* = 30.6, 15.4, 8.7 Hz, 3H), 2.64 (dd, *J* = 26.3, 9.5 Hz, 2H), 2.37-2.26 (m, 3H), 2.12-1.94 (m, 3H), 1.78 (t, *J* = 10.1 Hz, 1H), 1.61 (dd, *J* = 18.1, 7.9 Hz, 2H), 1.52-1.40 (m, 1H), 0.98 (dd, *J* = 20.1, 9.9 Hz, 1H).

Step 4: *2-((S)-1-(3,5-difluorobenzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide hydrochloride* ***(Example 36 HCl salt)***

To a stirring solution of *Example 36* (3.0 g, 5.82 mmol, 1.0 *eq.*) in MeOH/DCM (30/10 mL) was added HCl/Dioxane (2.2 mL, 8.73 mmol, 1.5 *eq.*). The reaction mixture was stirred at r.t. for 2 h. The mixture was concentrated *in vacuo* and then lyophilised with MeOH/H_2O to afford the *title compound* (3.2 g, 5.82 mmol, 100% yield) as a yellow solid. LCMS (ESI): 515.3 $[M+H]^+$, RT 5.227 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 10.98 (s, 1H), 8.50 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.72 (d, *J* = 6.0 Hz, 1H), 7.40 (dt, *J* = 19.9, 9.9 Hz, 4H), 6.99 (d, *J* = 9.1 Hz, 1H), 4.43-4.21 (m, 3H), 3.77 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.59 (dd, *J* = 11.9, 5.9 Hz, 2H), 3.53 (dd, *J* = 11.2, 3.5 Hz, 1H), 3.17 (s, 2H), 2.82-2.56 (m, 2H), 2.42-2.26 (m, 4H), 2.13-2.06 (m, 1H), 1.85-1.67 (m, 3H), 1.13 (s, 1H).

Example 37 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *3-(difluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 38 was prepared from *Intermediate 1* and *Intermediate 15* in accordance with *General Procedure 1 with HATU as the amide coupling reagent*.

Example 39 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *3-(chloromethyl)benzoic acid* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 40 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *4-(chloromethyl)benzoic acid* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 41 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *Intermediate 16* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 42 was prepared from *Intermediate 1, Intermediate 13 and PyBOP* in accordance with *General Procedure 1*.

Example 43 was prepared from *Intermediate 1, 2-(1-(t-butoxycarbonyl)piperidin-4-yl)acetic acid* and *4-(difluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 44 was prepared from *Intermediate 1, (R)-N-Boc-3-pyrrolidineacetic acid* and *3-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with HATU as the amide coupling reagent.*

Example 45 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *Intermediate 18* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 46 was prepared from *Intermediate 1, 2-[(3S)-1-tert-butoxycarbonylpyrrolidin-3-yl]acetic acid* and *3-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with HATU as the amide coupling reagent.*

Example 47 was prepared from *Intermediate 1, Intermediate 19* and *3-(bromomethyl)-5-(trifluoromethyl)pyridine* in accordance with *General Procedure 2B with HATU as the amide coupling reagent.*

Example 48 was prepared from *Intermediate 1, Intermediate 19* and *Intermediate 20* in accordance with *General Procedure 2B with HATU as the amide coupling reagent.*

Example 49 was prepared from *Intermediate 1, Intermediate 23, HATU and 3-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with HATU as the amide coupling reagent.*

Example 50 was prepared from *Intermediate 1, Intermediate 23 and 4-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with HATU as the amide coupling reagent.*

Example 51 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *3-chlorobenzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 52 was prepared from *Intermediate 1, 2-{6-[(tert-butoxy)carbonyl]-6-azaspiro[3.4]octan-2-yl}acetic acid* and *3-(difluoromethoxy) benzyl bromide* in accordance with *General Procedure 2B with HATU as the amide coupling reagent.*

Example 53 was prepared from *Intermediate 1* and *Intermediate 25* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 54 was prepared from *Intermediate 1* and *Intermediate 26* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 55 was prepared from *Intermediate 1, 2-(1-(t-butoxycarbonyl)piperidin-4-yl)acetic acid,* and *5-(bromomethyl)-1,1,3,3-tetramethylcyclo hexane* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 56 was prepared from *Intermediate 1, 2-{2-[(tert-butoxy)carbonyl]-2-azaspiro[3.3]heptan-6-yl}acetic acid* and *3-(difluoromethoxy) benzyl bromide* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 57 was prepared from *Intermediate 1, 2-(1-(t-butoxycarbonyl)piperidin-4-yl)acetic acid* and *4-(bromomethyl)-1,1-dimethylcyclohexane* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 58 was prepared from *Intermediate 1, 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)propanoic acid* and *3-(difluoromethoxy)benzyl bromide* in accordance with *General Procedure 2B with HATU as the amide coupling reagent.*

Example 59 was prepared from *Intermediate 1, 8-(tert-butoxycarbonyl)-2-oxa-8-azaspiro[4.5]decane-3-carboxylic acid* and *3-(trifluoromethoxy) benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 60 was prepared from *Intermediate 1* and *Intermediate 27* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 61 was prepared from *Intermediate 1* and *Intermediate 28* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 62 was prepared from *Intermediate 1* and *Intermediate 29* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 63 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *2-chlorobenzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 64 was prepared from *Intermediate 1* and *Intermediate 30* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 65 and **Example 66** were prepared from **Example 64** by chiral SFC in accordance w*ith General Procedure 5B.*

Example 67 was prepared from *Intermediate 1* and *Intermediate 31* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 68 and **Example 69** were prepared from **Example 67** by chiral SFC in accordance with *General Procedure 5E*.

Example 70 was prepared from *Intermediate 1, thiomorpholine-2,4-dicarboxylic acid 4-tert-butyl ester* and *4-(bromomethyl)-1,1-dimethylcyclohexane* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 71 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)morpholin-2-yl)acetic acid* and *4-(bromomethyl)-1,1-dimethylcyclohexane* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 72 and **Example 73** were prepared from **Example 71** by chiral SFC in accordance with *General Procedure 5F*.

Example 74 was prepared from *Intermediate 1, 2-(1-(t-butoxycarbonyl)piperidin-4-yl)acetic acid* and *3-(propan-2-yloxy)pyridine-2-carbaldehyde* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 75 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)azetidin-3-yl)acetic acid* and *3-(trifluoromethoxy)benzyl bromide* in accordance with *General Procedure 3C with T3P as the amide coupling reagent.*

Example 76 was prepared from *Intermediate 1, 2-(1-(t-butoxycarbonyl)piperidin-4-yl)acetic acid* and *2-(difluoromethoxy)benzaldehyde* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 77 was prepared from *Intermediate 1, 2-{4-[(tert-butoxy)carbonyl]-4-azaspiro[2.5]octan-7-yl}acetic acid* and *3-(propan-2-yloxy)pyridine-2-carbaldehyde* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 78 was prepared from *Intermediate 1* and *Intermediate 32* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 79 was prepared from *Intermediate 1, 2-{2-[(tert-butoxy)carbonyl]-6-oxa-2-azaspiro[3.4]octan-7-yl}acetic acid* and *3-(trifluoromethoxy) benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 80 and **Example 81** were prepared from **Example 79** and separated by chiral SFC in accordance with *General Procedure 5E.*

Example 82 was prepared from *Intermediate 1, 2-{2-[(tert-butoxy)carbonyl]-6-oxa-2-azaspiro[3.4]octan-7-yl}acetic acid* and *3-(difluoromethoxy) benzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 83 was prepared from *Intermediate 1, 2-{1-[(tert-butoxy)carbonyl]-2,2-dimethylpiperidin-4-ylacetic acid* and *3-(propan-2-yloxy)pyridine -2-carbaldehyde* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 84 was prepared from *Intermediate 1, 2-{2-[(tert-butoxy)carbonyl]-6-oxa-2-azaspiro[3.4]octan-7-yl}acetic acid* and *2-(cyclopentyloxy) benzaldehyde* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 85 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *Intermediate 33* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 86 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *2-(cyclopentyloxy)benzaldehyde* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 87 was prepared from *Intermediate 1, Intermediate 33* and *Intermediate 34* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 88 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)morpholin-2-yl)acetic acid* and *cyclohexanone* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 89 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *Intermediate 35* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 90 was prepared from *Intermediate 1, N-Boc-2-(2-morpholinyl)acetic acid* and *cyclopentanone* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 91 was prepared from *Intermediate 1, 2-{2-[(tert-butoxy)carbonyl]-6-oxa-2-azaspiro[3.4]octan-7-yl}acetic acid* and *Intermediate 36* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 92 was prepared from *Intermediate 1* and *Intermediate 37* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 93 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)-4-hydroxypiperidin-4-yl)acetic acid* and *Intermediate 36* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 94 was prepared from *Intermediate 1, 2-{4-[(tert-butoxy)carbonyl]-1,4-diazepan-1-yl}acetic acid* and *4-(bromomethyl)-1,1-dimethyl cyclohexane* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 95 was prepared from *Intermediate 1, Intermediate 22* and *3-tert-butyl-1,2-oxazole-5-carbaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 96 was prepared from *Intermediate 1, 2-{2-[(tert-butoxy)carbonyl]-6-oxa-2-azaspiro[3.4]octan-7-yl}acetic acid* and *4,4-dimethylcyclo hexane-1-carbaldehyde* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 97 and **Example 98**were separated from **Example 96** by chiral SFC in accordance with *General Procedure 5D*.

Example 99 was prepared from *Intermediate 1* and *Intermediate 38* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 100 and **Example 101** were prepared from **Example 99** and separated by chiral SFC in accordance with *General Procedure 5G*.

Example 102 was prepared from *Intermediate 1, 2-({1-[(tert-butoxy)carbonyl]piperidin-3-yl}oxy)acetic acid* and *2-(methylthio)benzaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example and **Example 104** were separated from **Example 102** by chiral SFC in accordance with *General Procedure 5G*.

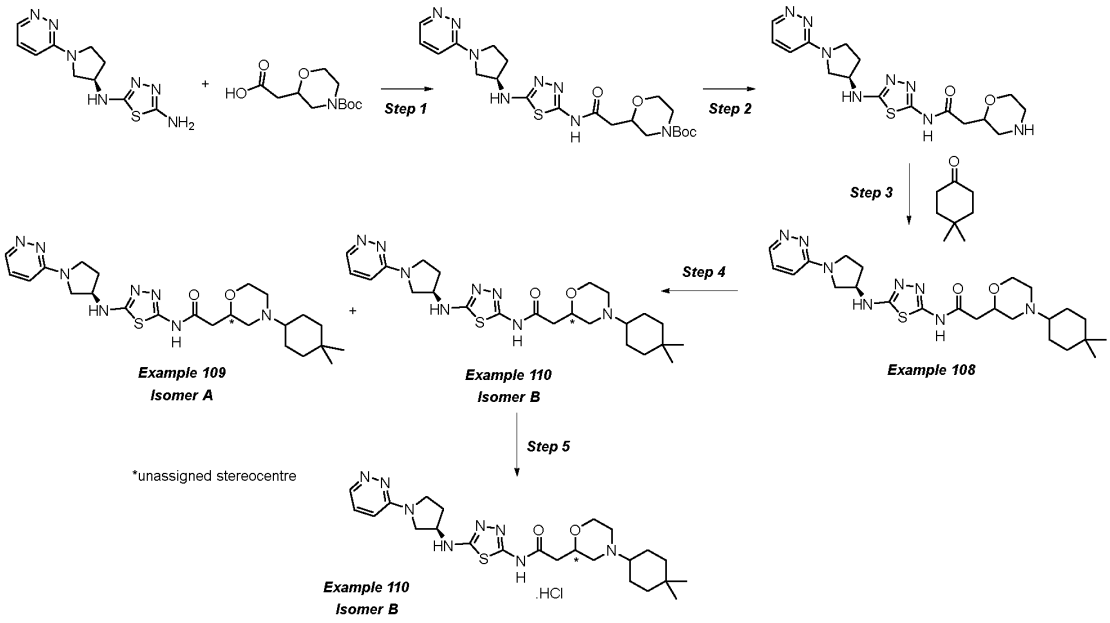
Example 105 was prepared from *Intermediate 1, 2-({1-[(tert-butoxy)carbonyl]piperidin-3-yl}oxy)acetic acid* and *Intermediate 36* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 106 and **Example 107** were prepared from **Example 105** by chiral SFC in accordance with *General Procedure 5B*.

Example 108 was prepared from *Intermediate 1, 2-carboxymethyl-morpholine-4-carboxylic acid tert-butyl ester* and *4,4-dimethylcyclohexanone* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 109 and **Example 110** were prepared from **Example 108** by chiral SFC in accordance with *General Procedure 5B.*

The HCl salt of *Example 110* was synthesised in the following route:



Step 1: *tert-butyl 2-(2-oxo-2-((5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)morpholine-4-carboxylate*

To a stirring solution of 2-(4-(*tert*-butoxycarbonyl)morpholin-2-yl)acetic acid (12.5 g, 51.0 mmol, 1.0 *eq.*) in DMF (240 mL) was added (R)-N^2-(1-(pyridazin-3-yl)pyrrolidin-3-yl)-1,3,4-thiadiazole-2,5-diamine (prepared according to the procedure of *Intermediate 1)* (12.4 g, 51.0 mmol, 1.0 *eq.*) and PyBOP (39.8 g, 76.5 mmol, 1.5 *eq.*). Then the DIPEA (29.1 g, 153 mmol, 3 *eq.*) was dropwise added. The reaction mixture was stirred at rt. for 2 h before reaction was completed. The reaction mixture was added to ice water, extracted with EtOAc and washed with brine. The organics were combined, concentrated *in vacuo* and the crude was purified flash chromatography (silica, DCM: MeOH= 10:1, V/V). Recrystallisation three times with PE and PE:EA=10:1 afforded the *title compound* (24.9 g, 50.7 mmol, 99.4% yield) as a purple solid. LCMS (ESI): 491.2 $[M+H]^+$, RT 1.350 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.01 (s, 1H), 8.49 (d, *J* = 3.9 Hz, 1H), 7.65 (d, *J* = 6.0 Hz, 1H), 7.35 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.91 (dd, *J* = 9.1, 0.9 Hz, 1H), 4.38 (dt, *J* = 10.1, 5.1 Hz, 1H), 3.84 (d, *J* = 11.7 Hz, 1H), 3.79-3.66 (m, 4H), 3.54 (ddd, *J* = 13.9, 11.9, 5.2 Hz, 3H), 3.36 (dd, *J* = 11.5, 8.9 Hz, 2H), 2.88 (d, *J* = 12.7 Hz, 1H), 2.58 (dd, *J* = 6.2, 3.3 Hz, 2H), 2.30 (td, *J* = 13.6, 7.8 Hz, 1H), 2.08 (td, *J* = 11.7, 5.3 Hz, 1H), 1.40 (s, 9H).

Step 2: *2-(morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide*

To a stirring solution of *tert*-butyl 2-(2-oxo-2-((5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)morpholine-4-carboxylate (24.9 g, 50.7 mmol, 1.0 *eq.*) in MeOH (1000 mL) was added HCl/Dioxane (190 mL, 760.5 mmol, 15 *eq.*). The reaction mixture was stirred at rt. for 4 h before the reaction was completed. The reaction mixture was concentrated *in vacuo* to afford the *title compound* (19.6 g, 50.1 mmol, 98.9% yield) as a brown solid. LCMS (ESI): 391.0 $[M+H]^+$, RT 1.000 minutes.

Step 3: *2-(4-(4,4-dimethylcyclohexyl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide* **(Example 108)**

To a stirring solution of 2-(morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide (19.6 g, 50.1 mmol, 1.0 *eq.*) in DCE (600 mL) was added TEA (25.3 g, 250.5 mmol, 5 *eq.*) and 4,4-dimethylcyclohexan-1-one (12.6 g, 100.2 mmol, 2.0 *eq.*). Then the reaction mixture was stirred at r.t. for 30 min followed by addition of STAB (85.0 g, 400.8 mmol, 8 *eq.*). The reaction mixture was stirred at r.t. for 16 h before the reaction was completed. The reaction mixture was concentrated *in vacuo* and re-dissolved in DCM and 1:1 mixture of H_2O and saturated sodium bicarbonate solution. The mixture was stirred for 15 min and phases were separated, and aqueous phase was extracted with DCM. Combined organic phases were washed with H_2O and brined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. Recrystallisation three times with Et_2O afforded the *title compound* (11.9 g, 23.8 mmol, 47.5% yield) as a light purple solid. LCMS (ESI): 501.4 $[M+H]^+$, RT 5.419 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (d, *J* = 3.8 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.90-6.84 (m, 1H), 4.38 (dd, *J* = 9.4, 4.8 Hz, 1H), 3.83-3.70 (m, 3H), 3.60-3.39 (m, 4H), 2.79 (d, *J* = 10.9 Hz, 1H), 2.64 (d, *J* = 10.8 Hz, 1H), 2.53 (d, *J* = 8.6 Hz, 1H), 2.25 (ddd, *J* = 31.3, 15.9, 8.4 Hz, 2H), 2.13-1.93 (m, 3H), 1.63-1.55 (m, 2H), 1.34 (dt, *J* = 25.3, 12.5 Hz, 4H), 1.21-1.01 (m, 3H), 0.87 (d, *J* = 6.4 Hz, 6H).

Step 4: *2-(4-(4,4-dimethylcyclohexyl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide Isomer A* (**Example 109**) and *2-(4-(4,4-dimethylcyclohexyl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide Isomer B* (**Example 110**)

Example 108 (11.9 g, 23.8 mmol) was separated using SFC chiral separation to afford the *title compounds*, **Example 109** (5.6 g, 11.2 mmol, 22.3% yield, ee%=100%) and **Example 110** (6.2 g, 12.4 mmol, 24.7% yield, ee%=98.9%).

SFC conditions: Vial: 2:A,5 Acq. Method Set: 15 25% MEOH DEA C3 OJ Injection #: 1 Processing Method: Chiral Hplc Injection Volume: 1.00 ul Channel Name: PDA Ch1 214nm @ 4.8nm Run Time: 8.0 Minutes Proc. Chnl. Descr.: PDA Ch1 214nm @ 4.8nm.

Example 109:
LCMS (ESI): 501.5 $[M+H]^+$, RT 5.501 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (d, *J* = 3.8 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.42-4.34 (m, 1H), 3.77 (ddd, *J* = 19.0, 13.3, 8.0 Hz, 3H), 3.61-3.38 (m, 4H), 2.78 (d, *J* = 11.0 Hz, 1H), 2.64 (d, *J* = 10.9 Hz, 1H), 2.55 (dd, *J* = 15.5, 8.5 Hz, 1H), 2.50-2.46 (m, 1H), 2.33-2.16 (m, 2H), 2.14-2.04 (m, 2H), 1.97 (t, *J* = 10.5 Hz, 1H), 1.57 (d, *J* = 11.2 Hz, 2H), 1.34 (dt, *J* = 25.1, 12.4 Hz, 4H), 1.19-1.06 (m, 2H), 0.87 (d, *J* = 6.4 Hz, 6H).

Example 110:
LCMS (ESI): 501.4 $[M+H]^+$, RT 5.478 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (dd, *J* = 4.4, 1.1 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.38 (dt, *J* = 10.2, 5.1 Hz, 1H), 3.77 (ddd, *J* = 17.1, 12.2, 6.9 Hz, 3H), 3.61-3.38 (m, 4H), 2.78 (d, *J* = 11.0 Hz, 1H), 2.64 (d, *J* = 10.8 Hz, 1H), 2.55 (dd, *J* = 14.9, 8.0 Hz, 1H), 2.50-2.46 (m, 1H), 2.34-2.16 (m, 2H), 2.13-2.04 (m, 2H), 1.97 (t, *J* = 10.5 Hz, 1H), 1.57 (d, *J* = 11.1 Hz, 2H), 1.42 – 1.27 (m, 4H), 1.14 (dd, *J* = 13.9, 10.9 Hz, 2H).

Step 5: *2-(4-(4,4-dimethylcyclohexyl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamid hydrochloride Isomer B* **(Example 110 HCl salt)**
To a stirring solution of 2-(4-(4,4-dimethylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide (1.5 g, 3.0 mmol, 1.0 *eq.*) in MeOH/DCM (10/5 mL) was added HCl/Dioxane (1.2 mL, 4.5 mmol, 1.5 *eq.*). The reaction mixture was stirred at rt. for 2 h. The mixture was concentrated *in vacuo* and then lyophilised with MeOH/H_2O to afford the *title compound* (1.4 g, 2.61 mmol, 86.9% yield) as a yellow solid.
LCMS (ESI): 501.4 $[M+H]^+$, RT 5.507 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (s, 1H), 11.09 (s, 1H), 8.48 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.70 (d, *J* = 6.0 Hz, 1H), 7.34 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.88 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.37 (tt, *J* = 29.3, 14.7 Hz, 2H), 3.93 (s, 2H), 3.76 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.64-3.44 (m, 4H), 3.07 (d, *J* = 71.2 Hz, 3H), 2.74-2.51 (m, 3H), 2.29 (dt, *J* = 13.3, 6.6 Hz, 1H), 2.09 (td, *J* = 11.9, 5.0 Hz, 1H), 1.89 (s, 2H), 1.62 (s, 2H), 1.46 (d, *J* = 12.5 Hz, 2H), 1.19 (t, *J* = 12.1 Hz, 2H), 0.90 (s, 6H).

Example 111 was prepared from *Intermediate 1* and *Intermediate 40* in accordance with *General Procedure 1 with HATU as the amide coupling reagent.*

Example 112 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *3,5-dimethylbenzyl bromide* in accordance with *General Procedure 2B with T3P as the amide coupling reagent*.

Example 113 was prepared from *Intermediate 1* and *Intermediate 41* in accordance with *General Procedure 2B with HATU as the amide coupling reagent*.

Example 114 and **Example 115** were prepared from *Intermediate 1, N-Boc-2-(2-morpholinyl)acetic acid* and *4-tert-butylcyclohexanone* in accordance with *General Procedure 2A with T3P as the amide coupling reagent*.

Example 116 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *4-ethyl-2-fluorobenzaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 117 was prepared from *Intermediate 1, N-Boc-2-(2-morpholinyl)acetic acid* and *3,3,4,4-tetramethylcyclopentan-1-one* in accordance with *General Procedure 2A with T3P as the amide coupling reagent.*

Example 118 was prepared from *Intermediate 1* and *(R)-(N-Boc-piperidin-3-yl)acetic acid* and *3,5-difluorobenzyl bromide* in accordance with *General Procedure 2B with HATU as the amide coupling reagent.*

Example 119 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *4-fluoro-3,5-dimethylbenzaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 120 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *3-fluoro-5-methylbenzaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 121 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *4-fluoro-3-methoxy-5-methylbenzaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 122 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *4-ethoxy-3,5-difluorobenzaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 123 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *3-fluoro-5-isopropoxybenzaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 124 was prepared from *Intermediate 1, 2-{3-[(tert-butoxy)carbonyl]-3-azaspiro[5.5]undecan-9-yl}acetic acid* and *5-ethyl-3-methyl-1,2-oxazole-4-carbaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 125 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *Intermediate 42* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 126 and **Example 127** were prepared from *Intermediate 1, 2-carboxymethyl-morpholine-4-carboxylic acid tert-butyl ester* and *Intermediate 43/ Intermediate 44* in accordance with *General Procedure 2B with T3P as the amide coupling reagent.*

Example 128 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *3-ethoxy-4,5-difluorobenzaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 129 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *3-fluoro-5-methoxy-4-methylbenzaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 130 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *Intermediate 45* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 131 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *2-ethyl-1-benzofuran-3-carbaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 132 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and Intermediate 46 in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 133 was prepared from *Intermediate 1, (S)-(1-Boc-piperidino)acetic acid* and *2,5-dimethyl-thiophene-3-carbaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 135 was prepared from *Intermediate 1, Intermediate 22* and *2,5-dimethyl-thiophene-3-carbaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent.*

Example 136 was prepared from *Intermediate 48* and *Intermediate 49* in accordance with *General Procedure 1 with HATU as the amide coupling reagent*.

Example 137 was prepared from *Intermediate 48, N-Boc-2-(2-morpholinyl)acetic acid* and *4,4-dimethylcyclohexanone* in accordance with *General Procedure 2A with HATU as the amide coupling reagent*.

Example 138 was prepared from *Intermediate 1, Intermediate 50* in accordance with *General Procedure 2A with HATU as the amide coupling reagent*.

Example 139 was prepared from *Intermediate 1, Intermediate 22* and *1-(tert-butyl)-1H-pyrrole-3-carbaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent*.

Example 140 was prepared from *Intermediate 1, Intermediate 22* and *1-tert-butylpyrazole-4-carbaldehyde* in accordance with *General Procedure 2A with HATU as the amide coupling reagent*.

Example 141 was prepared from *Intermediate 1* and *Intermediate 51* in accordance with *General Procedure 1 with HATU as the amide coupling reagent*.

Example 142 was prepared from *Intermediate 1* and *Intermediate 52* in accordance with *General Procedure 1 with T3P as the amide coupling reagent*.

Example 143 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)-4,4-difluoropiperidin-3-yl)acetic acid* and *spiro[2.5]octan-6-one* in accordance with *General Procedure 2A with HATU as the amide coupling reagent*.

Example 144 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)-4,4-difluoropiperidin-3-yl)acetic acid* and *cyclohexanone* in accordance with *General Procedure 2A with HATU as the amide coupling reagent*.

Example 145 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)-4,4-difluoropiperidin-3-yl)acetic acid* and *4,4-dimethylcyclohexanone* in accordance with *General Procedure 2A with HATU as the amide coupling reagent*.

Example 146 was prepared from *Intermediate 1, N-Boc-2-(2-morpholinyl)acetic acid and 4,4-diethylcyclohexan-1-one* in accordance with *General Procedure 2A with T3P as the amide coupling reagent*.

Example 147 and **Example 148** were prepared from **Example 146** using Chiral-Chromatography purification conditions: Column: DAICELCHIRALCEL®OJ: 250*25 mm 10 µm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (+0.1% 7.0 mol/L ammonia in MeOH); Flow rate: 140 ml/min.

Example 149 was prepared from *Intermediate 4*, *2-(4-(tert-butoxycarbonyl)morpholin-2-yl)acetic acid* and *4,4-dimethylcyclohexan-1-one* in accordance with General Procedure 2A with PyBOP as the amide coupling reagent.

Example 150 was prepared from *Intermediate 3* and *Intermediate 49* in accordance with *General Procedure 1 with HATU as the amide coupling reagent*.

Example 151 was prepared from *Intermediate 1* and *Intermediate 53* in accordance with *General Procedure 1 with HATU as the amide coupling reagent*.

Example 152 and **Example 153** were prepared from **Example 151** by chiral SFC using Chiral-Chromatography purification conditions: Phenomenex Lux Cellulose 1, 21.2 x 250 mm, 5 µm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (+ Ammonium Hydroxide 1.0 %); Flow rate: 50 g/min.

Example 154 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)-4,4-difluoropiperidin-3-yl)acetic acid cycloheptanone* in accordance with *General Procedure 2A with HATU as the amide coupling reagent*.

Example 155 was prepared from *Intermediate 1*, *2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *isopropyl 4-(bromomethyl)benzoate* in accordance with *General Procedure 2B* with *PyBOP* as the amide coupling reagent.

Example 156 was prepared from *Intermediate 1*, *2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *isopropyl 3-(bromomethyl)benzoate* in accordance with *General Procedure 2B* with *PyBOP* as the amide coupling reagent.

Example 157 was prepared from *Intermediate 1*, *benzyl 2-(piperidin-4-yl)acetate* and *3-methyl-5-(trifluoromethoxy)benzaldehyde* in accordance with *General Procedure 3C* with *PyBOP* as the amide coupling reagent.

Example 158 was prepared from *Intermediate 1, benzyl 2-(piperidin-4-yl)acetate and 2,4,6-trimethylbenzaldehyde* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 159 was prepared from *Intermediate 1, benzyl 2-(piperidin-4-yl)acetate and 2-methyl-4-(trifluoromethoxy)benzaldehyde* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 160 was prepared from *Intermediate 1*, *benzyl 2-(piperidin-4-yl)acetate* and *3-methyl-4-(trifluoromethyl)benzaldehyde* in accordance with *General Procedure 3C* with *PyBOP* as the amide coupling reagent.

Example 161 was prepared from *Intermediate 1*, *benzyl 2-(piperidin-4-yl)acetate* and *5-(trifluoromethyl)nicotinaldehyde* in accordance with *General Procedure 3C* with *PyBOP* as the amide coupling reagent.

Example 162 was prepared from *Intermediate 1*, *benzyl 2-(piperidin-4-yl)acetate* and *5-methoxy-6-(trifluoromethyl)picolinaldehyde* in accordance with *General Procedure 3C* with *PyBOP* as the amide coupling reagent.

Example 163 was prepared from *Intermediate 1, benzyl 2-(piperidin-4-yl)acetate* and *3-methyl-5-(trifluoromethoxy)benzaldehyde* in accordance with *General Procedure 3C* with *PyBOP* as the amide coupling reagent.

Example 164 *was* prepared from *Intermediate 1, 2-(1-(tert-butoxy carbonyl)piperidin-4-yl)acetic acid* and *3-(difluoromethoxy)-5-methylbenzaldehyde* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 165 *was* prepared from *Intermediate 1* and *2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *isobutyl 4-formylpicolinate* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 166 *was* prepared from *Intermediate 10* and *2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *2-(trifluoromethoxy)benzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 167 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *1-(bromomethyl)-4-fluoro-2-(trifluoromethoxy)benzene* in accordance with *General Procedure 2B* with *PyBOP* as the amide coupling reagent.

Example 168 *was* prepared from *Intermediate 1* and *2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *2-(difluoromethoxy)-5-methylbenzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 169 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *2-(isopropylthio)benzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 170 was prepared from *Intermediate 1, tert-butyl 4-((2-methoxy-2-oxoethyl)thio)piperidine-1-carboxylate* and *2-isopropoxybenzaldehyde* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 171 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *3-isopropoxybenzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 172 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *2-cyclobutoxybenzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 173 was prepared from *Intermediate 1, 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid* and *2-isopropoxy-4-methylbenzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 174 was prepared from *Intermediate 1, tert-butyl 7-(2-methoxy-2-oxoethyl)-2-azaspiro[3.5]nonane-2-carboxylate* and *3-(difluoromethoxy)benzaldehyde* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 175 was prepared from *Intermediate 1, Intermediate 57* and *1-(bromomethyl)-3-(trifluoromethoxy)benzene* in accordance with *General Procedure 3B* with *PyBOP* as the amide coupling reagent.

Example 176 was prepared from *Intermediate 1, (S)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid* and *2-isopropoxybenzaldehyde* in accordance with *General Procedure 3C* with *PyBOP* as the amide coupling reagent.

Example 177 was prepared from *Intermediate 1, (R)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid* and *2-isopropoxybenzaldehyde* in accordance with *General Procedure 3C* with *PyBOP* as the amide coupling reagent.

Example 178 was prepared from *Intermediate 1, (S)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid* and *2-(2-isopropoxyphenyl)acetaldehyde (Intermediate 62)* in accordance with *General Procedure 3C* with *PyBOP* as the amide coupling reagent.

Example 179 was prepared from *Intermediate 1, (R)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid* and *2-(2-isopropoxyphenyl)acetaldehyde (Intermediate 62)* in accordance with *General Procedure 3C* with *PyBOP* as the amide coupling reagent.

Example 180 was prepared from *Intermediate 1, 8-(tert-butyl) 3-methyl 2-oxa-8-azaspiro[4.5]decane-3,8-dicarboxylate* and *1-(bromomethyl)-3,5-dimethylbenzene* in accordance with *General Procedure 3B* with *PyBOP* as the amide coupling reagent.

Example 181 was prepared from *Intermediate 1, 8-(tert-butyl) 3-methyl 2-oxa-8-azaspiro[4.5]decane-3,8-dicarboxylate* and *2-isopropoxybenzaldehyde* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 182 was prepared from *Intermediate 1, 2-(3-(tert-butoxycarbonyl)-3-azaspiro[5.5]undecan-9-yl)acetic acid* and *5-(chloromethyl)-2-(difluoromethyl)pyridine* in accordance with *General Procedure 2B* with *PyBOP* as the amide coupling reagent.

Example 183 was prepared from *Intermediate 1, 2-(3-(tert-butoxycarbonyl)-3-azaspiro[5.5]undecan-9-yl)acetic acid* and *5-(trifluoromethyl)picolinaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 184 was prepared from *Intermediate 1, 2-(3-(tert-butoxycarbonyl)-3-azaspiro[5.5]undecan-9-yl)acetic acid* and *2,4,6-trimethylnicotinaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 185 was prepared from *Intermediate 1, 2-(3-(tert-butoxycarbonyl)-3-azaspiro[5.5]undecan-9-yl)acetic acid* and *5-chloro-2-(chloromethyl)pyridine* in accordance with *General Procedure 2B* with *PyBOP* as the amide coupling reagent.

Example 186 was prepared from *Intermediate 1, 2-(3-(tert-butoxycarbonyl)-3-azaspiro[5.5]undecan-9-yl)acetic acid* and *3-bromo-5-(chloromethyl)pyridine hydrochloride* in accordance with *General Procedure 2B* with *PyBOP* as the amide coupling reagent.

Example 187 was prepared from *Intermediate 1, 2-{6-[(tert-butoxy)carbonyl]-6-azaspiro[3.4]octan-2-yl}acetic acid* and *1-(bromomethyl)-3-(trifluoromethoxy)benzene* in accordance with *General Procedure 2B* with *PyBOP* as the amide coupling reagent.

Example 188 *and* **Example 189** were prepared from **Example 187** by chiral SFC in accordance with *General Procedure 5B*.

Example 190 was prepared from *Intermediate 1, 2-{6-[(tert-butoxy)carbonyl]-6-azaspiro[3.4]octan-2-yl}acetic acid* and *3-(difluoromethoxy)-5-methylbenzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 191 was prepared from *Intermediate 1, 2-{6-[(tert-butoxy)carbonyl]-6-azaspiro[3.4]octan-2-yl}acetic acid* and *2-isopropoxy-4-methylbenzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 192 *and* **Example 193** were prepared from **Example 191** by chiral SFC in accordance with *General Procedure 5B.*

Example 194 was prepared from *Intermediate 1, 8-(tert-butyl) 3-methyl 2-oxa-8-azaspiro[4.5]decane-3,8-dicarboxylate* and *3-(difluoromethoxy)benzaldehyde* in accordance with *General Procedure 3A*.

Example 195 *and* **Example 196** were prepared from **Example 194** by chiral SFC in accordance with *General Procedure 5E*.

Example 197 was prepared from *Intermediate 1, 2-(3-(tert-butoxycarbonyl)-3-azaspiro[5.5]undecan-9-yl)acetic acid* and *3-cyclobutoxypicolinaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 198 was prepared from *Intermediate 1, Intermediate 58* and *1-(bromomethyl)-3,5-dimethylbenzene in* accordance with *General Procedure 3B* with *PyBOP* as the amide coupling reagent.

Example 199 was prepared from *Intermediate 1, Intermediate 58* and *2-cyclobutoxybenzaldehyde* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 200 was prepared from *Intermediate 1, Intermediate 58* and *2-(isopropylthio)benzaldehyde* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 201 was prepared from *Intermediate 1, 2-(3-(tert-butoxycarbonyl)-3-azaspiro[5.5]undecan-9-yl)acetic acid* and *5-chloronicotinaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 202 was prepared from *Intermediate 1, 2-(3-(tert-butoxycarbonyl)-3-azaspiro[5.5]undecan-9-yl)acetic acid* and *4-bromopicolinaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 203 was prepared from *Intermediate 1, 2-(3-(tert-butoxycarbonyl)-3-azaspiro[5.5]undecan-9-yl)acetic acid* and *5-bromopicolinaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 204 was prepared from *Intermediate 1, tert-butyl 3-(2-methoxy-2-oxoethyl)-4-(3-(trifluoromethoxy)benzyl)piperazine-1-carboxylate* and *iodo-ethane* in accordance with *General Procedure 3B* with *PyBOP* as the amide coupling reagent.

Example 205 *and* **Example 206** were prepared from **Example 204** by chiral SFC in accordance with *General Procedure 5A.*

Example 207 was prepared from *Intermediate 1, Intermediate 60* and *2-isopropoxybenzaldehyde* in accordance with *General Procedure 3B*.

Example 208 *and* **Example 209** were prepared from **Example 207** by chiral SFC in accordance with *General Procedure 5D*.

Example 210 was prepared from *Intermediate 1, 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)propanoic acid* and *2-isopropoxybenzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 211 was prepared from *Intermediate 1, 2-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)acetic acid* and *2-(isopropylthio)benzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 212 was prepared from *Intermediate 1, 8-(tert-butyl) 3-methyl 2-oxa-8-azaspiro[4.5]decane-3,8-dicarboxylate* and *2-cyclobutoxybenzaldehyde* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 213 *and* **Example 214** were prepared from **Example 212** by chiral SFC in accordance with *General Procedure 5C.*

Example 215 *and* **Example 216** were prepared from **Example 91** using Chiral-Chromatography purification conditions: DAICELCHIRALPAK®IB: 250*25 mm 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (+0.1% 7.0 mol/L ammonia in MeOH); Flow rate: 80 ml/min.

Example 217 was prepared from *Intermediate 1, Intermediate 56* and *1-(bromomethyl)-2-methylbenzene* in accordance with *General Procedure 3B* with *PyBOP* as the amide coupling reagent.

Example 218 *and* **Example 219** were prepared from **Example 217** using Chiral-Chromatography purification conditions: DAICELCHIRALPAK®IB: 250*25 mm 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (+0.1% 7.0 mol/L ammonia in MeOH); Flow rate: 100 ml/min.

Example 220 was prepared from *Intermediate 1, Intermediate 61* and *1-(bromomethyl)-2-methylbenzene* in accordance with *General Procedure 3B* with *PyBOP* as the amide coupling reagent.

Example 221 *and* **Example 222** were prepared from **Example 220** by chiral SFC in accordance with *General Procedure 5A.*

Example 223 was prepared from *Intermediate 1, Intermediate 55* and *2-methylbenzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 224 *and* **Example 225** were prepared from **Example 223** by chiral SFC in accordance with *General Procedure 5A.*

Example 226 was prepared from *Intermediate 1*, *methyl 2-(morpholin-3-yl)acetate hydrochloride and cyclohexanone* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 227 *and* **Example 228** were prepared from **Example 226** by chiral SFC in accordance with *General Procedure 5C.*

Example 229 was prepared from *Intermediate 1, Intermediate 67* and *4,4-dimethylcyclohexanone* in accordance with *General Procedure 2A* with *T3P* as the amide coupling reagent.

A racemic mixture of **Example 230 and Example 231** was prepared from *Intermediate 1, Intermediate 59* and *4-(difluoromethoxy)benzaldehyde* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 230 *and* **Example 231** were then isolated using Chiral-Chromatography purification conditions: DAICELCHIRALPAK®IB: 250*25 mm 10 μm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: EtOH(+0.1% 7.0 mol/L Ammonia in MEOH); Flow rate: 120 ml/min.

Example 232 was prepared from *Intermediate 1, tert-butyl 4-((2-methoxy-2-oxoethyl)thio)piperidine-1-carboxylate* and *1-(1-chloroethyl)-2-isopropoxy benzene* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 233 *and* **Example 234** were prepared from **Example 232** by chiral SFC in accordance with *General Procedure 5D*.

Example 235 was prepared from *Intermediate 1, (S)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid* and *3,5-difluoro-4-methylbenzaldehyde* in accordance with *General Procedure 3C* with *PyBOP* as the amide coupling reagent.

Example 236 was prepared from *Intermediate 1, (S)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid* and *3,5-difluoro-2-methylbenzaldehyde* in accordance with *General Procedure 3C* with *PyBOP* as the amide coupling reagent.

Example 237 was prepared from *Intermediate 1, Intermediate 54* and *3,5-difluorobenzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 238 was prepared from *Intermediate 1, tert-butyl 4-(2-((2-methoxy-2-oxoethyl)(methyl)amino)propan-2-yl)piperidine-1-carboxylate* and *3-(trifluoromethoxy)benzaldehyde* in accordance with *General Procedure 3A* with *PyBOP* as the amide coupling reagent.

Example 239 was prepared from *Intermediate 1*, *Intermediate 63* and *4,4-dimethylcyclohexane-1-carbaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 240 was prepared from *Intermediate 1, (S)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid* and *1-(3,5-difluorophenyl)ethan-1-one* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 241 *and* **Example 242** were prepared from **Example 240** by chiral SFC in accordance with *General Procedure 5F*.

Example 243 was prepared from *2-(4-(tert-butoxycarbonyl)morpholin-2-yl)acetic acid*, *Intermediate 1* and *4-isopropylcyclohexan-1-one* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 244, Example 245, Example 246 *and* **Example 247** were prepared from **Example 243** by chiral SFC in accordance with *General Procedure 5E*.

Example 248 was prepared from *Intermediate 11*, *Intermediate 64* and *3-fluoro-5-methylbenzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 249 *and* **Example 250** were prepared from **Example 6** by chiral SFC in accordance with *General Procedure 5E*.

Example 251 was prepared from *2-(4-(tert-butoxycarbonyl)morpholin-2-yl)acetic acid*, *Intermediate 1* and *spiro[2.5]octan-6-one* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 252 *and* **Example 253** were prepared from **Example 251** by chiral SFC in accordance with *General Procedure 5G*.

Example 254 was prepared from *2-(4-(tert-butoxycarbonyl)morpholin-2-yl)acetic acid*, *Intermediate 1 and spiro[3.5]nonan-2-one* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 255 *and* **Example 256** were prepared from **Example 254** by chiral SFC in accordance with *General Procedure 5D*.

Example 257 was prepared from *Intermediate 1*, *tert-butyl 2,8-diazaspiro[4.5]decane-2-carboxylate* and *2-(isopropylthio)benzaldehyde* in accordance with *General Procedure 4* with *PyBOP* as the amide coupling reagent.

Example 258 was prepared from *Intermediate 1, (S)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid* and *4-ethyl-3-fluorobenzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 259 was prepared from *Intermediate 1, (S)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid* and *1-(3-fluoro-4-methylphenyl)ethan-1-one* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 260 *and* **Example 261** were prepared from **Example 259** by chiral SFC in accordance with *General Procedure 5F*.

Example 262 was prepared from *Intermediate 1, (S)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid and 1-(2-fluoro-4-methylphenyl)ethan-1-one* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 263 *and* **Example 264** were prepared from **Example 262** by chiral SFC in accordance with *General Procedure 5B*.

Example 265 was prepared from *Intermediate 1, (S)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid and spiro[3.4]octan-2-one* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 266 *and* **Example 267** were prepared from **Example 265** by chiral SFC in accordance with *General Procedure 5E*.

Example 268 was prepared from *2-(2-(tert-butoxycarbonyl)-2,6-diazaspiro[3.5]nonan-6-yl)acetic acid, Intermediate 1* and *3-fluoro-5-methylbenzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 269 was prepared from *2-(2-(tert-butoxycarbonyl)-2,6-diazaspiro[3.5]nonan-6-yl)acetic acid, Intermediate 1* and *2-(methylthio)benzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 270 was prepared from *2-(2-(tert-butoxycarbonyl)-2,6-diazaspiro[3.5]nonan-6-yl)acetic acid, Intermediate 1* and *2-(isopropylthio)benzaldehyde* in accordance with *General Procedure 2A* with *PyBOP* as the amide coupling reagent.

Example 271 was prepared from *Intermediate 1*, *2-(4-(tert-butoxycarbonyl)morpholin-2-yl)acetic acid* and *spiro[4.5]decan-8-one* in accordance with General Procedure 2A with PyBOP as the amide coupling reagent.

Example 272 *and* **Example 273** were prepared from **Example 271** by chiral SFC in accordance with General Procedure 5E.

Example 274 was prepared from *Intermediate 1*, *2-(4-(tert-butoxycarbonyl)morpholin-2-yl)acetic acid* and *spiro[3.5]nonan-7-one* in accordance with General Procedure 2A with PyBOP as the amide coupling reagent.

Example 275 *and* **Example 276** were prepared from **Example 274** by chiral SFC in accordance with General Procedure 5E.

Example 277 Example was prepared from *Intermediate 3*, *(S)-2-(1-(tert-butoxycarbonyl)piperidin-3-yl)acetic acid* and *tert-butyl 4-formylpiperidine-1-carboxylate* in accordance with General Procedure 2C with PyBOP as the amide coupling reagent.

Example 278 was prepared from *Intermediate 1*, *Intermediate 66* and *4,4-dimethylcyclohexane-1-carbaldehyde* in accordance with General Procedure 2A with PyBOP as the amide coupling reagent.

Example 279 *and* **Example 280** were prepared from **Example 278** by chiral SFC in accordance with General Procedure 5F.

Example 281 was prepared from *Intermediate 3*, *2-(4-(tert-butoxycarbonyl)morpholin-2-yl)acetic acid* and *4,4-dimethylcyclohexan-1-one* in accordance with General Procedure 2C with PyBOP as the amide coupling reagent.

Example 282 *and* **Example 283** were prepared from **Example 281** by chiral SFC in accordance with General Procedure 5E.

Example 284 was prepared from *Intermediate 1* and *Intermediate 65* in accordance with General Procedure 2A with PyBOP as the amide coupling reagent.

Example 285 was prepared from *Intermediate 2* and *Intermediate 49* in accordance with *General Procedure 1* with HATU as the amide coupling reagent.

Example 286 was prepared from *Intermediate 1*, *Intermediate 66* and *4,4-dimethylcyclohexanone* in accordance with General Procedure 2A with PyBOP as the amide coupling reagent.

Example 287 and Example 288 were prepared from **Example 286** by chiral SFC using Chiral-Chromatography purification conditions: Phenomenex Lux Cellulose 1, 21.2 x 250 mm, 5 µm; Mobile Phase A: Supercritical CO_2; Mobile Phase B: MeOH (+ Ammonium Hydroxide 1.0 %); Flow rate: 50 g/min.

Example 289 was prepared from *Intermediate 1, Intermediate 63* and *4,4-dimethylcyclohexanone* in accordance with *General Procedure 2A* with T3P as the amide coupling reagent.

Example 290 was prepared from *Intermediate 1, Intermediate 63* and *spiro[4.5]decan-8-one* in accordance with *General Procedure 2A* with T3P as the amide coupling reagent.

Example 291 was prepared from *Intermediate 1* and *Intermediate 68* in accordance with *General Procedure 1* with T3P as the amide coupling reagent.

Example 292 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *3-(trifluoromethoxy)benzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 293 was prepared from *Intermediate 3 and Intermediate 7* in accordance with *General Procedure 1 with PyBOP as the amide coupling reagent.*

Example 294 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid and 2-chloro-4-(trifluoromethyl) benzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 295 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *3-chloro-5-(trifluoromethyl) benzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 296 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *2-(trifluoromethoxy)benzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 297 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *3-fluoro-4-(trifluoromethyl) benzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 298 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *3-bromo-5-fluorobenzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 299 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *3-methoxy-4-(trifluoromethyl) benzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 300 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *4-chloro-3-fluorobenzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 301 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *3-chloro-5-fluorobenzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 302 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid and 3,4-difluorobenzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 303 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid and 3,5-difluorobenzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 304 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *3,5-difluoro-4-methoxybenzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 305 was prepared from *Intermediate 2, Intermediate 7* in accordance with *General Procedure 1 with PyBOP as the amide coupling reagent.*

Example 306 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *2-chloro-5-(trifluoromethoxy)benzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 307 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *3-chloro-4-(trifluoromethoxy)benzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 308 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *Intermediate 69* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 309 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *Intermediate 70* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 310 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *2,4-dichloro-6-fluorobenzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

Example 311 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *5-fluoro-2-(trifluoromethyl)benzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

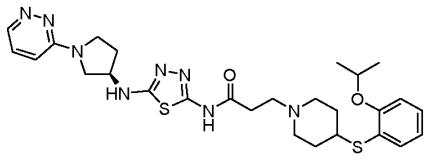
Example 312 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *3-fluoro-5-(trifluoromethyl)benzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

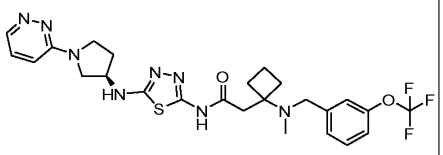
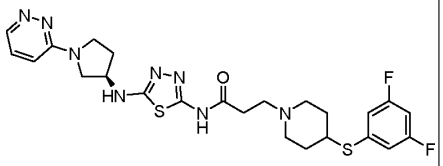
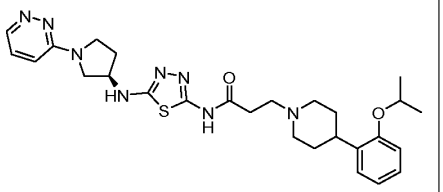
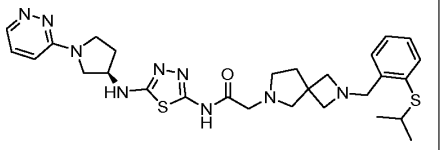
Example 313 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *Intermediate 71* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

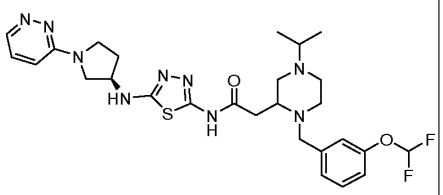
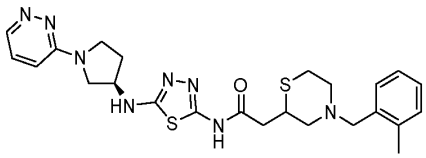
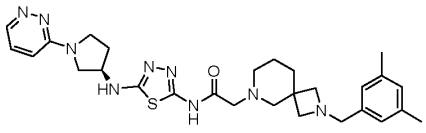
Example 314 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and 5-chloro-2-(trifluoromethoxy)benzaldehyde in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

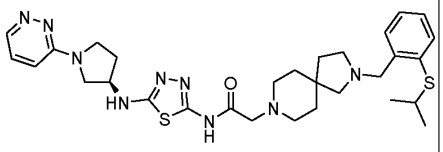
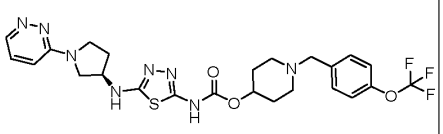
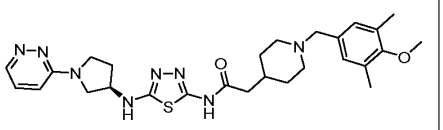
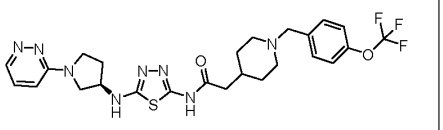
Example 315 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *2,3-difluorobenzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

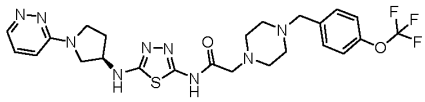
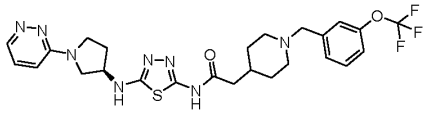
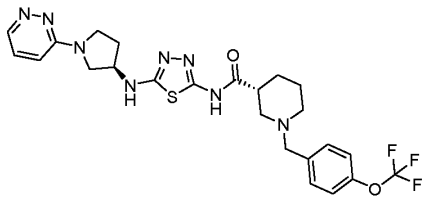
Example 316 was prepared from *Intermediate 1, 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid* and *3-(difluoromethoxy)benzaldehyde* in accordance with *General Procedure 2A with PyBOP as the amide coupling reagent.*

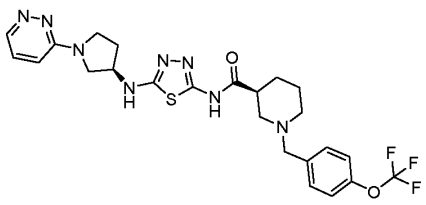
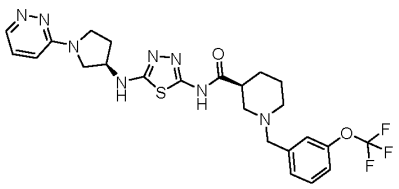
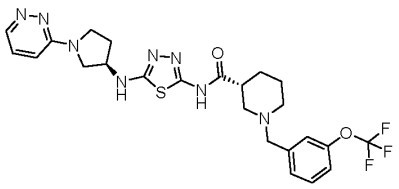
Example No.	Example Structure / Names	^{1}H NMR/LCMS Data
Example 1	 (*R*)-3-(4-((2-isopropoxyphenyl)thio)piperidin-1-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide	1H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1 H), 8.48 (dd, *J* =4.4 Hz, 1.2 Hz, 1 H), 7.62 (d, *J* =5.6 Hz, 1 H), 7.28-7.35 (m, 2 H), 7.16-7.20 (m, 1 H), 6.99 (d, *J* =8.0 Hz, 1 H), 6.86-6.90 (m, 2 H), 4.60-4.66 (m, 1 H), 4.35-4.41 (m, 1 H), 3.73-3.77 (m, 1 H), 3.48-3.60 (m, 3 H), 3.21-3.27 (m, 1 H), 2.77-2.85 (m, 2 H), 2.52-2.61 (m, 4 H), 2.25-2.33 (m, 1 H), 2.04-2.13 (m, 3 H), 1.84-1.87 (m, 2 H), 1.43-1.52 (m, 2 H), 1.27 (d, *J* =6.0 Hz, 6 H). LCMS (Method 16, ESI): 569.0 $[M+H]^+$, RT 1.546 minutes.

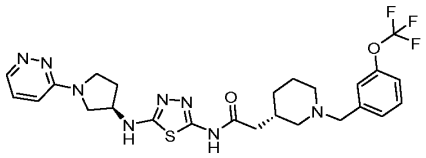
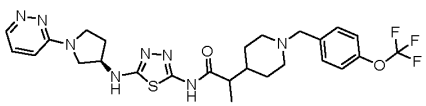
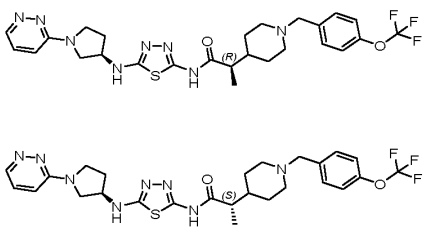
Example 2	 (*R*)-2-(1-(methyl(3-(trifluoromethoxy)benzyl)amino)cyclobutyl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 12.13 (s, 1 H), 8.48 (d, *J* =4.8 Hz, 1 H), 7.63 (d, *J* =6.0 Hz, 1 H), 7.46-7.42 (m, 1 H), 7.36-7.31 (m, 2 H), 7.26-7.23 (m, 1 H), 7.22-7.20 (m, 1 H), 6.87(d, *J* =9.2 Hz, 1 H), 4.44-4.35 (m, 1 H), 3.79-3.75 (m, 1 H), 3.62-3.46 (m, 5 H), 2.65 (s, 2 H), 2.36-2.31 (m, 2 H), 2.19-2.04 (m, 3 H), 2.02-1.99 (m, 3 H), 1.76-1.65 (m, 1 H), 1.62-1.56 (m, 1 H). LCMS (Method 13, ESI): 563.3 $[M+H]^+$, RT 5.987 minutes.
Example 3	 (*R*)-3-(4-((3,5-difluorophenyl)thio)piperidin-1-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide	1H NMR (400 MHz, DMSO-d_6): δ 12.02 (s, 1 H), 8.49-8.48 (m, 1 H), 7.62 (d, *J* =6.4 Hz, 1 H), 7.35-7.32 (m, 1 H), 7.12-7.04 (m, 3 H), 6.88-6.86 (m, 1 H), 4.39-4.38 (m, 1 H), 3.78-3.74 (m, 1 H), 3.59-3.48 (m, 4 H), 2.80-2.78 (m, 2 H), 2.63-2.60 (m, 2 H), 2.55-2.51 (m, 2 H), 2.30-2.27 (m, 1 H), 2.20-2.17 (m, 2 H), 2.14-2.07 (m, 1 H), 1.94-1.91 (m, 2 H), 1.51-1.48 (m, 2 H). LCMS (Method 16, ESI): 547.1 $[M+H]^+$, RT 1.417 minutes.
Example 4	 (*R*)-3-(4-(2-isopropoxyphenyl)piperidin-1-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide	1H NMR (400 MHz, DMSO-d_6): δ 12.12 (s, 1 H), 8.48 (d, *J* =4.8 Hz, 1 H), 7.63 (d, *J* =6.4 Hz, 1 H), 7.35-7.31 (m, 1 H), 7.15-7.10 (m, 2 H), 6.95-6.93 (m, 1 H), 6.88-6.84 (m, 2 H), 4.61-4.54 (m, 1 H), 4.42-4.36 (m, 1 H), 3.78-3.74 (m, 1 H), 3.59-3.50 (m, 3 H), 3.30-2.97 (m, 2 H), 2.87-2.78 (m, 1 H), 2.67-2.56 (m, 4 H), 2.34-2.26 (m, 1 H), 2.12-2.01 (m, 3 H), 1.70-1.53 (m, 4 H), 1.26-1.25 (m, 6 H).LCMS (Method 19, ESI): 537.1 $[M+H]^+$, RT 1.188 minutes.
Example 5	 (*R*)-2-(2-(2-(isopropylthio)benzyl)-2,6-diazaspiro[3.4]octan-6-yl)-*N*-(5-((1-	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.67 (s, 1H), 8.52 – 8.43 (m, 1H), 7.65 (d, *J* = 6.1 Hz, 1H), 7.41 – 7.31 (m, 3H), 7.25 – 7.18 (m, 2H), 6.87 (dd, *J* = 9.1, 1.1 Hz, 1H), 4.39 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.63 – 3.53 (m, 4H), 3.51 – 3.40 (m, 2H), 3.40 – 3.34 (m, 2H),

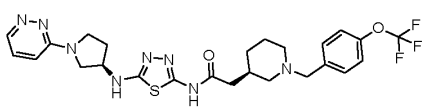
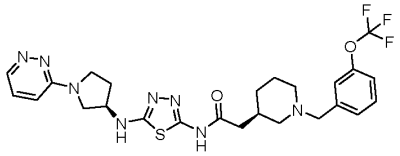
	(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	3.11 (dd, *J* = 30.7, 6.7 Hz, 4H), 2.76 (s, 2H), 2.57 (t, *J* = 6.9 Hz, 2H), 2.30 (td, *J* = 13.5, 7.8 Hz, 1H), 2.08 (td, *J* = 11.9, 5.0 Hz, 1H), 1.92 (t, *J* = 6.9 Hz, 2H), 1.22 (d, *J* = 6.6 Hz, 6H). LCMS (Method 15, ESI) 580.3 $[M+H]^+$, RT 0.744 minutes.
Example 6	 2-(1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.01 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.38-7.31 (m, 2H), 7.20-7.01 (m, 4H), 6.87 (dd, *J* = 9.2, 0.8 Hz, 1H), 4.41-4.34 (m, 1H), 3.80-3.73 (m, 2H), 3.57-3.36 (m, 4H), 3.02-2.93 (m, 1H), 2.77-2.62 (m, 5H), 2.33-2.25 (m, 5H), 2.08-2.07 (m, 1H), 0.92 (d, *J* = 12.0 Hz, 6H). LCMS (Method 15, ESI): 588.0 $[M+H]^+$, RT 0.908 minutes.
Example 7	 2-(4-(2-methylbenzyl)thiomorpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 8.48 (d, *J* =4.4 Hz, 1H), 7.62 (d, *J* =6.0 Hz, 1H), 7.33 (dd, *J* =8.8, 4.0 Hz, 1H), 7.21-7.20 (m, 1H), 7.12-7.08 (m, 3H), 6.87 (d, *J* =8.8 Hz, 1H), 4.40-4.37 (m, 1H), 3.78-3.73 (m, 1H), 3.59-3.49 (m, 3H), 3.42 (s, 2H), 3.20-3.19 (m, 1H), 2.80-2.67 (m, 3H), 2.62-2.54 (m, 4H), 2.46-2.42 (m, 1H), 2.32-2.27 (m, 4H), 2.11-2.04 (m, 1H). LCMS (Method 13, ESI): 511.3 $[M+H]^+$, RT 1.043 minutes.
Example 8	 (*R*)-2-(2-(3,5-dimethylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.67 (d, *J* = 5.6 Hz, 1H), 7.33 (dd, *J* = 9.6, 5.6 Hz, 1H), 6.88-6.83 (m, 4H), 4.40-4.38 (m, 1H), 3.78-3.74 (m, 1H), 3.59-3.56 (m, 2H), 3.52-3.49 (m, 1H), 3.47 (s, 2H), 3.22 (s, 2H), 2.98 (d, *J* = 6.8 Hz, 2H), 2.80 (d, *J* = 6.8 Hz, 2H), 2.53 (s, 2H), 2.38 (s, 2H), 2.32-2.25 (m, 1H), 2.22 (s, 6H), 2.09-2.08 (m, 1H), 1.47 (d, *J* = 8.4 Hz, 4H). LCMS (Method 21, ESI): 548.2 $[M+H]^+$, RT 1.567 minutes.

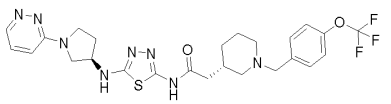
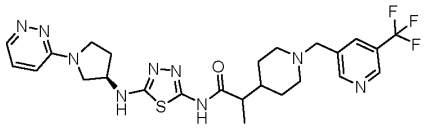
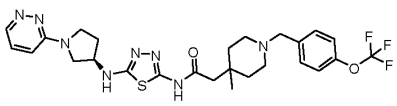
Example 9	 (*R*)-2-(2-(2-(isopropylthio)benzyl)-2,8-diazaspiro[4.5]decan-8-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.43-7.38 (m, 2H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.24-7.19 (m, 2H), 6.87 (dd, *J* = 8.4, 1.2 Hz, 1H), 4.39-4.38 (m, 1H), 3.77-3.73 (m, 1H), 3.63 (s, 2H), 3.58-3.55 (m, 2H), 3.52-3.45 (m, 3H), 3.18 (s, 2H), 2.43-2.37 (m, 4H), 2.32-2.27 (m, 4H), 2.11-2.04 (m, 1H), 1.55-1.47 (m, 6H), 1.21 (d, *J* = 6.4 Hz, 6H). LCMS (Method 13, ESI): 608.4 $[M+H]^+$, RT 1.056 minutes.
Example 10	 1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamate	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.49 (bs, 1H), 8.47 (d, *J* = 4.2 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.46 – 7.38 (m, 2H), 7.37 – 7.27 (m, 3H), 6.86 (d, *J* = 9.1 Hz, 1H), 4.72 – 4.61 (m, 1H), 4.40 – 4.29 (m, 1H), 3.73 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61 – 3.45 (m, 5H), 2.69 – 2.60 (m, 2H), 2.29 – 2.15 (m, 3H), 2.11 – 2.00 (m, 1H), 1.93 – 1.82 (m, 2H), 1.68 – 1.53 (m, 2H). LCMS (A analogous method to Method 7, ESI) 565.30 $[MH]^+$, RT 2.83 min.
Example 11	 2-{1-[(4-methoxy-3,5-dimethylphenyl)methyl]piperidin-4-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.48 (d, *J* = 3.9 Hz, 1H), 7.65 – 7.51 (m, 1H), 7.39 – 7.26 (m, 1H), 6.99 – 6.79 (m, 3H), 4.42 – 4.30 (m, 1H), 3.80 – 3.70 (m, 1H), 3.65 – 3.45 (m, 7H), 3.28 (s, 3H), 2.30-2.24 (m, 3H), 2.19 (s, 6H), 2.14 – 2.00 (m,1H), 1.93 – 1.78 (m, 2H), 1.78 – 1.63 (m, 1H), 1.59-1.51 (m, 2H), 1.27 – 1.11 (m, 2H). LCMS (A analogous method to Method 7, ESI) 537.32 $[MH]^+$, RT 2.70 min.
Example 12	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[4-	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 – 8.44 (m, 1H), 7.56 (dd, *J* = 6.0, 1.1 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.40-7.39 (m, 3H), 6.92 – 6.84 (m, 1H), 4.46 – 4.30 (m, 1H), 3.76 (dd, *J* = 10.5, 5.6 Hz, 1H), 3.60-3.51(m, 3H), 3.46 (s, 2H), 2.80-2.76 (m, 1H), 2.34 – 2.24 (m, 4H), 2.15 – 2.01

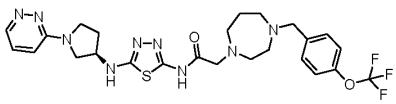
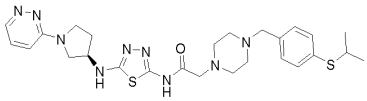
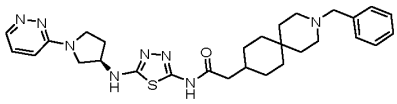
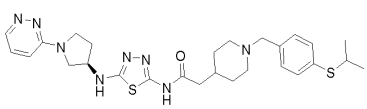
	(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetamide	(m, 1H), 1.99 – 1.86 (m, 2H), 1.81 – 1.66 (m, 1H), 1.65 – 1.54 (m, 2H), 1.31 – 1.12 (m, 3H). LCMS (A analogous method to Method 7, ESI) 563.33 $[MH]^+$, RT 2.85 min.
Example 15	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(4-{[4-(trifluoromethoxy)phenyl]methyl}piperazin-1-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.68 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.65 (d, *J* = 6.1 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.37 – 7.26 (m, 3H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.42 – 4.35 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.62 – 3.46 (m, 5H), 3.23 (s, 2H), 2.48 – 2.34 (m, 8H), 2.34 – 2.28 (m, 1H), 2.13 – 2.01 (m, 1H). LCMS (A analogous method to Method 7, ESI) 564.25 $[MH]^+$, RT 1.55 min.
Example 16	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetamide	^{1}H NMR (300 MHz, Methanol-d_4) δ 8.43 (d, *J* = 4.5 Hz, 1H), 7.45 – 7.30 (m, 3H), 7.27 (s, 1H), 7.21 – 7.14 (m, 1H), 6.97 (d, *J* = 9.3 Hz, 1H), 4.52 – 4.44 (m, 1H), 3.85 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.70 – 3.62 (m, 2H), 3.61 – 3.52 (m, 3H), 2.92 – 2.83 (m, 2H), 2.46 – 2.33 (m, 3H), 2.25 – 2.13 (m, 1H), 2.12 – 1.99 (m, 2H), 1.93 – 1.78 (m, 1H), 1.77 – 1.66 (m, 2H), 1.44 – 1.30 (m, 2H). LCMS (A analogous method to Method 7, ESI) 563.29 $[MH]^+$, RT 2.80 min.
Example 17	 (3*R*)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-1-{[4-(trifluoromethoxy)phenyl]methyl}piperidine-3-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.47 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.59 (d, *J* = 6.0 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.36 – 7.27 (m, 3H), 6.86 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.40 – 4.33 (m, 1H), 3.74 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.43 (m, 5H), 2.86 – 2.77 (m, 1H), 2.74 – 2.62 (m, 2H), 2.34 – 2.20 (m, 1H), 2.16 – 2.00 (m, 2H), 1.99 – 1.92 (m, 1H), 1.87 – 1.76 (m, 1H), 1.71 – 1.60 (m, 1H), 1.53 – 1.21 (m, 2H). LCMS (A analogous method to Method 7, ESI) 549.29 $[MH]^+$, RT 1.63 min.

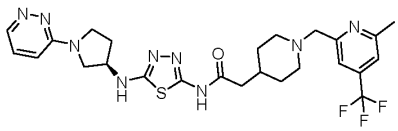
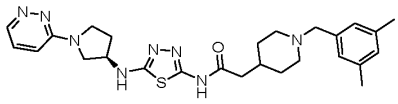
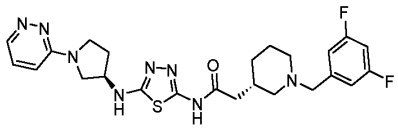
Example 18	 (3*S*)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-1-{[4-(trifluoromethoxy) phenyl]methyl}piperidine-3-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.35 – 7.27 (m, 3H), 6.86 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.41 – 4.32 (m, 1H), 3.74 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.51 (d, *J* = 3.4 Hz, 2H), 3.48 – 3.44 (m, 1H), 2.85 – 2.77 (m, 1H), 2.74 – 2.63 (m, 2H), 2.35 – 2.22 (m, 1H), 2.18 – 2.01 (m, 2H), 2.00 – 1.92 (m, 1H), 1.86 – 1.77 (m, 1H), 1.71 – 1.61 (m, 1H), 1.52 – 1.34 (m, 2H). LCMS (A analogous method to Method 7, ESI) 549.29 $[MH]^+$, RT 1.62 min.
Example 19	 (3*S*)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-1-{[3-(trifluoromethoxy) phenyl]methyl}piperidine-3-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.47 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.35 – 7.29 (m, 2H), 7.28 – 7.21 (m, 2H), 6.89 – 6.83 (m, 1H), 4.41 – 4.31 (m, 1H), 3.74 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.59 – 3.46 (m, 5H), 2.86 – 2.79 (m, 1H), 2.71 – 2.57 (m, 2H), 2.33 – 2.23 (m, 1H), 2.14 – 1.93 (m, 3H), 1.86 – 1.77 (m, 1H), 1.71 – 1.61 (m, 1H), 1.55 – 1.33 (m, 2H). LCMS (A analogous method to Method 7, ESI) 549.27 $[MH]^+$, RT 1.58 min.
Example 20	 (3*R*)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-1-{[3-(trifluoromethoxy) phenyl]methyl}piperidine-3-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.47 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.50 – 7.39 (m, 1H), 7.38 – 7.19 (m, 5H), 6.85 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.38 – 4.29 (m, 1H), 3.73 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.63 – 3.49 (m, 4H), 3.51 – 3.41 (m, 1H), 2.89 – 2.79 (m, 1H), 2.72 – 2.65 (m, 1H), 2.36 – 2.18 (m, 1H), 2.13 – 2.00 (m, 2H), 2.02 – 1.88 (m, 1H), 1.87 – 1.77 (m, 1H), 1.71 – 1.61 (m, 1H), 1.56 – 1.42 (m, 1H), 1.44 – 1.26 (m, 2H). LCMS (A analogous method to Method 7, ESI) 549.35 $[MH]^+$, RT 1.58 min.

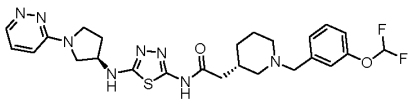
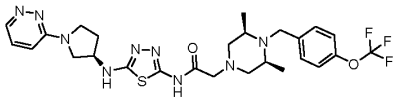
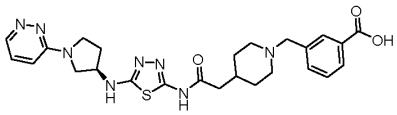
Example 21	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*S*)-1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-3-yl]acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.85 (s, 1H), 8.47 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.28 – 7.16 (m, 2H), 6.85 (dd, *J* = 9.3, 1.3 Hz, 1H), 4.39 – 4.29 (m, 1H), 3.74 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61 – 3.39 (m, 6H), 2.69 – 2.58 (m, 2H), 2.34 – 2.16 (m, 2H), 2.12 – 1.86 (m, 3H), 1.74 (t, *J* = 10.2 Hz, 1H), 1.68 – 1.54 (m, 2H), 1.51 – 1.35 (m, 1H), 1.02 – 0.84 (m, 1H). LCMS (A analogous method to Method 7, ESI) 563.28 [MH]$^+$, RT 1.56 min
Example 22	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)propanamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.48 (s, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.42 – 7.25 (m, 5H), 6.91 – 6.83 (m, 1H), 4.45 – 4.31 (m, 1H), 3.75 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.60 – 3.46 (m, 3H), 3.44 (s, 2H), 2.84 – 2.70 (m, 2H), 2.44 – 2.35 (m, 1H), 2.34 – 2.21 (m, 1H), 2.14 – 2.01 (m, 1H), 1.94 – 1.80 (m, 2H), 1.73 – 1.64 (m, 1H), 1.49 – 1.37 (m, 2H), 1.32 – 1.21 (m, 1H), 1.19 – 1.08 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H). LCMS (A analogous method to Method 7, ESI) 577.32 [MH]$^+$, RT 2.87 min.
Example 23 and Example 24 Isomers A and B	 One of isomers A and B is (*R*)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)propanamide and the other is (*S*)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)propanamide	1H NMR (400 MHz, DMSO-d$_6$): δ 11.80 (br s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.62 (d, *J* =5.6 Hz, 1 H), 7.39 (d, *J* =8.0 Hz, 2 H), 7.28-7.34 (m, 3 H), 6.86 (d, *J* =9.2 Hz, 1 H), 4.33-4.43 (m, 1 H), 3.73-3.77 (m, 1 H), 3.52-3.57 (m, 3 H), 3.43 (s, 2 H), 2.74-2.80 (m, 2 H), 2.36-2.45 (m, 1 H), 2.23-2.34 (m, 1 H), 2.03-2.14 (m, 1 H), 1.80-1.94 (m, 2 H), 1.66-1.69 (m, 1 H), 1.36-1.49 (m, 2 H), 1.18-1.32 (m, 1 H), 1.09-1.17 (m, 1 H), 1.04 (d, *J* =6.4 Hz, 3 H). 19F NMR (376 MHz, DMSO-d6): δ -56.79. LCMS (Method 13, ESI): 577.5 [M+H]$^+$, RT 6.051 minutes. 1H NMR (400 MHz, DMSO-d6): δ 11.89 (s, 1 H), 8.48 (dd, *J* =4.4 Hz, 1.2 Hz, 1 H),

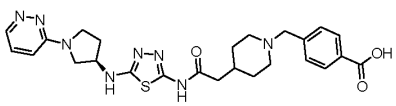
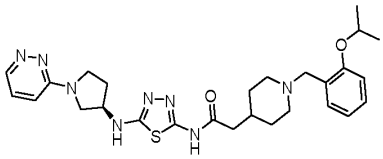
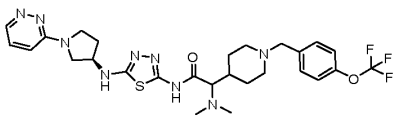
		7.62 (d, *J* =6.0 Hz, 1 H), 7.40 (d, *J* =8.4 Hz, 2 H), 7.28-7.35 (m, 3 H), 6.87 (dd, *J* =8.8 Hz, 1.2 Hz, 1 H), 4.34-4.44 (m, 1 H), 3.73-3.77 (m, 1 H), 3.48-3.58 (m, 3 H), 3.44 (s, 2 H), 2.75-2.81 (m, 2 H), 2.39-2.43 (m, 1 H), 2.08-2.34 (m, 1 H), 2.02-2.14 (m, 1 H), 1.79-1.93 (m, 2 H), 1.67-1.70 (m, 1 H), 1.36-1.48 (m, 2 H), 1.21-1.32 (m, 1 H), 1.09-1.11 (m, 1 H), 1.04 (d, *J* =7.2 Hz, 3 H). 19F NMR (376 MHz, DMSO-d_6): δ -56.79. LCMS (Method 13, ESI): 577.5 $[M+H]^+$, RT 6.086 minutes.
Example 25	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*R*)-1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-3-yl]acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.60 (d, *J* = 6.1 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.29 – 7.24 (m, 2H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.41 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.50 (m, 4H), 3.43 – 3.36 (m, 1H), 2.67 – 2.56 (m, 2H), 2.34 – 2.23 (m, 3H), 2.12 – 1.90 (m, 3H), 1.76 (t, *J* = 10.1 Hz, 1H), 1.67 – 1.53 (m, 2H), 1.50 – 1.37 (m, 1H), 1.05 – 0.91 (m, 1H). LCMS (A analogous method to Method 7, ESI) 563.24 $[MH]^+$, RT 1.59 min.
Example 26	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*R*)-1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-3-yl]acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.48 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.60 (d, *J* = 6.0 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.26 – 7.19 (m, 2H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.41 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.64 – 3.39 (m, 5H), 2.73 – 2.56 (m, 2H), 2.35 – 2.21 (m, 3H), 2.13 – 1.90 (m, 3H), 1.76 (t, *J* = 10.2 Hz, 1H), 1.68 – 1.54 (m, 2H), 1.51 – 1.36 (m, 1H), 1.04 – 0.89 (m, 1H). LCMS (A analogous method to Method 7, ESI) 563.27 $[MH]^+$, RT 1.56 min.

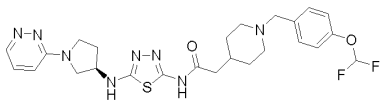
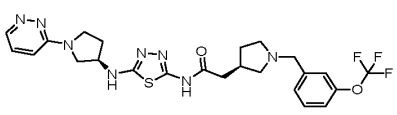
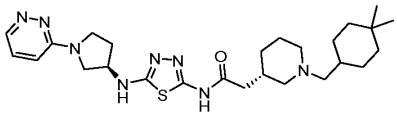
Example 27	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*S*)-1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-3-yl]acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.58 (d, *J* = 6.0 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.86 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.41 – 4.32 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61 – 3.49 (m, 3H), 3.50 – 3.34 (m, 2H), 2.69 – 2.56 (m, 2H), 2.33 – 2.21 (m, 3H), 2.12 – 1.90 (m, 3H), 1.75 (t, *J* = 10.1 Hz, 1H), 1.68 – 1.54 (m, 2H), 1.48 – 1.36 (m, 1H), 1.04 – 0.90 (m, 1H). LCMS (A analogous method to Method 7, ESI) 563.24 [MH]$^+$, RT 1.58 min
Example 28	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[5-(trifluoromethyl)pyridin-3-yl]methyl}piperidin-4-yl)propanamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.89 – 8.83 (m, 1H), 8.78 (s, 1H), 8.51 – 8.43 (m, 1H), 8.05 (s, 1H), 7.63 (d, *J* = 6.1 Hz, 1H), 7.37 – 7.29 (m, 1H), 6.87 (dt, *J* = 9.1, 1.3 Hz, 1H), 4.42 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.61 – 3.45 (m, 5H), 2.84 – 2.70 (m, 2H), 2.44 – 2.34 (m, 1H), 2.33 – 2.22 (m, 1H), 2.13 – 2.02 (m, 1H), 2.00 – 1.85 (m, 2H), 1.73 – 1.66 (m, 1H), 1.47 – 1.37 (m, 2H), 1.32 – 1.22 (m, 1H), 1.20 – 1.09 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H). LCMS (A analogous method to Method 6, ESI) 562.23 [MH]$^+$, RT 5.98 min; 562.23 [MH]$^+$, RT 6.04 min; d.r. = 56.32:41.73.
Example 29	 2-(4-methyl-1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.56 (d, *J* = 6.0 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.36 – 7.26 (m, 3H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.41 – 4.30 (m, 1H), 3.75 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.61 – 3.49 (m, 3H), 3.47 (s, 2H), 2.43 – 2.37 (m, 2H), 2.35 – 2.29 (m, 3H), 2.29 – 2.23 (m, 2H), 2.13 – 2.02 (m, 1H), 1.60 – 1.49 (m, 2H), 1.41 – 1.31 (m, 2H), 1.01 – 0.95 (m, 3H). LCMS A analogous method to Method 7, ESI) 577.28 [MH]$^+$, RT 2.89 min.

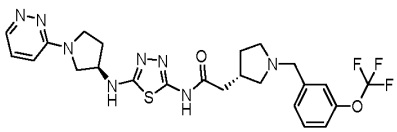
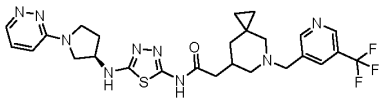
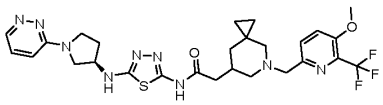
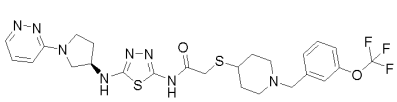
Example 30	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(4-{[4-(trifluoromethoxy)phenyl]methyl}-1,4-diazepan-1-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.64 (d, *J* = 6.1 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.35 – 7.27 (m, 3H), 6.87 (dd, *J* = 9.1, 1.4 Hz, 1H), 4.42 – 4.35 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.63 (s, 2H), 3.59 – 3.53 (m, 2H), 3.50 (dd, *J* = 11.0, 3.6 Hz, 1H), 3.40 (s, 2H), 2.82 – 2.72 (m, 4H), 2.65 – 2.57 (m, 4H), 2.33 – 2.25 (m, 1H), 2.12 – 2.03 (m, 1H), 1.76 – 1.67 (m, 2H). LCMS (A analogous method to Method 7, ESI) 578.19 [MH]$^+$, RT 1.47 min.
Example 31	 2-(4-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperazin-1-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.54 – 8.44 (m, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.39 – 7.29 (m, 3H), 7.25 (d, *J* = 8.2 Hz, 2H), 6.88 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.38 (dt, *J* = 9.9, 5.1 Hz, 1H), 3.76 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.62 – 3.49 (m, 3H), 3.45 (d, *J* = 6.7 Hz, 1H), 3.41 (s, 2H), 2.80 – 2.72 (m, 2H), 2.35- 2.29 (m, 3H), 2.15 – 2.02 (m, 1H), 1.90 (t, *J* = 10.7 Hz, 2H), 1.80 – 1.66 (m, 1H), 1.64 – 1.53 (m, 2H), 1.26 - 1.13 (m, 8H). LCMS (A analogous method to Method 7, ESI) 554.42 [MH]$^+$, RT 2.79 min.
Example 32	 2-{3-benzyl-3-azaspiro[5.5]undecan-9-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.1 Hz, 1H), 7.36 – 7.19 (m, 6H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.41 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.60 – 3.46 (m, 3H), 3.42 (s, 2H), 2.32 – 2.24 (m, 7H), 2.13 – 2.01 (m, 1H), 1.74 – 1.63 (m, 1H), 1.63 – 1.54 (m, 2H), 1.49 – 1.39 (m, 4H), 1.32 – 1.25 (m, 2H), 1.15 – 0.97 (m, 4H). LCMS (A analogous method to Method 7, ESI) 547.02 [MH]$^+$, RT 1.45 min.
Example 33		^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.49 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.66 (d, *J* = 6.1 Hz, 1H), 7.37 – 7.30 (m, 3H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.88 (dd, *J* = 9.2,

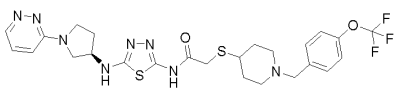
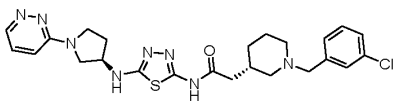
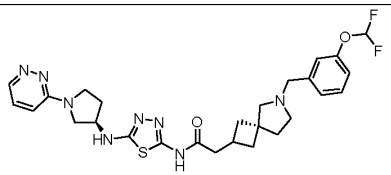
	2-(1-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	1.3 Hz, 1H), 4.46 – 4.33 (m, 1H), 3.76 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.63 – 3.41 (m, 6H), 3.23 (s, 2H), 2.49 – 2.33 (m, 8H), 2.33 – 2.28 (m, 1H), 2.17 – 2.00 (m, 1H), 1.23 (d, *J* = 6.6 Hz, 6H). LCMS (A analogous method to Method 7, ESI) 553.52 $[MH]^+$, RT 2.88 min.
Example 34	 2-(1-{[6-methyl-4-(trifluoromethyl)pyridin-2-yl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.47 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.57 – 7.46 (m, 3H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.86 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.41 – 4.31 (m, 1H), 3.74 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.64 – 3.45 (m, 5H), 2.82 – 2.73 (m, 2H), 2.55 (s, 3H), 2.31 – 2.25 (m, 3H), 2.11 – 1.97 (m, 3H), 1.79 – 1.65 (m, 1H), 1.65 – 1.54 (m, 2H), 1.31 – 1.15 (m, 2H). LCMS (A analogous method to Method 7, ESI) 562.55 $[MH]^+$, RT 2.58 min.
Example 35	 2-{1-[(3,5-dimethylphenyl)methyl]piperidin-4-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.47 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.91 – 6.82 (m, 4H), 4.41 – 4.31 (m, 1H), 3.74 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61 – 3.45 (m, 3H), 2.78 – 2.70 (m, 2H), 2.33 – 2.24 (m, 3H), 2.24 (s, 6H), 2.12 – 2.01 (m, 1H), 1.91 – 1.81 (m, 2H), 1.75 – 1.64 (m, 1H), 1.61 – 1.53 (m, 2H), 1.24 – 1.11 (m, 2H). LCMS (Method 7, ESI) 507.46 $[MH]^+$, RT 4.06 min.
Example 36	 2-[(3*S*)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.5 Hz, 1H), 7.11 – 6.96 (m, 3H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.41 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.43 (m, 5H), 2.71 – 2.55 (m, 2H), 2.34 – 2.25 (m, 3H), 2.13 – 1.91 (m, 3H), 1.77 (t, *J* = 10.1 Hz, 1H), 1.68 – 1.55 (m, 2H), 1.52 – 1.38 (m, 1H), 1.04 – 0.90 (m, 1H). LCMS (A analogous method to Method 7, ESI) 512.22 $[MH]^+$, RT 2.50 min.

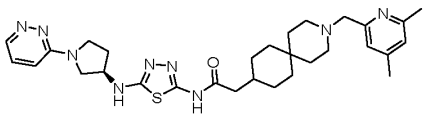
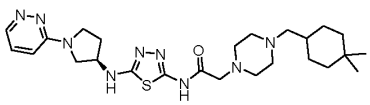
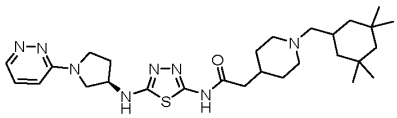
Example 37	 2-[(3*S*)-1-{[3-(difluoromethoxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 11.91 (s, 1H), 8.48 (dd, *J* = 4.5, 1.1 Hz, 1H), 7.63 (d, *J* = 6.1 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.21 (t, *J* = 74 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.08 (s, 1H), 7.03 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.88 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.45 – 4.32 (m, 1H), 3.76 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61 – 3.49 (m, 3H), 3.49 – 3.38 (m, 2H), 2.70 (s, 2H), 2.33 – 2.26 (m, 3H), 2.14 – 1.88 (m, 3H), 1.77 (td, *J* = 10.2, 4.5 Hz, 1H), 1.70 – 1.53 (m, 2H), 1.54 – 1.36 (m, 1H), 1.08 – 0.89 (m, 1H). LCMS (A analogous method to Method 7, ESI) 545.17 [MH]$^+$, RT 2.55 min.
Example 38	 2-[(3*R*,5*S*)-3,5-dimethyl-4-{[4-(trifluoromethoxy)phenyl]methyl}piperazin-1-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.48 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.44 – 4.33 (m, 1H), 3.79 – 3.69 (m, 3H), 3.61 – 3.46 (m, 3H), 3.19 (s, 2H), 2.76 – 2.66 (m, 2H), 2.65 – 2.55 (m, 2H), 2.33 – 2.25 (m, 1H), 2.15 – 2.05 (m, 1H), 2.05 – 1.96 (m, 2H), 0.88 (d, *J* = 6.1 Hz, 6H). LCMS (A analogous method to Method 7, ESI) 592.25 [MH]$^+$, RT 2.75 min.
Example 39	 3-[(4-{[(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamoyl]methyl}piperidin-1-yl)methyl]benzoic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.88 – 7.85 (m, 1H), 7.85 – 7.77 (m, 1H), 7.62 (d, *J* = 6.1 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.46 – 7.39 (m, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.43 – 4.31 (m, 1H), 3.75 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.60 – 3.45 (m, 6H), 2.78 – 2.74 (m, 1H), 2.35 – 2.27 (m, 3H), 2.12 – 2.01 (m, 1H), 1.98 – 1.87 (m, 2H), 1.78 – 1.66 (m, 1H), 1.63 – 1.53 (m, 2H), 1.30 – 1.12 (m, 2H). LCMS (Method 7, ESI) 523.22 [MH]$^+$, RT 3.07 min.

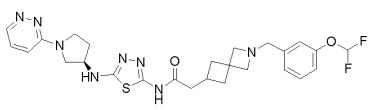
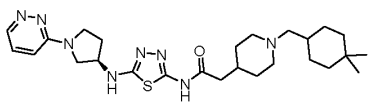
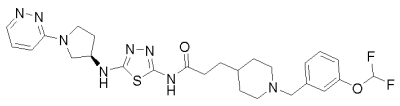
Example 40	 4-[(4-{[(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamoyl]methyl}piperidin-1-yl)methyl]benzoic acid	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.92 – 7.85 (m, 2H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.33 (dd, *J* = 9.2, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.42 – 4.32 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.44 (m, 6H), 2.80 – 2.75 (m, 1H), 2.35 – 2.27 (m, 3H), 2.13 – 2.01 (m, 1H), 1.99 – 1.88 (m, 2H), 1.78 – 1.65 (m, 1H), 1.63 – 1.54 (m, 2H), 1.29 – 1.13 (m, 2H). LCMS (Method 7, ESI) 523.27 [MH]$^+$, RT 2.94 min.
Example 41	 2-(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.90 (bs, 1H), 8.47 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.57 – 7.47 (m, 1H), 7.39 – 7.29 (m, 1H), 7.28 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.21 – 7.12 (m, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.92 – 6.82 (m, 2H), 4.57 (p, *J* = 6.0 Hz, 1H), 4.41 – 4.29 (m, 1H), 3.74 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.46 (m, 3H), 3.39 (s, 2H), 2.82 – 2.75 (m, 2H), 2.30 – 2.26 (m, 3H), 2.12 – 2.01 (m, 1H), 1.98 – 1.88 (m, 2H), 1.76 – 1.64 (m, 1H), 1.62 – 1.53 (m, 2H), 1.25 (d, *J* = 6.0 Hz, 6H), 1.22 – 1.11 (m, 2H). LCMS (A analogous method to Method 7, ESI) 537.45 [MH]$^+$, RT 2.83 min.
Example 42	 2-(dimethylamino)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.99 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.67 (d, *J* = 6.1 Hz, 1H), 7.44 – 7.25 (m, 5H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.44 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.59 – 3.43 (m, 5H), 3.07 (d, *J* = 10.3 Hz, 1H), 2.80 – 2.70 (m, 2H), 2.34 – 2.25 (m, 1H), 2.21 (s, 3H), 2.21 (s, 3H), 2.11 – 2.02 (m, 1H), 1.99 – 1.65 (m, 4H), 1.33 – 1.07 (m, 3H). LCMS (Method 6, ESI) 606.57 [MH]$^+$, RT 4.45 min; 606.28 [MH]$^+$, RT 4.53 min; d.r. = 53.74:41.66.

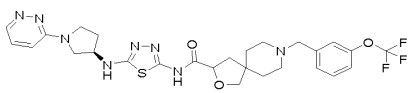
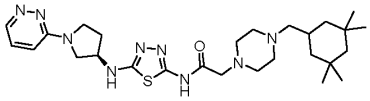
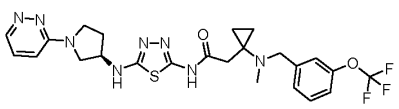
Example 43	 2-(1-{[4-(difluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.36 – 7.29 (m, 3H), 7.20 (t, *J* = 74.3 Hz, 1H), 7.15 – 7.06 (m, 2H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.43 – 4.29 (m, 1H), 3.74 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.62 – 3.45 (m, 3H), 3.40 (s, 2H), 2.77 – 2.69 (m, 2H), 2.36 – 2.22 (m, 3H), 2.13 – 2.02 (m, 1H), 1.96 – 1.84 (m, 2H), 1.77 – 1.65 (m, 1H), 1.63 – 1.54 (m, 2H), 1.29 – 1.09 (m, 2H). LCMS (A analogous method to Method 7, ESI) 545.60 $[MH]^+$, RT 2.11 min.
Example 44	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*R*)-1-{[3-(trifluoromethoxy)phenyl]methyl}pyrrolidin-3-yl]acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.28 – 7.19 (m, 2H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.41 – 4.32 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.61 – 3.46 (m, 5H), 2.67 – 2.60 (m, 1H), 2.48 – 2.45 (m, 4H), 2.35 – 2.23 (m, 2H), 2.19 – 2.01 (m, 2H), 1.99 – 1.88 (m, 1H), 1.45 – 1.32 (m, 1H). LCMS (A analogous method to Method 7, ESI) 549.20 $[MH]^+$, RT 1.76 min.
Example 45	 2-[(3*S*)-1-[(4,4-dimethylcyclohexyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 11.93 (s, 1H), 8.49 (dd, *J* = 4.4, 1.0 Hz, 1H), 7.64 (d, *J* = 6.1 Hz, 1H), 7.34 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.88 (dd, *J* = 9.2, 1.1 Hz, 1H), 4.47 – 4.32 (m, 1H), 3.76 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.63 – 3.46 (m, 3H), 2.70 – 2.58 (m, 1H), 2.35 – 2.24 (m, 4H), 2.14 – 2.00 (m, 3H), 2.02 – 1.90 (m, 1H), 1.90 – 1.76 (m, 1H), 1.70 – 1.47 (m, 5H), 1.45 – 1.26 (m, 4H), 1.17 – 0.92 (m, 5H), 0.86 (d, *J* = 8.4 Hz, 6H). LCMS (A analogous method to Method 7, ESI) 513.34 $[MH]^+$, RT 2.88 min.

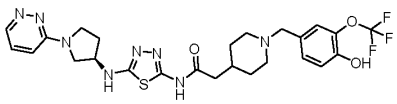
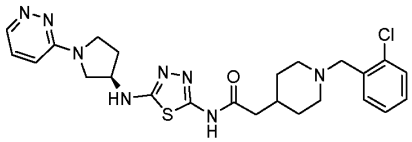
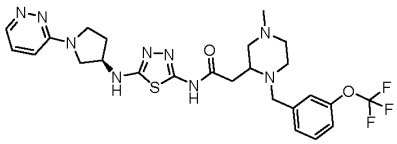
Example 46	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*S*)-1-{[3-(trifluoromethoxy)phenyl]methyl} pyrrolidin-3-yl]acetamide	^{1}H NMR (300 MHz, Methanol-d_4) δ 8.43 (d, *J* = 4.6 Hz, 1H), 7.46 – 7.33 (m, 3H), 7.32 – 7.27 (m, 1H), 7.22 – 7.15 (m, 1H), 6.97 (dd, *J* = 9.3, 1.3 Hz, 1H), 4.54 – 4.42 (m, 1H), 3.85 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.77 – 3.55 (m, 5H), 2.92 – 2.84 (m, 1H), 2.72 – 2.59 (m, 3H), 2.58 – 2.52 (m, 2H), 2.46 – 2.30 (m, 2H), 2.25 – 2.05 (m, 2H), 1.63 – 1.49 (m, 1H). LCMS (A analogous method to Method 7, ESI) 549.24 [MH]$^+$, RT 1.76 min.
Example 47	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(5-{[5-(trifluoromethyl)pyridin-3-yl]methyl}-5-azaspiro[2.5]octan-7-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 11.93 (s, 1H), 8.88 – 8.83 (m, 1H), 8.83 – 8.77 (m, 1H), 8.49 (dd, *J* = 4.5, 1.2 Hz, 1H), 8.06 (s, 1H), 7.57 (d, *J* = 5.9 Hz, 1H), 7.34 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.88 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.37 (tt, *J* = 9.1, 4.5 Hz, 1H), 3.76 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.71 – 3.47 (m, 5H), 2.84 – 2.74 (m, 1H), 2.38 – 2.17 (m, 5H), 2.15 – 2.02 (m, 1H), 2.00 – 1.87 (m, 2H), 1.33 (dd, *J* = 12.9, 10.0 Hz, 1H), 1.16 – 1.05 (m, 1H), 0.36 – 0.18 (m, 4H). LCMS (Method 6, ESI) 574.17 [MH]$^+$, RT 5.21 min.
Example 48	 2-(5-{[5-methoxy-6-(trifluoromethyl)pyridin-2-yl]methyl}-5-azaspiro[2.5]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.49 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.63 (d, *J* = 6.1 Hz, 1H), 7.34 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.88 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.43 – 4.32 (m, 1H), 3.90 (d, *J* = 2.6 Hz, 3H), 3.76 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.66 – 3.45 (m, 5H), 2.74 – 2.67 (m, 1H), 2.44 – 2.30 (m, 3H), 2.23 (s, 2H), 2.15 – 2.03 (m, 1H), 1.97 (d, *J* = 11.9 Hz, 2H), 1.37 – 1.26 (m, 1H), 1.19 – 1.09 (m, 1H), 0.29 (s, 4H). LCMS (A analogous method to Method 7, ESI) 604.22 [MH]$^+$, RT 2.78 min.
Example 49		^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (s, 1H), 8.48 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.28 – 7.19 (m,

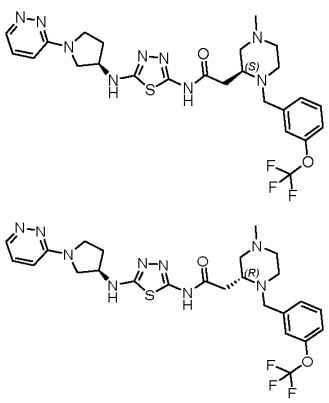
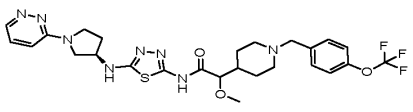
	N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)sulfanyl]acetamide	2H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.42 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.59 – 3.47 (m, 5H), 3.40 (s, 2H), 2.84 – 2.68 (m, 3H), 2.34 – 2.26 (m, 1H), 2.13 – 1.98 (m, 3H), 1.96 – 1.86 (m, 2H), 1.53 – 1.37 (m, 2H). LCMS (A analogous method to Method 7, ESI) 595.17 $[MH]^+$, RT 2.75 min.
Example 50	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)sulfanyl]acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.43 – 7.27 (m, 5H), 6.87 (dd, *J* = 9.1, 1.3 Hz, 1H), 4.42 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.44 (m, 5H), 3.40 (s, 2H), 2.84 – 2.68 (m, 3H), 2.34 – 2.26 (m, 1H), 2.12 – 1.97 (m, 3H), 1.95 – 1.85 (m, 2H), 1.53 – 1.38 (m, 2H). LCMS (A analogous method to Method 7, ESI) 595.18 $[MH]^+$, RT 2.77 min.
Example 51	 2-[(3*S*)-1-[(3-chlorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.48 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.62 (d, *J* = 6.1 Hz, 1H), 7.37 – 7.21 (m, 5H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.43 – 4.32 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.60 – 3.47 (m, 3H), 3.43 (d, *J* = 8.5 Hz, 2H), 2.70 – 2.57 (m, 2H), 2.33 – 2.26 (m, 3H), 2.12 – 1.92 (m, 3H), 1.81 – 1.70 (m, 1H), 1.67 – 1.54 (m, 2H), 1.50 – 1.36 (m, 1H), 1.03 – 0.89 (m, 1H). LCMS (A analogous method to Method 7, ESI) 513.18 $[MH]^+$, RT 2.50 min.
Example 52	 2-(6-{[3-(difluoromethoxy)phenyl]methyl}-6-azaspiro[3.4]octan-2-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 11.85 (s, 1H), 8.49 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.59 (d, *J* = 6.0 Hz, 1H), 7.38 – 7.30 (m, 3H), 7.21 (t, *J* = 74.3 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.88 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.44 – 4.30 (m, 1H), 3.76 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.61 – 3.46 (m, 5H), 2.47 – 2.29 (m, 7H), 2.29 – 2.08 (m, 1H), 2.14 – 1.97 (m, 3H), 1.87 (t, *J* = 6.8 Hz,

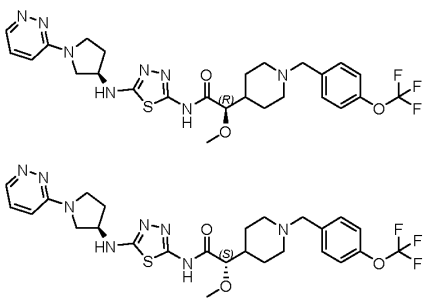
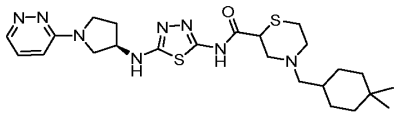
		2H), 1.78 – 1.65 (m, 2H). LCMS (Method 6, ESI) 571.41 $[MH]^+$, RT 5.69 min.
Example 53	 2-{3-[(4,6-dimethylpyridin-2-yl)methyl]-3-azaspiro[5.5]undecan-9-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.60 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.02 (s, 1H), 6.91 (s, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.43 – 4.32 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.59 – 3.46 (m, 3H), 3.45 (s, 2H), 2.37 (s, 3H), 2.35 – 2.26 (m, 7H), 2.25 (s, 3H), 2.13 – 2.01 (m, 1H), 1.74 – 1.55 (m, 3H), 1.50 – 1.39 (m, 4H), 1.34 – 1.26 (m, 2H), 1.15 – 0.97 (m, 4H). LCMS (Method 7, ESI) 576.31 $[MH]^+$, RT 4.13 min.
Example 54	 2-{4-[(4,4-dimethylcyclohexyl)methyl]piperazin-1-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.48 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.62 (d, *J* = 6.1 Hz, 1H), 7.37 – 7.21 (m, 5H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.43 – 4.32 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.60 – 3.47 (m, 3H), 3.43 (d, *J* = 8.5 Hz, 2H), 2.70 – 2.57 (m, 2H), 2.33 – 2.26 (m, 3H), 2.12 – 1.92 (m, 3H), 1.81 – 1.70 (m, 1H), 1.67 – 1.54 (m, 2H), 1.50 – 1.36 (m, 1H), 1.03 – 0.89 (m, 1H). LCMS (A analogous method to Method 7, ESI) 514.31 $[MH]^+$, RT 1.55 min.
Example 55	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-{1-[(3,3,5,5-tetramethylcyclohexyl)methyl]piperidin-4-yl}acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.48 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.42 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.46 (m, 3H), 2.80 – 2.72 (m, 2H), 2.33 – 2.27 (m, 3H), 2.12 – 1.98 (m, 3H), 1.87 – 1.73 (m, 3H), 1.72 – 1.63 (m, 1H), 1.61 – 1.52 (m, 2H), 1.48 – 1.39 (m, 2H), 1.24 – 1.13 (m, 3H), 0.99 (d, *J* = 13.9 Hz, 1H), 0.95 (s, 6H), 0.85 (s, 6H), 0.59 (t, *J* = 12.4 Hz, 2H). LCMS (A analogous method to Method 7, ESI) 541.64 $[MH]^+$, RT 2.01 min.

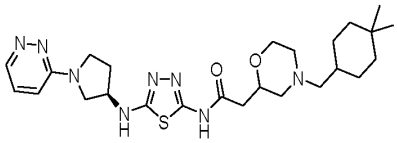
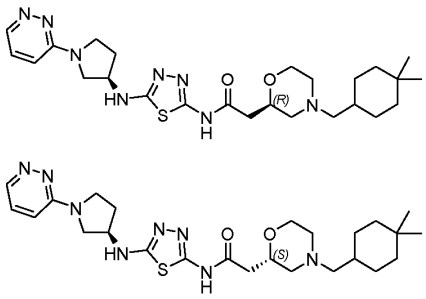
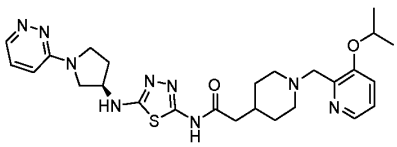
Example 56	 2-(2-{[3-(difluoromethoxy)phenyl]methyl}-2-azaspiro[3.3]heptan-6-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 8.33 – 8.26 (m, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.21 (t, *J* = 74.1 Hz, 1H), 7.13 – 7.09 (m, 1H), 7.05 – 6.99 (m, 1H), 6.87 (dd, *J* = 9.1, 1.4 Hz, 1H), 4.41 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.58 – 3.53 (m, 2H), 3.51 – 3.46 (m, 4H), 3.15 (s, 2H), 3.06 (s, 2H), 2.46 – 2.42 (m, 2H), 2.31 – 2.24 (m, 1H), 2.23 – 2.16 (m, 2H), 2.11 – 2.03 (m, 1H), 1.82 – 1.74 (m, 2H). LCMS (A analogous method to Method 7, ESI) 557.23 $[MH]^+$, RT 2.62 min.
Example 57	 2-{1-[(4,4-dimethylcyclohexyl)methyl]piperidin-4-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.47 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.53 – 7.38 (m, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.86 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.42 – 4.30 (m, 1H), 3.74 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.61 – 3.44 (m, 3H), 2.78 – 2.69 (m, 2H), 2.32 – 2.22 (m, 3H), 2.12 – 2.01 (m, 3H), 1.84 – 1.72 (m, 2H), 1.71 – 1.63 (m, 1H), 1.60 – 1.47 (m, 4H), 1.38 – 1.26 (m, 3H), 1.22 – 0.96 (m, 6H), 0.87 (s, 3H), 0.84 (s, 3H). LCMS (A analogous method to Method 7, ESI) 513.39 $[MH]^+$, RT 1.72 min.
Example 58	 3-(1-{[3-(difluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)propanamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.1 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.22 (t, *J* = 74.2 Hz, 1H), 7.18 – 7.13 (m, 1H), 7.08 (s, 1H), 7.06 – 7.01 (m, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.42 – 4.32 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.46 (m, 3H), 3.44 (s, 2H), 2.79 – 2.74 (m, 1H), 2.39 (t, *J* = 7.6 Hz, 3H), 2.33 – 2.27 (m, 1H), 2.13 – 2.02 (m, 1H), 1.95 – 1.82 (m, 2H), 1.65 – 1.56 (m, 2H), 1.55 – 1.44 (m, 2H), 1.22 – 1.09 (m, 3H). LCMS (A analogous method to Method 7, ESI) 559.34 $[MH]^+$, RT 2.68 min.

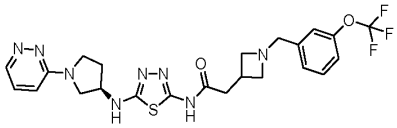
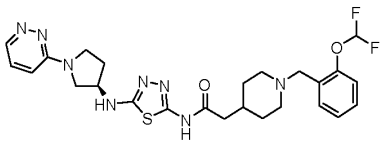
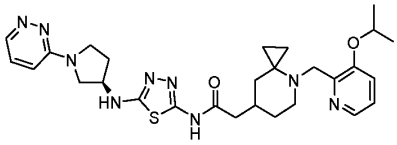
Example 59	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-8-{[3-(trifluoromethoxy)phenyl]methyl}-2-oxa-8-azaspiro[4.5]decane-3-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.81 (s, 1H), 8.48 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.51 – 7.40 (m, 1H), 7.36 – 7.30 (m, 2H), 7.29 – 7.20 (m, 2H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.55 (t, *J* = 7.8 Hz, 1H), 4.43 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.66 (s, 2H), 3.59 – 3.46 (m, 5H), 2.38 – 2.25 (m, 5H), 2.21 – 2.01 (m, 2H), 1.73 (dd, *J* = 12.6, 7.5 Hz, 1H), 1.59 – 1.49 (m, 4H). LCMS (Method 4, ESI) 605.27 [MH]$^+$, RT 1.68 min.Chiral HPLC (A analogous method to Method 12, 254 nm) RT_1 8.05 min; RT_2 15.04 min; d.r.= 49.67:49.76.
Example 60	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-{4-[(3,3,5,5-tetramethylcyclohexyl)methyl]piperazin-1-yl}acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.65 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.42 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61 – 3.46 (m, 3H), 3.22 (s, 2H), 2.39 – 2.25 (m, 5H), 2.13 – 2.00 (m, 3H), 1.90 – 1.72 (m, 1H), 1.49 – 1.39 (m, 2H), 1.21 (d, *J* = 13.4 Hz, 1H), 1.00 (d, *J* = 13.5 Hz, 1H), 0.95 (s, 6H), 0.85 (s, 6H), 0.60 (t, *J* = 12.4 Hz, 2H). LCMS (A analogous method to Method 7, ESI) 542.37 [MH]$^+$, RT 1.82 min.
Example 61	 2-{1-[methyl({[3-(trifluoromethoxy)phenyl]methyl})amino]cyclopropyl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 12.06 (s, 1H), 8.49 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.65 (d, *J* = 6.1 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.34 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.28 – 7.18 (m, 2H), 7.16 (s, 1H), 6.88 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.45 – 4.33 (m, 1H), 3.82 – 3.70 (m, 3H), 3.63 – 3.48 (m, 3H), 2.69 (s, 2H), 2.38 – 2.28 (m, 1H), 2.14 - 2.04 (m, 4H), 0.66 (d, *J* = 11.1 Hz, 4H). LCMS (A analogous method to Method 7, ESI) 549.18 [MH]$^+$, RT 1.84 min.

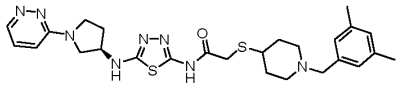
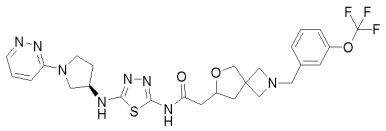
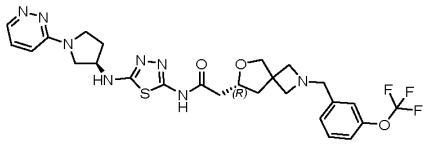
Example 62	 2-(1-{[4-hydroxy-3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (s, 1H), 10.04 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.15 – 7.05 (m, 2H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.42 – 4.29 (m, 1H), 3.74 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.61 – 3.46 (m, 3H), 2.80 – 2.72 (m, 2H), 2.34 – 2.27 (m, 3H), 2.13 – 2.01 (m, 1H), 1.97 – 1.83 (m, 2H), 1.74 – 1.64 (m, 1H),1.63 – 1.52 (m, 2H), 1.22 – 1.11 (m, 2H). LCMS (Method 7, ESI) 579.25 [MH]$^+$, RT 3.81 min.
Example 63	 2-{1-[(2-chlorophenyl)methyl]piperidin-4-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.47 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.41 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.36 – 7.23 (m, 3H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.41 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.46 (m, 5H), 2.83 – 2.74 (m, 2H), 2.34 – 2.25 (m, 3H), 2.12 – 1.96 (m, 3H), 1.80 – 1.66 (m, 1H), 1.65 – 1.54 (m, 2H), 1.28 – 1.14 (m, 2H). LCMS (Method 7, ESI) 513.27 [MH]$^+$, RT 1.32 min.
Example 64	 2-(4-methyl-1-{[3-(trifluoromethoxy)phenyl]methyl}piperazin-2-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 12.05 (s, 1H), 8.49 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.34 (dd, *J* = 8.8, 4.9 Hz, 2H), 7.27 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.88 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.39 (d, *J* = 4.5 Hz, 1H), 3.85 (d, *J* = 14.1 Hz, 1H), 3.76 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.62 – 3.42 (m, 5H), 3.00 (s, 1H), 2.81 (dd, *J* = 15.0, 4.4 Hz, 2H), 2.27 (s, 6H), 2.13 (s, 4H). LCMS (Method 6, ESI) 578.23 [MH]$^+$, RT 6.64 min; 578.19 [MH]$^+$, RT 6.71 min; d.r. = 49.94:49.53.

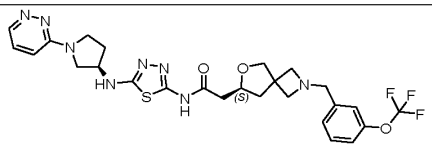
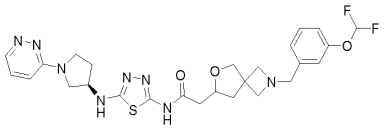
Example 65 and Example 66 Isomers A and B	 One of isomers A and B is 2-((*S*)-4-methyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((*R*)-4-methyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 12.02 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.63 (d, *J* =6.0 Hz, 1 H), 7.43 (t, *J* =8.0 Hz, 1 H), 7.31-7.35 (m, 2 H), 7.26 (s, 1 H), 7.21 (d, *J* =7.6 Hz, 1 H), 6.87 (d, *J* =9.2 Hz, 1 H), 4.35-4.43 (m, 1 H), 3.73-3.86 (m, 2 H), 3.42-3.59 (m, 4 H), 2.96-3.04 (m, 1 H), 2.78-2.83 (m, 1 H), 2.59-2.66 (m, 2 H), 2.34-2.50 (m, 1 H), 2.25-2.30 (m, 5 H), 2.07-2.14 (m, 4 H). LCMS (Method 16, ESI): 578.1 $[M+H]^+$, RT 1.383 minutes. Chiral SFC (General Procedure 5B): RT 4.012 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 12.02 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.63 (d, *J* =6.0 Hz, 1 H), 7.43 (t, *J* =8.0 Hz, 1 H), 7.32-7.35 (m, 2 H), 7.26 (s, 1 H), 7.21 (d, *J* =8.0 Hz, 1 H), 6.87 (d, *J* =9.2 Hz, 1 H), 4.35-4.42 (m, 1 H), 3.73-3.86 (m, 2 H), 3.42-3.59 (m, 4 H), 2.95-3.05 (m, 1 H), 2.78-2.83 (m, 1 H), 2.57-2.65 (m, 2 H), 2.34-2.51 (m, 1 H), 2.25-2.29 (m, 5 H), 2.04-2.14 (m, 4 H). LCMS (Method 16, ESI): 578.1 $[M+H]^+$, RT 1.383 minutes. Chiral SFC (General Procedure 5B): RT 5.429 minutes.
Example 67	 2-methoxy-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 12.05 (s, 1H), 8.49 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.70 (d, *J* = 6.0 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.26 (m, 3H), 6.88 (dt, *J* = 9.1, 1.1 Hz, 1H), 4.40 (d, *J* = 5.5 Hz, 1H), 3.80 – 3.67 (m, 2H), 3.55 (dt, *J* = 16.9, 8.7 Hz, 3H), 3.45 (s, 2H), 3.24 (d, *J* = 0.9 Hz, 3H), 2.78 (d, *J* = 11.3 Hz, 2H), 2.36 – 2.28 (m, 1H), 2.09 (dd, *J* = 12.0, 6.1 Hz, 1H), 1.87 (t, *J* = 11.5 Hz, 2H), 1.66 (d, *J* = 11.4 Hz, 2H), 1.44 – 1.26 (m, 3H). LCMS (Method 6, ESI) 593.16 $[MH]^+$, RT 6.15 min; 593.22 $[MH]^+$, RT 6.17 min.

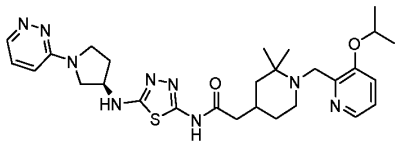
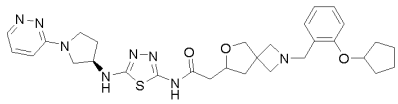
Example 68 and Example 69 Isomers A and B	 One of isomers A or B is (*R*)-2-methoxy-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)acetamide and the other is (*S*)-2-methoxy-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.70 (d, *J* =6.0 Hz, 1 H), 7.26-7.41 (m, 5 H), 6.87 (d, *J* =9.2 Hz, 1 H), 4.35-4.43 (m, 1 H), 3.73-3.78 (m, 2 H), 3.42-3.59 (m, 5 H), 3.23 (s, 3 H), 2.72-2.83 (m, 2 H), 2.25-2.33 (m, 1 H), 1.92-2.12 (m, 1 H), 1.80-1.85 (m, 2 H), 1.60-1.75 (m, 2 H), 1.25-1.43 (m, 3 H). LCMS (Method 15, ESI): 593.2 $[M+H]^+$, RT 1.159 minutes. Chiral SFC (General Procedure 5E): RT 1.078 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.70 (d, *J* =6.0 Hz, 1 H), 7.26-7.40 (m, 5 H), 6.87 (d, *J* =8.8 Hz, 1 H), 4.36-4.43 (m, 1 H), 3.70-3.77 (m, 2 H), 3.44-3.57 (m, 5 H), 3.24 (s, 3 H), 2.72-2.85 (m, 2 H), 2.28-2.32 (m, 1 H), 1.93-2.12 (m, 1 H), 1.80-1.86 (m, 2 H), 1.60-1.71 (m, 2 H), 1.28-1.43 (m, 3 H). LCMS (Method 15, ESI): 593.2 $[M+H]^+$, RT 1.159 minutes. Chiral SFC (General Procedure 5E): RT 1.561 minutes.
Example 70	 4-[(4,4-dimethylcyclohexyl)methyl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)thiomorpholine-2-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 12.21 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.74 – 7.60 (m, 1H), 7.33 (dd, *J* = 9.2, 4.5 Hz, 1H), 6.99 – 6.81 (m, 1H), 4.45 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.70 – 3.64 (m, 1H), 3.62 – 3.45 (m, 3H), 2.95 – 2.78 (m, 3H), 2.69 – 2.57 (m, 2H), 2.36 – 2.24 (m, 1H), 2.20 (d, *J* = 6.9 Hz, 2H), 2.13 – 2.01 (m, 1H), 1.67 – 1.38 (m, 3H), 1.36 – 1.22 (m, 3H), 1.20 – 0.97 (m, 4H), 0.87 (s, 3H), 0.84 (d, *J* = 1.8 Hz, 3H). LCMS (Method 8, ESI) 517.30 $[MH]^+$, RT 2.84 min. Chiral HPLC (Method 12, 254 nm) RT_1 11.40 min; RT_2 13.30 min; d.r.= 49.47:50.26.

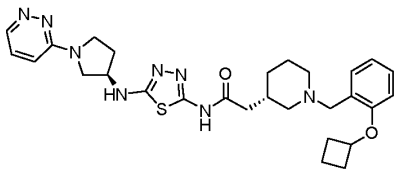
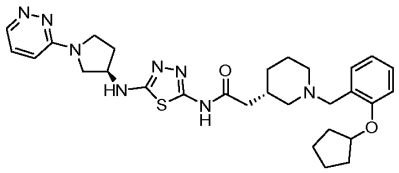
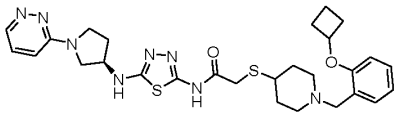
Example 71	 2-{4-[(4,4-dimethylcyclohexyl)methyl]morpholin-2-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.44 – 4.31 (m, 1H), 3.75 (s, 3H), 3.62 – 3.40 (m, 4H), 2.73 – 2.64 (m, 1H), 2.64 – 2.53 (m, 2H), 2.36 – 2.29 (m, 1H), 2.17 – 2.00 (m, 3H), 1.99 – 1.84 (m, 1H), 1.80 – 1.64 (m, 1H), 1.60 – 1.48 (m, 2H), 1.46 – 1.28 (m, 3H), 1.20 – 0.95 (m, 4H), 0.87 (s, 3H), 0.85 (s, 3H).LCMS (Method 1, ESI) 515.22 [MH]$^+$, RT 5.84 min. Chiral HPLC (Method 12, 254 nm) RT_1 9.69 min; RT_2 11.24 min; d.r.= 47.04:52.27.
Example 72 and Example 73 Isomers A and B	 One of isomers A or B is 2-((*R*)-4-((4,4-dimethylcyclohexyl)methyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((*S*)-4-((4,4-dimethylcyclohexyl)methyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d$_6$): δ 11.93 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.63 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 6.87 (d, *J* =8.8 Hz, 1 H), 4.35-4.42 (m, 1 H), 3.71-3.87 (m, 3 H), 3.42-3.59 (m, 4 H), 2.54-2.76 (m, 2 H), 2.25-2.34 (m, 1 H), 1.93-2.14 (m, 4 H), 1.53-1.73 (m, 3 H), 1.24-1.42 (m, 5 H), 1.04-1.16 (m, 4 H), 0.86 (d, *J* =12.0 Hz, 6 H). LCMS (Method 13, ESI): 515.4 [M+H]$^+$, RT 5.993 minutes. 1H NMR (400 MHz, DMSO-d$_6$): δ 11.93 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.63 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 6.87 (d, *J* =8.8 Hz, 1 H), 4.34-4.42 (m, 1 H), 3.71-3.88 (m, 3 H), 3.46-3.59 (m, 4 H), 2.51-2.77 (m, 2 H), 2.25-2.34 (m, 1 H), 1.90-2.14 (m, 4 H), 1.53-1.76 (m, 3 H), 1.24-1.41 (m, 5 H), 1.01-1.16 (m, 4 H), 0.86 (d, *J* =11.6 Hz, 6 H). LCMS (Method 19, ESI): 515.4 [M+H]$^+$, RT 5.981 minutes.
Example 74		^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 8.04 (dd, *J* = 4.6, 1.3 Hz, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.22 (dd, *J*

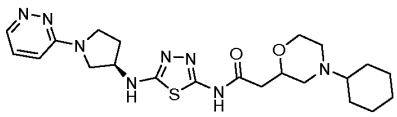
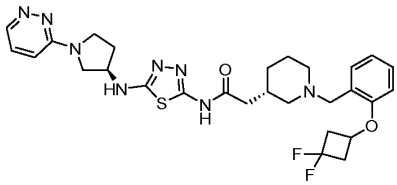
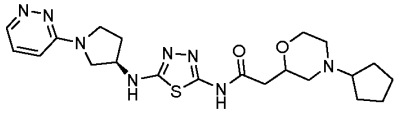
	2-(1-{[3-(propan-2-yloxy)pyridin-2-yl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	= 8.3, 4.6 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.63 (p, *J* = 6.0 Hz, 1H), 4.43 – 4.31 (m, 1H), 3.74 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.60 – 3.45 (m, 5H), 2.88 – 2.77 (m, 2H), 2.29 – 2.22 (m, 3H), 2.12 – 1.96 (m, 3H), 1.72 – 1.58 (m, 1H), 1.59 – 1.47 (m, 2H), 1.26 (d, *J* = 6.0 Hz, 6H), 1.21 – 1.06 (m, 2H). LCMS (Method 7, ESI) 538.33 $[MH]^+$, RT 2.55 min.
Example 75	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[3-(trifluoromethoxy)phenyl]methyl}azetidin-3-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.71 (d, *J* = 6.1 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.38 – 7.29 (m, 3H), 7.25 – 7.16 (m, 1H), 6.87 (dt, *J* = 9.2, 1.2 Hz, 1H), 4.43 – 4.35 (m, 1H), 4.09 – 4.00 (m, 1H), 3.80 – 3.68 (m, 4H), 3.60 – 3.47 (m, 3H), 2.70 – 2.64 (m, 1H), 2.59 – 2.55 (m, 2H), 2.43 – 2.35 (m, 2H), 2.34 – 2.27 (m, 1H), 2.14 – 2.02 (m, 1H). LCMS (Method 6, ESI) 535.13 $[MH]^+$, RT 6.06 min; 535.16 $[MH]^+$, RT 6.12 min.
Example 76	 2-(1-{[2-(difluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 11.92 (s, 1H), 8.49 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.59 (d, *J* = 5.9 Hz, 1H), 7.44 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.25 (td, *J* = 7.4, 1.2 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 74.7 Hz, 1H) 6.91 – 6.85 (m, 1H), 4.43 – 4.33 (m, 1H), 3.76 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.64 – 3.42 (m, 5H), 2.78 (d, *J* = 2.8 Hz, 2H), 2.36 – 2.27 (m, 3H), 2.16 – 2.03 (m, 1H), 2.03 – 1.90 (m, 2H), 1.86 – 1.64 (m, 1H), 1.59 (dd, *J* = 12.7, 3.1 Hz, 2H), 1.30 – 1.13 (m, 2H). LCMS (Method 6) 545.40 $[MH]^+$, RT 5.36 min.
Example 77	 2-(4-{[3-(propan-2-yloxy)pyridin-2-yl]methyl}-4-azaspiro[2.5]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.99 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.19 (dd, *J* = 8.3, 4.7 Hz, 1H), 6.87 (dd, *J* = 9.1, 1.3 Hz, 1H), 4.65 (h, *J* = 6.1, 5.6 Hz, 1H), 4.44 – 4.32 (m, 1H), 3.87 – 3.71 (m, 3H),

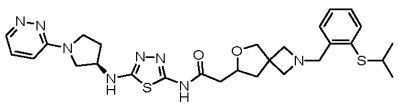
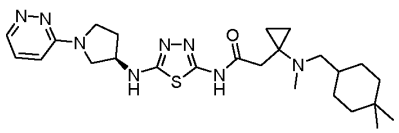
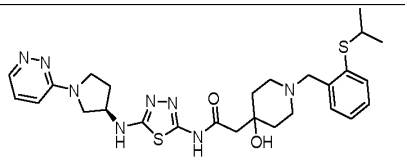
	yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	3.64 – 3.46 (m, 3H), 2.84 – 2.75 (m, 1H), 2.60 – 2.53 (m, 1H), 2.38 – 2.25 (m, 3H), 2.13 – 2.00 (m, 2H), 1.84 – 1.73 (m, 1H), 1.66 – 1.52 (m, 1H), 1.29 – 1.21 (m, 7H), 0.83 – 0.69 (m, 2H), 0.46 – 0.34 (m, 2H), 0.31 – 0.25 (m, 1H). LCMS (Method 6, ESI) 564.21 $[MH]^+$, RT 5.73 min.
Example 78	 2-({1-[(3,5-dimethylphenyl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 12.10 (s, 1H), 8.49 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.68 (d, *J* = 6.1 Hz, 1H), 7.34 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.98 – 6.80 (m, 4H), 4.48 – 4.32 (m, 1H), 3.76 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.63 – 3.47 (m, 3H), 3.40 (s, 2H), 3.36 (s, 2H), 2.74 (dd, *J* = 3.9, 2.0 Hz, 3H), 2.38 – 2.22 (m, 7H), 2.16 – 1.84 (m, 5H), 1.54 – 1.36 (m, 2H). LCMS (A analogous method to Method 7, ESI) 539.33 $[MH]^+$, RT 1.90 min.
Example 79	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(2-{[3-(trifluoromethoxy)phenyl]methyl}-6-oxa-2-azaspiro[3.4]octan-7-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.35 – 7.27 (m, 2H), 7.24 – 7.20 (m, 2H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.42 – 4.33 (m, 1H), 4.22 – 4.13 (m, 1H), 3.86 (d, *J* = 8.8 Hz, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.70 (d, *J* = 8.8 Hz, 1H), 3.59 (s, 2H), 3.58 – 3.54 (m, 2H), 3.52 – 3.47 (m, 1H), 3.22 – 3.11 (m, 4H), 2.61 – 2.54 (m, 2H), 2.31 – 2.26 (m, 1H), 2.25 – 2.18 (m, 1H), 2.12 – 2.03 (m, 1H), 1.76 (dd, *J* = 12.7, 7.4 Hz, 1H). LCMS (A analogous method to Method 7, ESI) 591.09 $[MH]^+$, RT 2.72 min. Chiral HPLC (Method 31, 254 nm) RT_1 11.38 min; RT_2 16.96 min; d.r.= 48.99:48.89.
Example 80 and Example 81 Isomers A and B		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.48 (d, *J* = 4.5 Hz, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.35 – 7.28 (m, 2H), 7.22 (d, *J* = 6.6 Hz, 2H), 6.87 (dd, *J* = 9.2, 1.1 Hz, 1H), 4.38 (dd, *J* = 9.8, 4.6 Hz, 1H), 4.21 – 4.11 (m, 1H),

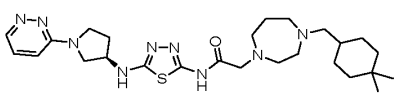
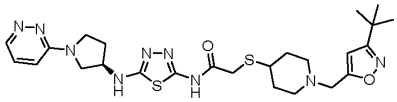
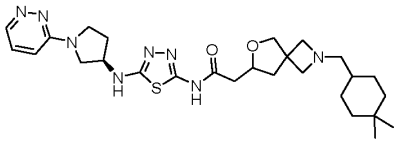
	 One of isomers A and B is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-2-(3-(trifluoromethoxy)benzyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)acetamide and the other is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-2-(3-(trifluoromethoxy)benzyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)acetamide	3.87 (d, *J* = 8.8 Hz, 1H), 3.77 – 3.67 (m, 2H), 3.61 – 3.46 (m, 5H), 3.17 (dt, *J* = 12.1, 6.6 Hz, 4H), 2.61 – 2.52 (m, 2H), 2.33 – 2.19 (m, 2H), 2.08 (dt, *J* = 11.4, 5.5 Hz, 1H), 1.76 (dd, *J* = 12.7, 7.4 Hz, 1H). LCMS (Method 15, ESI): 591.2 $[M+H]^+$, RT 0.820 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.48 (dd, *J* = 4.4, 1.1 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.35 – 7.28 (m, 2H), 7.22 (d, *J* = 6.5 Hz, 2H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.38 (dd, *J* = 9.8, 4.5 Hz, 1H), 4.21 – 4.13 (m, 1H), 3.87 (d, *J* = 8.8 Hz, 1H), 3.78 – 3.67 (m, 2H), 3.53 (ddd, *J* = 14.9, 14.4, 8.4 Hz, 5H), 3.23 – 3.09 (m, 4H), 2.62 – 2.51 (m, 2H), 2.26 (ddd, *J* = 19.3, 12.8, 6.2 Hz, 2H), 2.08 (dt, *J* = 12.1, 5.9 Hz, 1H), 1.76 (dd, *J* = 12.8, 7.4 Hz, 1H). LCMS (Method 15, ESI): 591.2 $[M+H]^+$, RT 0.814 minutes.
Example 82	 2-(2-{[3-(difluoromethoxy)phenyl]methyl}-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.48 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.62 (d, *J* = 6.1 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.22 (t, *J* = 74.2 Hz, 1H), 7.15 – 7.12 (m, 1H), 7.08 – 6.99 (m, 2H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.42 – 4.32 (m, 1H), 4.23 – 4.11 (m, 1H), 3.86 (d, *J* = 8.8 Hz, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.70 (d, *J* = 8.7 Hz, 1H), 3.61 – 3.52 (m, 4H), 3.54 – 3.45 (m, 1H), 3.22 – 3.09 (m, 4H), 2.63 – 2.53 (m, 2H), 2.32 – 2.16 (m, 2H), 2.13 – 2.03 (m, 1H), 1.76 (dd, *J* = 12.7, 7.4 Hz, 1H). LCMS (Method 8, ESI) 573.36 $[MH]^+$, RT 2.57 min. Chiral HPLC (A analogous method to Method 12, 254 nm) RT_1 14.37 min; RT_2 18.52 min; d.r.= 49.73:49.66.

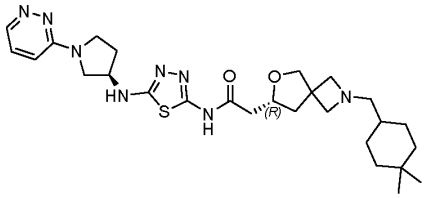
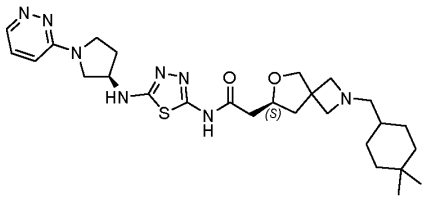
Example 83	 2-(2,2-dimethyl-1-{[3-(propan-2-yloxy)pyridin-2-yl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 8.00 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.60 (d, *J* = 6.1 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.20 (dd, *J* = 8.3, 4.6 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.67 (p, *J* = 6.0 Hz, 1H), 4.41 – 4.32 (m, 1H), 4.08 (d, *J* = 12.0 Hz, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.61 – 3.45 (m, 3H), 2.93 (d, *J* = 12.0 Hz, 1H), 2.76 – 2.70 (m, 1H), 2.34 – 2.23 (m, 2H), 2.22 – 2.15 (m, 2H), 2.13 – 2.01 (m, 1H), 2.01 – 1.85 (m, 1H), 1.50 – 1.34 (m, 2H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.25 (d, *J* = 6.0 Hz, 3H), 1.23 (s, 3H), 1.06 (t, *J* = 12.5 Hz, 1H), 0.97 (s, 3H), 0.95 – 0.84 (m, 1H). LCMS (Method 3, ESI) 566.29 $[MH]^+$, RT 4.06 min.Chiral HPLC (A analogous method to Method 12, 254 nm) RT_1 7.87 min; RT_2 9.63 min; d.r.= 53.96:45.61.
Example 84	 2-(2-{[2-(cyclopentyloxy)phenyl]methyl}-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.47 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.54 – 7.39 (m, 1H), 7.32 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.21 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.19 – 7.13 (m, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.89 – 6.82 (m, 2H), 4.85 – 4.77 (m, 1H), 4.41 – 4.33 (m, 1H), 4.16 (p, *J* = 6.8 Hz, 1H), 3.85 (d, *J* = 8.8 Hz, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.68 (d, *J* = 8.8 Hz, 1H), 3.62 – 3.53 (m, 2H), 3.51 – 3.48 (m, 1H), 3.46 (s, 2H), 3.21 – 3.17 (m, 1H), 3.17 – 3.11 (m, 3H), 2.58 – 2.52 (m, 1H), 2.48 – 2.38 (m, 1H), 2.31 – 2.24 (m, 1H), 2.22 – 2.15 (m, 1H), 2.11 – 2.02 (m, 1H), 1.91 – 1.82 (m, 2H), 1.78 – 1.67 (m, 5H), 1.63 – 1.55 (m, 2H). LCMS (Method 8, ESI) 591.33 $[MH]^+$, RT 2.91 min. Chiral HPLC (A analogous method to Method 12, 254 nm) RT_1 18.58 min; RT_2 21.96 min; d.r.= 50.03:47.30.

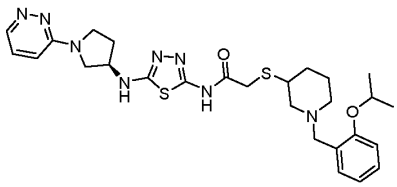
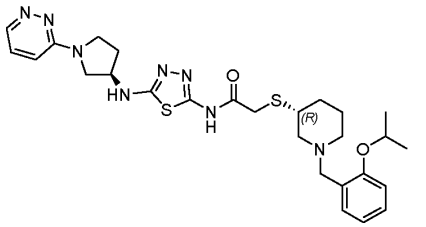
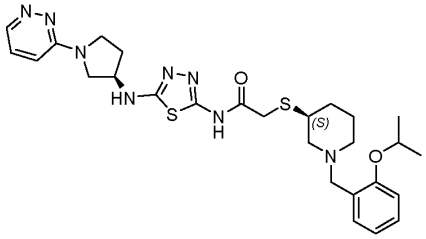
Example 85	 2-[(3*S*)-1-[(2-cyclobutoxyphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 11.92 (s, 1H), 8.54 – 8.44 (m, 1H), 7.63 (d, *J* = 6.1 Hz, 1H), 7.34 (dd, *J* = 9.2, 4.5 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.21 – 7.10 (m, 1H), 6.92 – 6.83 (m, 2H), 6.82 – 6.74 (m, 1H), 4.73 – 4.56 (m, 1H), 4.39 (dtt, *J* = 5.3, 4.4, 2.9 Hz, 1H), 3.82 – 3.71 (m, 1H), 3.63 – 3.41 (m, 5H), 2.68 (d, *J* = 11.6 Hz, 2H), 2.43 – 2.28 (m, 5H), 2.15 – 1.91 (m, 5H), 1.84 – 1.56 (m, 5H), 1.54 – 1.38 (m, 1H), 1.06 – 0.87 (m, 1H). LCMS (A analogous method to Method 7, ESI) 549.47 [MH]$^+$, RT 1.63 min.
Example 86	 2-[(3*S*)-1-{[2-(cyclopentyloxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.18 – 7.13 (m, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.87 (dd, *J* = 9.1, 1.4 Hz, 1H), 6.84 – 6.80 (m, 1H), 4.84 – 4.76 (m, 1H), 4.42 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.61 – 3.46 (m, 3H), 3.38 (s, 2H), 2.78 – 2.57 (m, 2H), 2.32 – 2.24 (m, 3H), 2.12 – 2.03 (m, 1H), 2.02 – 1.89 (m, 2H), 1.89 – 1.78 (m, 2H), 1.74 – 1.50 (m, 9H), 1.49 – 1.35 (m, 1H), 1.00 – 0.84 (m, 1H). LCMS (A analogous method to Method 7, ESI) 563.32 [MH]$^+$, RT 1.74 min.
Example 87	 2-({1-[(2-cyclobutoxyphenyl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 12.10 (s, 1H), 8.49 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.68 (d, *J* = 6.0 Hz, 1H), 7.34 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.28 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.17 (td, *J* = 7.9, 1.7 Hz, 1H), 6.89 (ddd, *J* = 7.4, 5.4, 1.0 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 1H), 4.67 (p, *J* = 7.0 Hz, 1H), 4.45 – 4.33 (m, 1H), 3.77 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.61 – 3.48 (m, 3H), 3.45 (s, 2H), 3.41 (s, 2H), 2.78 (d, *J* = 11.2 Hz, 2H), 2.47 – 2.35 (m, 3H), 2.35 – 2.25 (m, 1H), 2.16 - 1.96 (m, 5H), 1.97 – 1.86 (m, 2H), 1.85 – 1.71 (m, 1H), 1.70 – 1.57 (m,

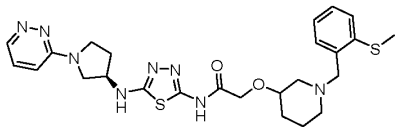
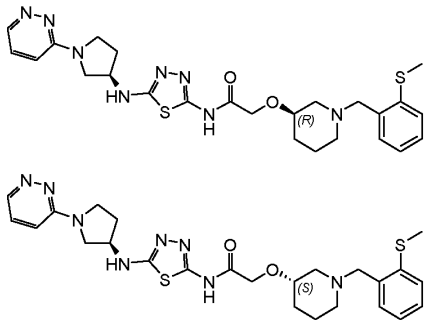
		1H), 1.46 (qd, *J* = 11.3, 3.4 Hz, 2H). LCMS (Method 6, ESI) 580.93 $[MH]^+$, RT 6.77 min.
Example 88	 2-(4-cyclohexylmorpholin-2-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.63 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.42 – 4.33 (m, 1H), 3.82 – 3.69 (m, 3H), 3.62 – 3.47 (m, 3H), 3.45 – 3.38 (m, 1H), 2.77 – 2.71 (m, 1H), 2.63 – 2.57 (m, 1H), 2.56 – 2.52 (m, 1H), 2.35 – 2.14 (m, 3H), 2.12 – 2.03 (m, 1H), 2.03 – 1.96 (m, 1H), 1.78 – 1.69 (m, 4H), 1.59 – 1.52 (m, 1H), 1.25–1.01 (m, 6H). LCMS (A analogous method to Method 7, ESI) 473.40 $[MH]^+$, RT 2.29 min.
Example 89	 2-[(3*S*)-1-{[2-(3,3-difluorocyclobutoxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.37 – 7.27 (m, 2H), 7.21 – 7.15 (m, 1H), 6.95 – 6.89 (m, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 6.85 – 6.82 (m, 1H), 4.82 – 4.70 (m, 1H), 4.42 – 4.32 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.53 – 3.46 (m, 1H), 3.45 – 3.42 (m, 2H), 3.22 – 3.10 (m, 2H), 2.74 – 2.60 (m, 4H), 2.35 – 2.24 (m, 3H), 2.11 – 2.03 (m, 1H), 2.02 – 1.93 (m, 2H), 1.80 – 1.72 (m, 1H), 1.66 – 1.55 (m, 2H), 1.49 – 1.38 (m, 1H), 1.00 – 0.89 (m, 1H). LCMS (A analogous method to Method 7, ESI) 585.12 $[MH]^+$, RT 2.79 min.
Example 90	 2-(4-cyclopentylmorpholin-2-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.1, 1.4 Hz, 1H), 4.41 – 4.34 (m, 1H), 3.85 – 3.69 (m, 3H), 3.61 – 3.54 (m, 2H), 3.52 – 3.50 (m, 1H), 3.49 – 3.45 (m, 1H), 3.44 – 3.40 (m, 1H), 2.84 – 2.79 (m, 1H), 2.73 – 2.69 (m, 1H), 2.46 – 2.38 (m, 2H), 2.31 – 2.22 (m, 1H), 2.12 – 2.03 (m, 1H), 2.02 – 1.94 (m, 1H), 1.82

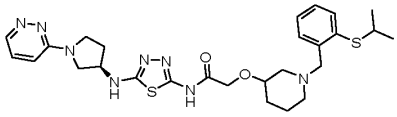
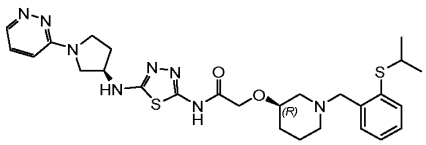
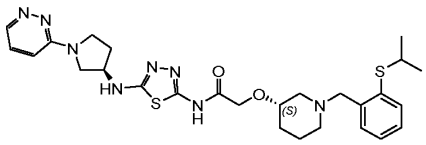
		– 1.70 (m, 3H), 1.64 – 1.54 (m, 2H), 1.54 – 1.43 (m, 2H), 1.37 – 1.25 (m, 2H). LCMS (Method 8, ESI) 459.23 $[MH]^+$, RT 3.66 min.
Example 91	 2-(2-{[2-(propan-2-ylsulfanyl)phenyl]methyl}-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.21 – 7.14 (m, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.91 – 6.84 (m, 2H), 4.57 (hept, *J* = 6.0 Hz, 1H), 4.43 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.46 (m, 3H), 3.42 (s, 2H), 3.39 (s, 2H), 2.83 – 2.71 (m, 3H), 2.37 – 2.25 (m, 1H), 2.13 – 1.99 (m, 3H), 1.94 – 1.86 (m, 2H), 1.53 – 1.36 (m, 2H), 1.24 (d, *J* = 6.0 Hz, 6H). LCMS (Method 8, ESI) 581.25 $[MH]^+$, RT 2.82 min. Chiral HPLC (A analogous method to Method 12, 254 nm) RT_1 12.93 min; RT_2 15.24 min; d.r.= 47.46:51.16.
Example 92	 2-(1-{[(4,4-dimethylcyclohexyl)methyl](methyl)amino}cyclopropyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, Methanol-d_4) δ 8.57 – 8.38 (m, 1H), 7.49 (dd, *J* = 9.3, 4.4 Hz, 1H), 7.19 – 7.05 (m, 1H), 4.59 – 4.46 (m, 1H), 3.90 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.77 – 3.60 (m, 3H), 2.82 (s, 3H), 2.64 (s, 2H), 2.51 – 2.37 (m, 1H), 2.30 – 2.17 (m, 1H), 1.67 – 1.49 (m, 3H), 1.45 – 1.37 (m, 2H), 1.34 (dd, *J* = 10.6, 3.4 Hz, 2H), 1.29 – 1.10 (m, 4H), 1.01 – 0.87 (m, 10H). LCMS (A analogous method to Method 7, ESI) 499.30 $[MH]^+$, RT 1.65 min.
Example 93	 2-(4-hydroxy-1-{[2-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.74 (bs, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.62 (d, *J* = 6.1 Hz, 1H), 7.44 – 7.29 (m, 3H), 7.27 – 7.16 (m, 2H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.63 – 4.43 (m, 1H), 4.42 – 4.29 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.61 – 3.42 (m, 6H), 2.48 – 2.22 (m, 7H), 2.13 – 2.02 (m, 1H), 1.67 – 1.48 (m, 4H), 1.20 (d, *J* = 6.6 Hz, 6H). LCMS (A

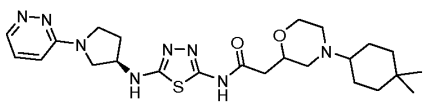
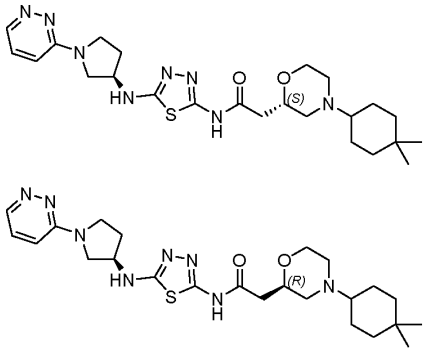
		analogous method to Method 7, ESI) 569.26 $[MH]^+$, RT 2.82 min.
Example 94	 2-{4-[(4,4-dimethylcyclohexyl)methyl]-1,4-diazepan-1-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 11.58 (s, 1H), 8.49 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H), 7.34 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.88 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.40 (ddd, *J* = 8.3, 5.8, 4.0 Hz, 1H), 3.76 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.54 (dtd, *J* = 15.8, 7.9, 3.5 Hz, 3H), 3.39 (s, 2H), 2.78 – 2.69 (m, 4H), 2.64 – 2.55 (m, 4H), 2.31 (dt, *J* = 19.8, 6.8 Hz, 3H), 2.09 (dt, *J* = 11.9, 5.5 Hz, 1H), 1.70 (hept, *J* = 4.6, 3.9 Hz, 2H), 1.61 – 1.49 (m, 2H), 1.33 (d, *J* = 12.1 Hz, 3H), 1.20 – 0.96 (m, 4H), 0.88 (s, 3H), 0.85 (s, 3H). LCMS (A analogous method to Method 7, ESI) 528.34 $[MH]^+$, RT 2.77 min.
Example 95	 2-({1-[(3-*tert*-butyl-1,2-oxazol-5-yl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d6) δ 12.10 (s, 1H), 8.49 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.34 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.88 (dd, *J* = 9.2, 1.3 Hz, 1H), 6.39 (s, 1H), 4.49 – 4.30 (m, 1H), 3.76 (dd, *J* = 11.2, 5.9 Hz, 1H), 3.63 – 3.47 (m, 5H), 3.39 (s, 2H), 2.87 – 2.70 (m, 3H), 2.38 – 2.25 (m, 1H), 2.19 – 2.02 (m, 3H), 1.98 – 1.83 (m, 2H), 1.48 (dd, *J* = 11.8, 8.4 Hz, 2H), 1.26 (s, 9H). LCMS (A analogous method to Method 7, ESI) 558.26 $[MH]^+$, RT 2.64 min.
Example 96	 2-{2-[(4,4-dimethylcyclohexyl)methyl]-6-oxa-2-azaspiro[3.4]octan-7-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.47 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.55 – 7.46 (m, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.86 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.42 – 4.32 (m, 1H), 4.15 (p, *J* = 7.0 Hz, 1H), 3.82 (d, *J* = 8.7 Hz, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.65 (d, *J* = 8.7 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.52 – 3.45 (m, 1H), 3.10 (d, *J* = 6.6 Hz, 1H), 3.06 – 3.02 (m, 3H), 2.59 – 2.53 (m, 1H), 2.48 – 2.40 (m, 1H), 2.36 – 2.23 (m, 1H), 2.19 (d, *J* = 6.7 Hz, 2H), 2.17 – 2.12 (m, 1H), 2.12 –

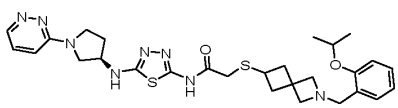
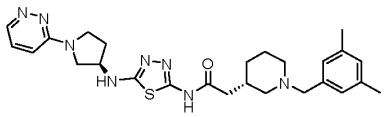
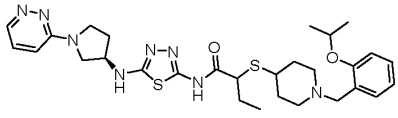
		2.02 (m, 1H), 1.71 (dd, *J* = 12.7, 7.4 Hz, 1H), 1.56 – 1.45 (m, 2H), 1.36 – 1.25 (m, 2H), 1.15 – 1.08 (m, 2H), 1.08 – 1.04 (m, 1H), 1.03 – 0.95 (m, 2H), 0.86 (s, 3H), 0.82 (s, 3H). LCMS (Method 8, ESI) 541.30 $[MH]^+$, RT 2.83 min. Chiral HPLC (A analogous method to Method 12, 254 nm) RT_1 7.00 min; RT_2 9.30 min; d.r.= 47.40:52.60.
Example 97 and Example 98 Isomers A and B	  One of isomers A and B is 2-((*R*)-2-((4,4-dimethylcyclohexyl)methyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((*S*)-2-((4,4-dimethylcyclohexyl)methyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (dd, *J* = 8.8, 1.2 Hz, 1H), 4.40-4.36 (m, 1H), 4.17-4.14 (m, 1H), 3.83 (d, *J* = 8.8 Hz, 1H), 3.77-3.73 (m, 1H), 3.66 (d, *J* = 8.8 Hz, 1H), 3.59-3.48 (m, 3H), 3.13 – 3.06 (m, 4H), 2.60-2.55 (m, 1H), 2.32-2.27 (m, 1H), 2.22-2.15 (m, 3H), 2.10-2.04 (m, 1H), 1.75-1.70 (m, 1H), 1.49 (d, *J* = 12.0 Hz, 2H), 1.32-1.23 (m, 4H), 1.13-1.09 (m, 2H), 1.06-0.99 (m, 2H), 0.84 (d, *J* = 14.1 Hz, 6H). LCMS (Method 13, ESI): 541.5 $[M+H]^+$, RT 1.177 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.39-4.38 (m, 1H), 4.17-4.14 (m, 1H), 3.82 (d, *J* = 8.8 Hz, 1H), 3.77-3.73 (m, 1H), 3.66 (d, *J* = 8.8 Hz, 1H), 3.59-3.48 (m, 3H), 3.13-3.06 (m, 4H), 2.60-2.55 (m, 1H), 2.30-2.29 (m, 1H), 2.22-2.15 (m, 3H), 2.10-2.05 (m, 1H), 1.75-1.70 (m, 1H), 1.49 (d, *J* = 12.0 Hz, 2H), 1.32-1.23 (m, 4H), 1.13-1.09 (m, 2H), 1.06-0.99 (m, 2H), 0.84 (d, *J* = 14.0 Hz, 6H). LCMS (Method 13, ESI): 541.4 $[M+H]^+$, RT 1.171 minutes.

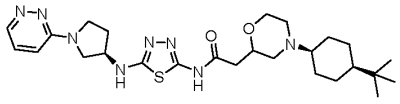
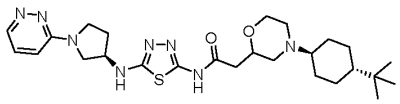
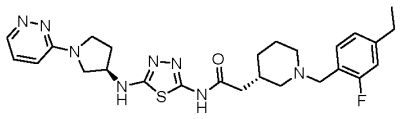
Example 99	 2-[(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-3-yl)sulfanyl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.26 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.19 – 7.12 (m, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.90 – 6.81 (m, 2H), 4.56 (hept, *J* = 6.1 Hz, 1H), 4.42 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61 – 3.54 (m, 2H), 3.53 – 3.48 (m, 1H), 3.44 (s, 2H), 3.37 (s, 2H), 2.98 – 2.87 (m, 2H), 2.63 – 2.55 (m, 1H), 2.33 – 2.23 (m, 1H), 2.12 – 1.98 (m, 3H), 1.89 – 1.83 (m, 1H), 1.72 – 1.63 (m, 1H), 1.54 – 1.40 (m, 1H), 1.24 (d, *J* = 6.0 Hz, 6H), 1.22 – 1.14 (m, 1H). LCMS (A analogous method to Method 7, ESI) 569.26 $[MH]^+$, RT 2.81 min.
Example 100 and Example 101 Isomers A and B	  One of isomers A and B is 2-(((*R*)-1-(2-isopropoxybenzyl)piperidin-3-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-(((*S*)-1-(2-isopropoxybenzyl)piperidin-3-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-*d6*) δ12.07 (s, 1H), 8.48 (dd, *J* = 3.6 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.26 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.18-7.13 (m, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.86 (m, 2H), 4.59-4.53 (m, 1H), 4.40-4.37 (m, 1H), 3.77-3.73 (m, 1H), 3.59-3.50 (m, 3H), 3.44 (s, 2H), 3.37 (s, 2H), 2.96-2.89 (m, 2H), 2.60-2.58 (m, 1H), 2.33-2.25 (m, 1H), 2.11-2.01 (m, 3H), 1.88-1.85 (m, 1H), 1.70-1.65 (m, 1H), 1.48-1.45 (m, 1H), 1.24-1.18 (m, 7H). LCMS (Method 13, ESI): 569.2 $[M+H]^+$, RT 1.003 minutes. ^{1}H NMR (400 MHz, DMSO-*d6*) δ12.07 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.26-7.16 (m, 2H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.43-4.35 (m, 1H), 4.15 (s, 2H), 3.76 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.60-3.40 (m, 7H), 2.88 (d, *J* = 8.4 Hz, 1H), 2.59-2.54 (m, 1H), 2.36-2.26 (m, 1H), 2.13-1.97 (m, 3H), 1.95-1.88 (m, 1H), 1.70-1.61 (m, 1H), 1.43-

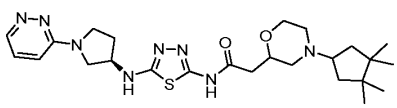
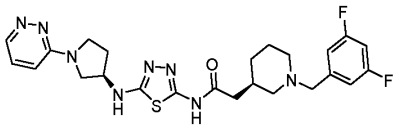
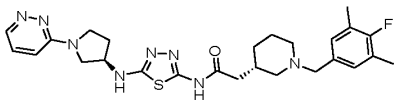
		1.32 (m, 1H), 1.25-1.15 (m, 7H). LCMS (Method 15, ESI): 569.2 $[M+H]^+$, RT 0.998 minutes.
Example 102	 2-[(1-{[2-(methylsulfanyl)phenyl]methyl}piperidin-3-yl)oxy]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.76 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.67 (d, *J* = 6.1 Hz, 1H), 7.37 – 7.22 (m, 4H), 7.16 – 7.05 (m, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.42 – 4.35 (m, 1H), 4.15 (s, 2H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.59 – 3.41 (m, 7H), 2.93 – 2.84 (m, 1H), 2.41 (s, 3H), 2.34 – 2.26 (m, 1H), 2.13 – 1.88 (m, 4H), 1.70 – 1.60 (m, 1H), 1.45 – 1.29 (m, 1H), 1.27 – 1.14 (m, 1H). LCMS (Method 2, ESI) 541.39 $[MH]^+$, RT 4.21 min. Chiral HPLC (A analogous method to Method 12, 254 nm) RT_1 13.23 min; RT_2 18.31 min; d.r.= 48.32:49.85.
Example 103 and Example 104 Isomers A and B	 One of isomers A and B is 2-(((*R*)-1-(2-(methylthio)benzyl)piperidin-3-yl)oxy)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-(((*S*)-1-(2-(methylthio)benzyl)piperidin-3-yl)oxy)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, MeOD-d_4) δ 8.42 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.40-7.36 (m, 1H), 7.33-7.23 (m, 3H), 7.13-7.09 (m, 1H), 6.97 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.51-4.49 (m, 1H), 4.23-4.12 (m, 2H), 3.88-3.84 (m, 1H), 3.69 – 3.59 (m, 6H), 2.73 (d, *J* = 11.6 Hz, 1H), 2.50-2.40 (m, 3H), 2.43-2.38 (m, 4H), 2.23-2.20 (m, 1H), 1.84-1.81 (m, 2H), 1.57-1.51 (m, 2H). LCMS (Method 13, ESI): 541.3 $[M+H]^+$, RT 1.044 minutes. Chiral SFC (General Procedure 5G): RT 2.492 minutes. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.42 (d, *J* = 4.0 Hz, 1H), 7.40-7.30 (m, 4H), 7.17 (t, *J* = 7.2 Hz, 1H), 6.97 (dd, *J* = 9.2, 0.8 Hz, 1H), 4.52-4.47 (m, 1H), 4.28-4.16 (m, 2H), 3.86 (dd, *J* = 11.2, 5.6 Hz, 2H), 3.69-3.58 (m, 5H), 2.89-2.71 (m, 4H), 2.46-2.37 (m, 4H), 2.24-2.18 (m, 1H), 1.93-1.90 (m, 1H), 1.82-1.79 (m, 1H), 1.69-1.58 (m, 2H). LCMS (Method 13, ESI): 541.3 $[M+H]^+$, RT 1.044 minutes. Chiral SFC (General Procedure 5G): RT 3.390 minutes.

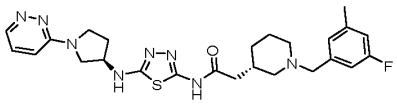
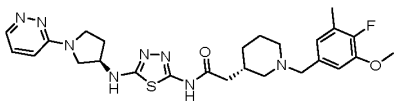
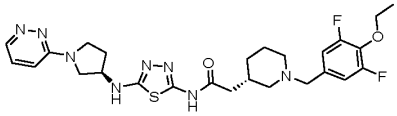
Example 105	 2-[(1-{[2-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-3-yl)oxy]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.77 (s, 1H), 8.48 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.47 – 7.29 (m, 3H), 7.29 – 7.15 (m, 2H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.42 – 4.34 (m, 1H), 4.13 (s, 2H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.62 – 3.42 (m, 7H), 2.92 – 2.83 (m, 1H), 2.61 – 2.54 (m, 1H), 2.36 – 2.21 (m, 1H), 2.13 – 1.87 (m, 4H), 1.70 – 1.60 (m, 1H), 1.44 – 1.30 (m, 1H), 1.26 – 1.22 (m, 1H), 1.21 (s, 3H), 1.19 (s, 3H). LCMS (Method 2, ESI) 569.19 [MH]$^+$, RT 5.00 min. Chiral HPLC (Method 12, 254 nm) RT_1 8.55 min; RT_2 12.69 min; d.r.= 45.52:46.10.
Example 106 and Example 107 Isomers A and B	  One of isomers A and B is 2-(((*R*)-1-(2-(isopropylthio)benzyl)piperidin-3-yl)oxy)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-(((*S*)-1-(2-(isopropylthio)benzyl)piperidin-3-yl)oxy)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-*d6*) δ11.78 (s, 1H), 8.48 (dd, *J* = 3.6 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.26-7.17 (m, 2H), 6.86 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.40-4.37 (m, 1H), 4.15 (s, 2H), 3.76 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.62-3.39 (m, 7H), 2.88 (d, *J* = 8.4 Hz, 1H), 2.60-2.58 (m, 1H), 2.33-2.25 (m, 1H), 2.14-2.01 (m, 3H), 1.88-1.85 (m, 1H), 1.70-1.60 (m, 1H), 1.42-1.30 (m, 1H), 1.25-1.19 (m, 7H). LCMS (Method 15, ESI): 569.2 [M+H]$^+$, RT 1.015 minutes. ^{1}H NMR (400 MHz, DMSO-*d6*) δ11.77 (s, 1H), 8.48 (dd, *J* = 3.6 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.26-7.17 (m, 2H), 6.86 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.40-4.37 (m, 1H), 4.15 (s, 2H), 3.76 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.62-3.39 (m, 7H), 2.88 (d, *J* = 8.4 Hz, 1H), 2.60-2.58 (m, 1H), 2.33-2.25 (m, 1H), 2.14-2.01 (m, 3H), 1.88-1.85 (m, 1H), 1.70-1.60 (m, 1H), 1.42-1.30 (m, 1H), 1.25-1.19 (m, 7H). LCMS (Method

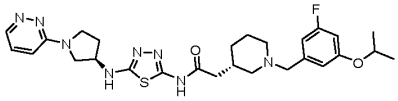
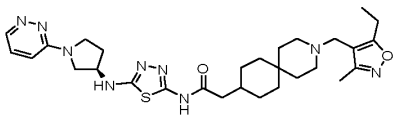
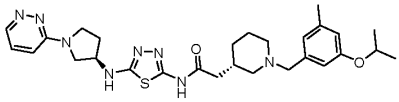
		13, ESI): 569.4 $[M+H]^+$, RT 1.021 minutes.
Example 108	 2-[4-(4,4-dimethylcyclohexyl)morpholin-2-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.43 – 4.32 (m, 1H), 3.83 – 3.70 (m, 3H), 3.60 – 3.51 (m, 2H), 3.49 – 3.37 (m, 2H), 2.82 – 2.75 (m, 1H), 2.68 – 2.60 (m, 1H), 2.36 – 2.02 (m, 5H), 1.97 (t, *J* = 10.5 Hz, 1H), 1.63 – 1.52 (m, 2H), 1.43 – 1.29 (m, 4H), 1.28 – 1.07 (m, 3H), 0.87 (s, 3H), 0.86 (s, 3H). LCMS (Method 6, ESI) 501.30 $[MH]^+$, RT 2.70 min; 501.44 $[MH]^+$, RT 2.73 min. Chiral HPLC (A analogous method to Method 12, 254 nm) RT_1 12.80 min; RT_2 15.72 min; d.r.= 47.28:52.72
Example 109 and Example 110 Isomers A and B	 One of isomers A and B is 2-((*S*)-4-(4,4-dimethylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((*R*)-4-(4,4-dimethylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-*d6*) δ11.93 (s, 1H), 8.48 (dd, *J* = 4.4, 1.1 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.40-4.37 (m, 1H), 3.77-3.72 (m, 3H), 3.57-3.42 (m, 4H), 2.78 (d, *J* = 11.0 Hz, 1H), 2.64 (d, *J* = 10.8 Hz, 1H), 2.55-2.46 (m, 2H), 2.34-2.16 (m, 2H), 2.13-1.97 (m, 3H) , 1.57 (d, *J* = 11.0 Hz, 2H), 1.42 – 1.27 (m, 4H), 1.14-1.11 (m, 2H), 0.86 (d, *J* = 6.4 Hz, 6H). LCMS (Method 15, ESI): 501.1 $[M+H]^+$, RT 1.04 minutes. Chiral SFC (General Procedure 5B): RT 0.902 minutes. ^{1}H NMR (400 MHz, DMSO-*d6*) δ11.94 (s, 1H), 8.48 (dd, *J* = 4.4, 1.1 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.40-4.37 (m, 1H), 3.77-3.72 (m, 3H), 3.57-3.42 (m, 4H), 3.01-2.98 (m, 1H),2.78-2.66 (m, 2H), 2.59-2.57 (m, 1H), 2.34-2.27 (m, 2H), 2.10-1.98 (m, 3H) , 1.57 (d, *J* = 11.0 Hz, 2H), 1.42 – 1.27 (m,

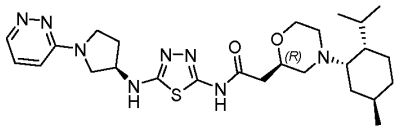
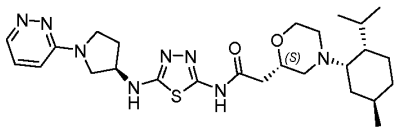
		4H), 1.14-1.11 (m, 2H), 0.86 (d, *J* = 6.4 Hz, 6H). LCMS (Method 15, ESI): 501.1 $[M+H]^+$, RT 1.04 minutes. Chiral SFC (General Procedure 5B): RT 1.369 minutes.
Example 111	 2-[(2-{[2-(propan-2-yloxy)phenyl]methyl}-2-azaspiro[3.3]heptan-6-yl)sulfanyl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (s, 1H), 8.48 (dd, *J* = 4.4, 1.1 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.24 – 7.13 (m, 2H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.92 – 6.81 (m, 2H), 4.57 (dt, *J* = 12.3, 6.1 Hz, 1H), 4.44 – 4.33 (m, 1H), 3.76 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.62 – 3.38 (m, 7H), 3.29 – 3.12 (m, 5H), 2.47 – 2.41 (m, 2H), 2.36 – 2.25 (m, 1H), 2.17 – 2.04 (m, 1H), 2.04 – 1.91 (m, 2H), 1.25 (d, *J* = 6.0 Hz, 6H). LCMS (Method 8, ESI) 581.29 $[MH]^+$, RT 2.88 min.
Example 112	 2-[(3*S*)-1-[(3,5-dimethylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.48 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.88 – 6.82 (m, 4H), 4.41 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61 – 3.47 (m, 3H), 3.38 – 3.33 (m, 1H), 3.31 – 3.26 (m, 1H), 2.65 – 2.59 (m, 1H), 2.31 – 2.23 (m, 3H), 2.22 (s, 6H), 2.12 – 2.03 (m, 1H), 2.02 – 1.85 (m, 2H), 1.74 – 1.66 (m, 1H), 1.66 – 1.55 (m, 2H), 1.48 – 1.36 (m, 1H), 1.01 – 0.89 (m, 1H). LCMS (A analogous method to Method 7, ESI) 507.32 $[MH]^+$, RT 2.70 min.
Example 113	 2-[(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-4-yl)sulfanyl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)butanamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 12.13 (s, 1H), 8.63 – 8.40 (m, 1H), 7.69 (d, *J* = 6.0 Hz, 1H), 7.35 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.93 – 6.84 (m, 2H), 4.58 (pd, *J* = 7.1, 6.6, 1.8 Hz, 1H), 4.40 (ddd, *J* = 6.1, 4.9, 3.0 Hz, 1H), 3.77 (dd, *J* = 11.0, 5.9 Hz, 1H), 3.64 – 3.46 (m, 4H), 3.46 (s, 2H), 2.86 – 2.67 (m, 3H), 2.40 – 2.24 (m, 1H), 2.15 – 2.00 (m, 3H), 2.00 – 1.87 (m, 1H), 1.87 – 1.75

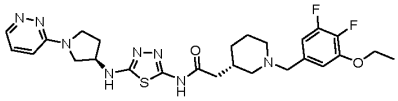
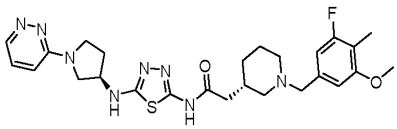
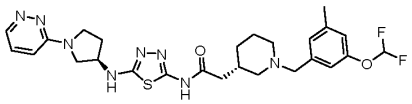
		(m, 2H), 1.72 – 1.56 (m, 1H), 1.54 – 1.36 (m, 2H), 1.26 (dd, *J* = 6.0, 1.5 Hz, 6H), 0.89 (t, *J* = 7.2 Hz, 3H). LCMS (A analogous method to Method 7, ESI) 597.28 $[MH]^+$, RT 2.99 min.
Example 114	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-{4-[(1s,4s)-4-tert-butylcyclohexyl]morpholin-2-yl}acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (dd, *J* = 4.5, 1.1 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.46 – 4.31 (m, 1H), 3.84 – 3.68 (m, 3H), 3.61 – 3.35 (m, 6H), 2.81 – 2.68 (m, 1H), 2.67 – 2.57 (m, 1H), 2.36 – 1.92 (m, 5H), 1.89 – 1.70 (m, 4H), 1.29 – 0.86 (m, 5H), 0.82 (s, 9H). LCMS (Method 4, ESI) 529.32 $[MH]^+$, RT 1.95 min. Chiral HPLC (A analogous method to Method 12, 254 nm) RT_1 11.68 min; RT_2 15.04 min; d.r.= 49.11:50.89.
Example 115	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-{4-[(1r,4r)-4-tert-butylcyclohexyl]morpholin-2-yl}acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.62 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.46 – 4.30 (m, 1H), 3.89 – 3.72 (m, 3H), 3.61 – 3.37 (m, 4H), 2.95 – 2.86 (m, 1H), 2.81 – 2.71 (m, 1H), 2.58 – 2.53 (m, 2H), 2.38 – 2.23 (m, 1H), 2.14 – 2.01 (m, 2H), 2.01 – 1.93 (m, 2H), 1.85 (td, *J* = 11.1, 2.9 Hz, 1H), 1.64 (t, *J* = 10.5 Hz, 1H), 1.41 – 1.18 (m, 6H), 1.13 – 0.97 (m, 1H), 0.82 (s, 9H). LCMS (A analogous method to Method 7, ESI) 529.32 $[MH]^+$, RT 1.84 min. Chiral HPLC (Method 36, 254 nm) RT_1 7.99 min; RT_2 9.00 min; d.r.= 47.65:52.19
Example 116	 2-[(3*S*)-1-[(4-ethyl-2-fluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (bs, 1H), 8.47 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.57 – 7.46 (m, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.00 – 6.91 (m, 2H), 6.86 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.42 – 4.32 (m, 1H), 3.75 (dd, *J* = 11.1, 5.9 Hz, 1H), 3.60 – 3.46 (m, 3H),

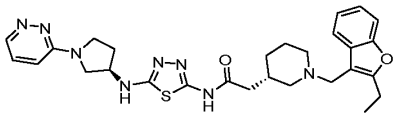
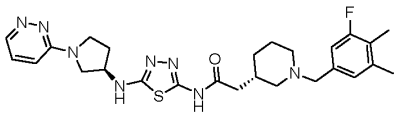
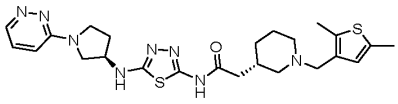
	yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	3.42 (s, 2H), 2.68 – 2.54 (m, 5H), 2.29 – 2.24 (m, 2H), 2.12 – 2.02 (m, 1H), 2.02 – 1.88 (m, 2H), 1.78 – 1.68 (m, 1H), 1.67 – 1.52 (m, 2H), 1.49 – 1.36 (m, 1H), 1.14 (t, *J* = 7.6 Hz, 3H), 1.01 – 0.86 (m, 1H). LCMS (A analogous method to Method 7, ESI) 525.30 $[MH]^+$, RT 2.71 min.
Example 117	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[4-(3,3,4,4-tetramethylcyclopentyl)morpholin-2-yl]acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (d, *J* = 9.3 Hz, 1H), 4.43 – 4.33 (m, 1H), 3.85 – 3.66 (m, 3H), 3.60 – 3.39 (m, 4H), 2.84 – 2.76 (m, 1H), 2.70 – 2.63 (m, 1H), 2.59 – 2.52 (m, 3H), 2.32 – 2.24 (m, 1H), 2.12 – 2.02 (m, 1H), 1.90 – 1.80 (m, 1H), 1.68 – 1.59 (m, 3H), 1.57 – 1.47 (m, 2H), 0.86 (s, 6H), 0.83 (s, 6H). LCMS (Method 5, ESI) 515.30 $[MH]^+$, RT 1.44 min. Chiral HPLC (A analogous method to Method 12, 254 nm) RT_1 9.48 min; RT_2 11.89 min; d.r.= 49.05:50.10.
Example 118	 2-[(3*R*)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.22 – 6.92 (m, 3H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.41 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.61 – 3.43 (m, 5H), 2.67 – 2.54 (m, 1H), 2.36 – 2.23 (m, 4H), 2.13 – 1.92 (m, 3H), 1.86 – 1.70 (m, 1H), 1.70 – 1.55 (m, 2H), 1.54 – 1.38 (m, 1H), 1.09 – 0.87 (m, 1H). LCMS (A analogous method to Method 7, ESI) 515.29 $[MH]^+$, RT 2.49 min.
Example 119	 2-[(3*S*)-1-[(4-fluoro-3,5-dimethylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.57 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 2H), 6.86 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.43 – 4.31 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.62 – 3.46 (m, 3H), 3.30 – 3.23 (m, 2H), 2.67 – 2.58 (m, 2H), 2.33 – 2.25 (m, 3H), 2.17

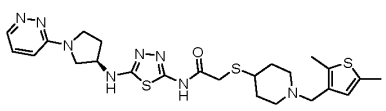
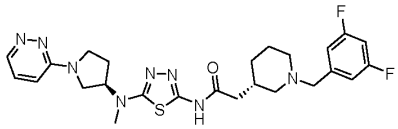
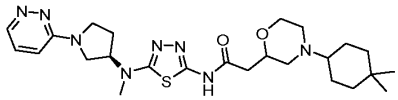
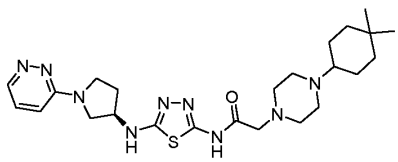
		(s, 3H), 2.16 (s, 3H), 2.13 – 2.03 (m, 1H), 2.01 – 1.83 (m, 2H), 1.75 – 1.51 (m, 3H), 1.50 – 1.36 (m, 1H), 1.02 – 0.88 (m, 1H). LCMS (A analogous method to Method 7, ESI) 525.29 $[MH]^+$, RT 2.75 min.
Example 120	 2-[(3*S*)-1-[(3-fluoro-5-methylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.59 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.92 (s, 1H), 6.90 – 6.83 (m, 3H), 4.42 – 4.32 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.53 – 3.47 (m, 1H), 3.46 – 3.31 (m, 3H), 2.65 – 2.58 (m, 1H), 2.32 – 2.24 (m, 6H), 2.12 – 2.03 (m, 1H), 2.03 – 1.89 (m, 2H), 1.78 – 1.69 (m, 1H), 1.67 – 1.55 (m, 2H), 1.50 – 1.38 (m, 1H), 1.02 – 0.91 (m, 1H). LCMS (A analogous method to Method 7, ESI) 511.22 $[MH]^+$, RT 2.58 min.
Example 121	 2-[(3*S*)-1-[(4-fluoro-3-methoxy-5-methylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.48 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.62 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.89 – 6.84 (m, 2H), 6.70 (d, *J* = 6.3 Hz, 1H), 4.42 – 4.34 (m, 1H), 3.78 (s, 3H), 3.77 – 3.72 (m, 1H), 3.60 – 3.52 (m, 2H), 3.50 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.39 – 3.35 (m, 3H), 2.65 – 2.59 (m, 1H), 2.31 – 2.27 (m, 3H), 2.17 (d, *J* = 2.2 Hz, 3H), 2.11 – 2.03 (m, 1H), 2.02 – 1.89 (m, 2H), 1.76 – 1.68 (m, 1H), 1.66 – 1.55 (m, 2H), 1.49 – 1.39 (m, 1H), 1.04 – 0.91 (m, 1H). LCMS (A analogous method to Method 7, ESI) 541.24 $[MH]^+$, RT 2.64 min.
Example 122	 2-[(3*S*)-1-[(4-ethoxy-3,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.56 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 7.06 – 7.00 (m, 2H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.41 – 4.33 (m, 1H), 4.08 (q, *J* = 7.0 Hz, 2H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.53 – 3.46 (m, 1H), 3.43 – 3.35 (m, 2H), 2.66 – 2.56 (m, 2H), 2.32 – 2.24 (m, 3H),

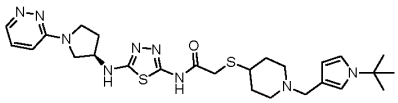
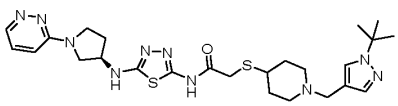
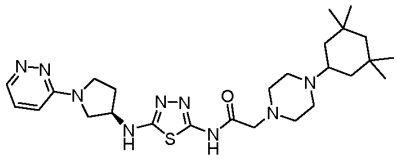
		2.11 – 2.03 (m, 1H), 2.03 – 1.91 (m, 2H), 1.75 (t, *J* = 10.2 Hz, 1H), 1.67 – 1.55 (m, 2H), 1.51 – 1.39 (m, 1H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.03 – 0.92 (m, 1H). LCMS (A analogous method to Method 7, ESI) 559.37 $[MH]^+$, RT 2.70 min.
Example 123	 2-[(3*S*)-1-{[3-fluoro-5-(propan-2-yloxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.59 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 6.67 – 6.59 (m, 3H), 4.62 – 4.54 (m, 1H), 4.41 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.52 (m, 2H), 3.50 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.43 – 3.34 (m, 2H), 2.69 – 2.58 (m, 2H), 2.31 – 2.23 (m, 3H), 2.11 – 2.02 (m, 1H), 2.01 – 1.90 (m, 2H), 1.79 – 1.69 (m, 1H), 1.66 – 1.55 (m, 2H), 1.49 – 1.38 (m, 1H), 1.23 (d, *J* = 6.0 Hz, 6H), 1.02–0.90 (m, 1H). LCMS (A analogous method to Method 7, ESI) 555.23 $[MH]^+$, RT 2.80 min.
Example 124	 2-{3-[(5-ethyl-3-methyl-1,2-oxazol-4-yl)methyl]-3-azaspiro[5.5]undecan-9-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.40 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.50 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.19 (s, 2H), 2.69 (q, *J* = 7.5 Hz, 2H), 2.34 – 2.22 (m, 7H), 2.15 (s, 3H), 2.12 – 2.02 (m, 1H), 1.74 – 1.64 (m, 1H), 1.63 – 1.53 (m, 2H), 1.47 – 1.37 (m, 4H), 1.28 – 1.23 (m, 2H), 1.15 (t, *J* = 7.6 Hz, 3H), 1.13 – 0.97 (m, 4H). LCMS (A analogous method to Method 7, ESI) 580.34 $[MH]^+$, RT 1.44 min.
Example 125	 2-[(3*S*)-1-{[3-methyl-5-(propan-2-yloxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 6.62 – 6.59 (m, 2H), 6.56 (s, 1H), 4.52

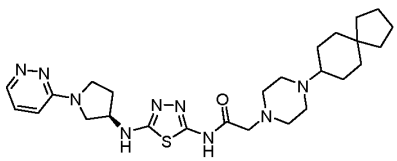
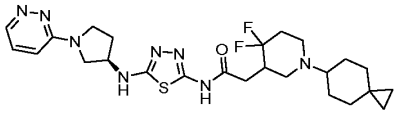
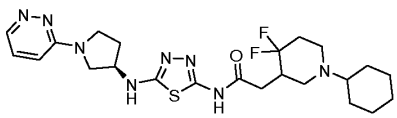
	{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	(hept, *J* = 6.1 Hz, 1H), 4.42 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.60 – 3.46 (m, 3H), 3.39 – 3.23 (m, 2H), 2.65 – 2.59 (m, 2H), 2.31 – 2.26 (m, 3H), 2.21 (s, 3H), 2.15 – 2.03 (m, 1H), 2.02 – 1.86 (m, 2H), 1.76 – 1.67 (m, 1H), 1.67 – 1.55 (m, 2H), 1.47 – 1.39 (m, 1H), 1.22 (d, *J* = 6.0 Hz, 6H), 1.06 – 0.85 (m, 1H). LCMS (A analogous method to Method 7, ESI) 551.19 $[MH]^+$, RT 2.88 min.
Example 126 and Example 127 Isomers A and B	  One of isomers A and B is 2-{(*R*)-4-[(1*S*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]morpholin-2-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-{(*S*)-4-[(1*S*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]morpholin-2-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide. Examples 126 and Example 127 each represent a mixture of Isomer A and Isomer B, distinguished by their diastereomeric ratios.	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.44 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.40 (dd, *J* = 9.2, 4.5 Hz, 1H), 6.94 (dd, *J* = 9.3, 1.3 Hz, 1H), 5.46 – 5.36 (m, 1H), 4.45 – 4.38 (m, 1H), 4.25 – 4.14 (m, 1H), 4.00 – 3.93 (m, 1H), 3.90 – 3.82 (m, 1H), 3.77 – 3.69 (m, 1H), 3.67 – 3.60 (m, 3H), 3.30 – 3.26 (m, 1H), 3.17 – 3.10 (m, 1H), 3.10 – 2.99 (m, 1H), 2.95 – 2.82 (m, 1H), 2.69 – 2.60 (m, 2H), 2.44 – 2.34 (m, 1H), 2.28 – 2.20 (m, 1H), 2.19 – 2.06 (m, 1H), 1.97 – 1.84 (m, 2H), 1.82 – 1.74 (m, 1H), 1.46 – 1.30 (m, 4H), 1.10 – 0.98 (m, 1H), 0.92 – 0.85 (m, 9H). LCMS (A analogous method to Method 8, ESI) 529.23 $[MH]^+$, RT 3.91 min; 529.23 $[MH]^+$, RT 4.20 min; d.r. = 86.27:9.09. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.44 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.40 (dd, *J* = 9.2, 4.5 Hz, 1H), 6.94 (dd, *J* = 9.3, 1.3 Hz, 1H), 5.44 – 5.34 (m, 1H), 4.44 – 4.38 (m, 1H), 4.21 – 4.08 (m, 1H), 4.00 – 3.91 (m, 1H), 3.89 – 3.82 (m, 1H), 3.78 – 3.69 (m, 1H), 3.69 – 3.58 (m, 3H), 3.29 – 3.22 (m, 1H), 3.15 – 2.96 (m, 2H), 2.89 – 2.80 (m, 1H), 2.71 – 2.58 (m, 2H), 2.45 – 2.33 (m, 1H), 2.28 – 2.15 (m, 2H), 2.14 – 2.01 (m, 1H), 1.97 – 1.85 (m, 2H), 1.82 – 1.74 (m, 1H), 1.46 – 1.34 (m, 3H), 1.10 – 0.98 (m, 1H), 0.91 – 0.84 (m, 9H). LCMS (A analogous method to Method 8, ESI)

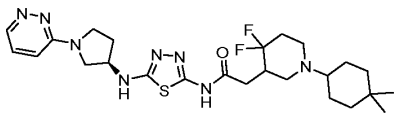
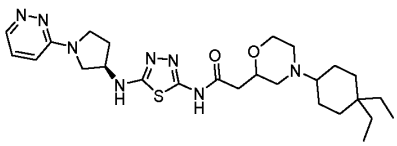
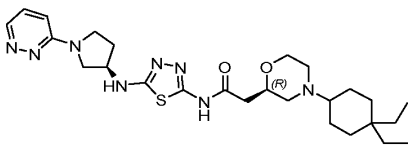
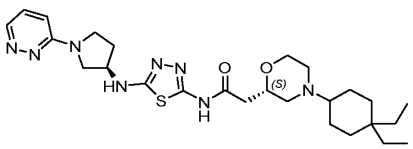
		529.23 [MH]+, RT 3.96 min; 529.22 [MH]+, RT 4.11 min, d.r. = 22.46:71.70.
Example 128	 2-[(3*S*)-1-[(3-ethoxy-4,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.93 – 6.82 (m, 3H), 4.42 – 4.33 (m, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.62 – 3.52 (m, 2H), 3.50 (dd, *J* = 11.1, 3.5 Hz, 1H), 3.43 – 3.35 (m, 2H), 2.67 – 2.57 (m, 2H), 2.34 – 2.22 (m, 3H), 2.12 – 2.03 (m, 1H), 2.03 – 1.91 (m, 2H), 1.80 – 1.69 (m, 1H), 1.67 – 1.56 (m, 2H), 1.52 – 1.39 (m, 1H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.04 – 0.90 (m, 1H). LCMS (A analogous method to Method 7, ESI) 559.27 [MH]+, RT 1.56 min.
Example 129	 2-[(3*S*)-1-[(3-fluoro-5-methoxy-4-methylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.1, 1.3 Hz, 1H), 6.71 (s, 1H), 6.67 (d, *J* = 10.2 Hz, 1H), 4.42 – 4.33 (m, 1H), 3.78 (s, 3H), 3.75 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.61 – 3.46 (m, 3H), 3.44 – 3.35 (m, 2H), 2.70 – 2.58 (m, 2H), 2.32 – 2.24 (m, 3H), 2.11 – 2.03 (m, 1H), 2.02 – 1.90 (m, 5H), 1.78 – 1.69 (m, 1H), 1.67 – 1.55 (m, 2H), 1.51 – 1.38 (m, 1H), 1.04 – 0.89 (m, 1H). LCMS (Method 9, ESI) 541.38 [MH]+, RT 5.80 min.
Example 130	 2-[(3*S*)-1-{[3-(difluoromethoxy)-5-methylphenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 7.17 (t, *J* = 74.4 Hz, 1H), 6.97 – 6.94 (m, 1H), 6.90 – 6.82 (m, 3H), 4.42 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.62 – 3.46 (m, 3H), 3.47 – 3.34 (m, 2H), 2.71 – 2.56 (m, 2H), 2.33 – 2.24 (m, 6H), 2.12 – 2.03 (m, 1H), 2.03 – 1.87 (m, 2H), 1.74 (t, *J* = 10.2 Hz, 1H), 1.67 – 1.54 (m, 2H), 1.50 – 1.37 (m, 1H), 1.02 – 0.89

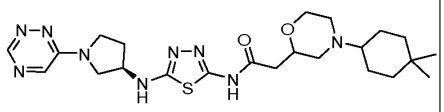
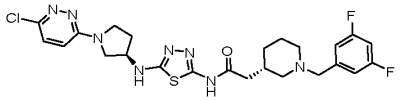
		(m, 1H). LCMS (Method 9, ESI) 559.31 $[MH]^+$, RT 6.00 min.
Example 131	 2-[(3*S*)-1-[(2-ethyl-1-benzofuran-3-yl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.48 (dd, *J* = 4.6, 1.3 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.47 – 7.41 (m, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.23 – 7.13 (m, 2H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.43 – 4.29 (m, 1H), 3.79 – 3.71 (m, 1H), 3.59 – 3.45 (m, 5H), 2.82 – 2.68 (m, 4H), 2.32 – 2.25 (m, 3H), 2.12 – 2.03 (m, 1H), 2.00 – 1.89 (m, 2H), 1.82 – 1.70 (m, 1H), 1.66 – 1.53 (m, 2H), 1.48 – 1.32 (m, 1H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.03 – 0.89 (m, 1H). LCMS (A analogous method to Method 7, ESI) 547.01 $[MH]^+$, RT 1.65 min.
Example 132	 2-[(3*S*)-1-[(3-fluoro-4,5-dimethylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (bs, 1H), 8.47 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.55 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.90 – 6.86 (m, 2H), 6.86 – 6.82 (m, 1H), 4.43 – 4.31 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.64 – 3.43 (m, 3H), 3.41 – 3.34 (m, 2H), 2.68 – 2.57 (m, 2H), 2.35 – 2.23 (m, 3H), 2.21 (s, 3H), 2.13 – 2.02 (m, 4H), 2.02 – 1.85 (m, 2H), 1.79 – 1.67 (m, 1H), 1.67 – 1.53 (m, 2H), 1.50 – 1.37 (m, 1H), 1.02 – 0.85 (m, 1H). LCMS (A analogous method to Method 7, ESI) 525.15 $[MH]^+$, RT 2.76 min..
Example 133	 2-[(3*S*)-1-[(2,5-dimethylthiophen-3-yl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.1, 1.4 Hz, 1H), 6.53 (s, 1H), 4.44 – 4.32 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61 – 3.47 (m, 3H), 3.22 (s, 2H), 2.70 – 2.55 (m, 2H), 2.36 – 2.27 (m, 6H), 2.25 (s, 3H), 2.13 – 2.01 (m, 1H), 2.00 – 1.83 (m, 2H), 1.77 – 1.66 (m, 1H), 1.66 – 1.52 (m, 2H), 1.47 – 1.32 (m, 1H), 1.02 – 0.84 (m, 1H). LCMS (A analogous method to Method 7, ESI) 513.31 $[MH]^+$, RT 2.67 min.

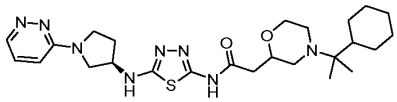
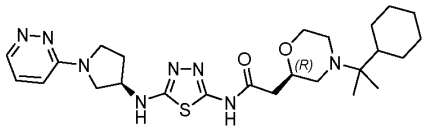
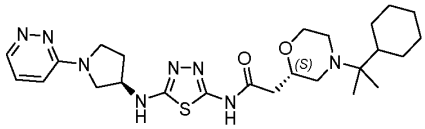
Example 135	 2-({1-[(2,5-dimethylthiophen-3-yl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 6.57 – 6.50 (m, 1H), 4.42 – 4.33 (m, 1H), 3.76 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.47 (m, 3H), 3.39 (s, 2H), 3.24 (s, 2H), 2.80 – 2.67 (m, 3H), 2.32 (s, 3H), 2.29 – 2.23 (m, 4H), 2.14 – 2.04 (m, 1H), 2.04 – 1.83 (m, 4H), 1.48 – 1.32 (m, 2H). LCMS (A analogous method to Method 7, ESI) 545.12 [MH]$^+$, RT 2.75 min.
Example 136	 2-[(3*S*)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{methyl[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.99 (s, 1H), 8.51 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.36 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.12 – 6.96 (m, 3H), 6.90 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.75 (p, *J* = 7.5 Hz, 1H), 3.83 – 3.63 (m, 2H), 3.59 – 3.43 (m, 4H), 2.98 (s, 3H), 2.72 – 2.58 (m, 2H), 2.35 – 2.22 (m, 4H), 2.08 – 1.92 (m, 2H), 1.86 – 1.73 (m, 1H), 1.70 – 1.54 (m, 2H), 1.54 – 1.36 (m, 1H), 1.07 – 0.90 (m, 1H). LCMS (A analogous method to Method 7, ESI) 529.26 [MH]$^+$, RT 1.38 min.
Example 137	 2-[4-(4,4-dimethylcyclohexyl)morpholin-2-yl]-*N*-(5-{methyl[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.51 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.36 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.90 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.75 (p, *J* = 7.0 Hz, 1H), 3.86 – 3.63 (m, 4H), 3.59 – 3.37 (m, 3H), 2.98 (s, 3H), 2.85 – 2.76 (m, 1H), 2.69 – 2.60 (m, 1H), 2.32 – 2.14 (m, 4H), 2.14 – 2.03 (m, 1H), 2.02 – 1.93 (m, 1H), 1.62 – 1.52 (m, 2H), 1.43 – 1.07 (m, 7H), 0.87 (s, 3H), 0.86 (s, 3H). LCMS (A analogous method to Method 7, ESI) 515.14 [MH]$^+$, RT 1.46 min.
Example 138		^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.65 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.43 – 4.35 (m, 1H), 3.75 (dd, *J* = 11.1,

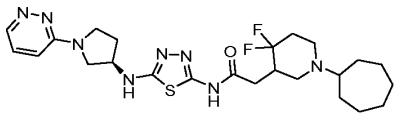
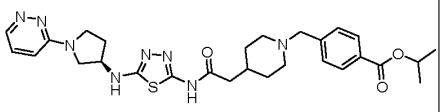
	2-[4-(4,4-dimethylcyclohexyl)piperazin-1-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	5.7 Hz, 1H), 3.59 – 3.47 (m, 3H), 3.20 (s, 2H), 2.32 – 2.24 (m, 1H), 2.16 – 2.02 (m, 2H), 1.62 – 1.52 (m, 2H), 1.43 – 1.26 (m, 4H), 1.21 – 1.07 (m, 2H), 0.87 (s, 3H), 0.85 (s, 3H). LCMS (A analogous method to Method 7, ESI) 500.15 $[MH]^+$, RT 1.34 min.
Example 139	 2-({1-[(1-*tert*-butyl-1*H*-pyrrol-3-yl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.64 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 6.78 (t, *J* = 2.6 Hz, 1H), 6.75 – 6.70 (m, 1H), 5.90 – 5.84 (m, 1H), 4.45 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61 – 3.53 (m, 2H), 3.53 – 3.47 (m, 1H), 3.38 (s, 2H), 3.22 (s, 2H), 2.80 – 2.71 (m, 3H), 2.35 – 2.24 (m, 1H), 2.12 – 2.03 (m, 1H), 1.96 – 1.83 (m, 4H), 1.47 – 1.33 (m, 2H), 1.43 (s, 9H). LCMS (A analogous method to Method 7, ESI) 556.25 $[MH]^+$, RT 2.78 min.
Example 140	 2-({1-[(1-*tert*-butyl-1*H*-pyrazol-4-yl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.63 (s, 1H), 7.62 – 7.57 (m, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.29 (s, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.42 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.61 – 3.54 (m, 2H), 3.53 – 3.47 (m, 1H), 3.37 (s, 2H), 3.29 (s, 2H), 2.79 – 2.70 (m, 3H), 2.31 – 2.24 (m, 1H), 2.12 – 2.02 (m, 1H), 1.99 – 1.84 (m, 4H), 1.48 (s, 9H), 1.45 – 1.36 (m, 2H). LCMS (A analogous method to Method 9, ESI) 557.11 $[MH]^+$, RT 3.57 min.
Example 141	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[4-	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.45 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.41 (dd, *J* = 9.3, 4.5 Hz, 1H), 6.99 (dd, *J* = 9.3, 1.3 Hz, 1H), 4.56 – 4.47 (m, 1H), 3.88 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.73 – 3.58 (m, 3H), 2.93 – 2.78 (m, 4H), 2.78 – 2.63 (m, 4H), 2.48 – 2.38 (m, 1H), 2.27 – 2.18 (m, 1H),

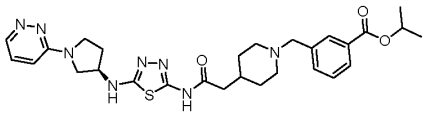
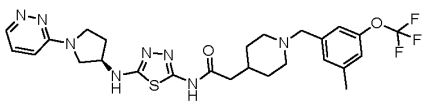
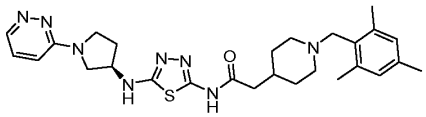
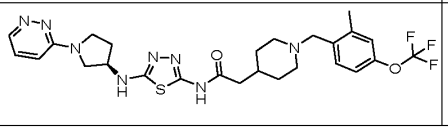
	(3,3,5,5-tetramethylcyclohexyl)piperazin-1-yl]acetamide	1.71 (d, *J* = 12.0 Hz, 2H), 1.35 – 1.27 (m, 3H), 1.18 – 1.09 (m, 3H), 1.08 (s, 6H), 0.98 (s, 6H). LCMS (A analogous method to Method 7, ESI) 528.19 $[MH]^+$, RT 2.04 min.
Example 142	 *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(4-{spiro[4.5]decan-8-yl}piperazin-1-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.66 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.44 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.60 – 3.47 (m, 3H), 3.23 (s, 2H), 2.59 – 2.51 (m, 9H), 2.32 – 2.25 (m, 1H), 2.12 – 2.03 (m, 1H), 1.74 – 1.61 (m, 2H), 1.58 – 1.44 (m, 6H), 1.36 (t, *J* = 6.9 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.27 – 1.16 (m, 3H). LCMS (A analogous method to Method 7, ESI) 526.29 $[MH]^+$, RT 2.01 min.
Example 143	 2-(4,4-difluoro-1-{spiro[2.5]octan-6-yl}piperidin-3-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.47 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.48 – 7.41 (m, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.86 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.43 – 4.32 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.63 – 3.52 (m, 2H), 3.52 – 3.46 (m, 1H), 2.82 – 2.74 (m, 2H), 2.69 – 2.60 (m, 1H), 2.47 – 2.36 (m, 3H), 2.34 – 2.20 (m, 3H), 2.13 – 1.80 (m, 3H), 1.70 – 1.60 (m, 4H), 1.40 – 1.23 (m, 2H), 0.94 – 0.85 (m, 2H), 0.28 – 0.21 (m, 2H), 0.18 – 0.10 (m, 2H). LCMS (Method 10, ESI) 533.27 $[MH]^+$, RT 2.65 min. Chiral HPLC (Method 28, 254 nm) RT_1 14.31 min; RT_2 16.86 min; d.r.= 50.91:49.09.
Example 144	 2-(1-cyclohexyl-4,4-difluoropiperidin-3-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.62 (s, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.44 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.63 – 3.53 (m, 2H), 3.53 – 3.46 (m, 1H), 2.78 – 2.73 (m, 2H), 2.72 – 2.64 (m, 1H), 2.47 – 2.38 (m, 3H), 2.37 – 2.32 (m, 1H),

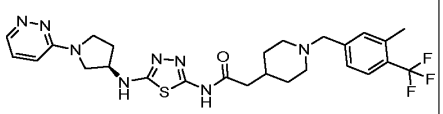
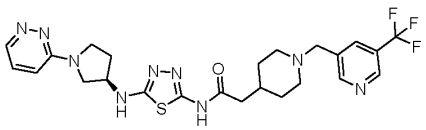
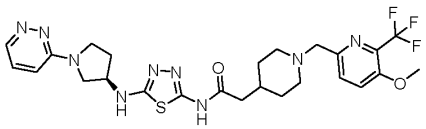
		2.31 – 2.28 (m, 1H), 2.27 – 2.20 (m, 1H), 2.16 – 1.79 (m, 3H), 1.76 – 1.67 (m, 4H), 1.62 – 1.49 (m, 1H), 1.27 – 1.11 (m, 4H), 1.12 – 0.94 (m, 1H). LCMS (Method 8, ESI) 507.05 [MH]+, RT 2.46 min. Chiral HPLC (Method 11, 254 nm) RT_1 16.15 min; RT_2 20.22 min; d.r.= 48.49:51.51.
Example 145	 2-[1-(4,4-dimethylcyclohexyl)-4,4-difluoropiperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.48 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.3, 1.4 Hz, 1H), 4.42 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.61 – 3.53 (m, 2H), 3.53 – 3.47 (m, 1H), 2.81 – 2.74 (m, 2H), 2.70 – 2.67 (m, 1H), 2.47 – 2.37 (m, 3H), 2.32 – 2.20 (m, 3H), 2.12 – 1.80 (m, 3H), 1.55 – 1.44 (m, 2H), 1.41 – 1.27 (m, 4H), 1.20 – 1.09 (m, 2H), 0.88 – 0.82 (m, 6H). LCMS (A analogous method to Method 6, ESI) 535.11 [MH]+, RT 4.25 & 4.47 min.
Example 146	 2-[4-(4,4-diethylcyclohexyl)morpholin-2-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.94 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.43 – 4.32 (m, 1H), 3.86 – 3.67 (m, 3H), 3.61 – 3.37 (m, 4H), 2.86 – 2.73 (m, 1H), 2.69 – 2.57 (m, 1H), 2.36 – 2.22 (m, 2H), 2.22 – 2.01 (m, 3H), 2.01 – 1.89 (m, 1H), 1.62 – 1.41 (m, 4H), 1.39 – 1.21 (m, 5H), 1.19 – 1.10 (m, 2H), 1.07 – 0.93 (m, 2H), 0.77 – 0.65 (m, 6H). LCMS (Method 6, ESI) 529.34 [MH]+, RT 4.54 min.
Example 147 and Example 148 Isomers A and B	 	1H NMR (400 MHz, CD3OD) δ 8.43-8.42 (m, 1H), 7.38 (dd, *J* = 9.2Hz, 4.4Hz, 1H), 6.98-6.95 (m, 1H), 4.51-4.47 (m, 1H), 3.99-3.96 (m, 1H), 3.87-3.83 (m, 2H), 3.68-3.57 (m, 4H), 2.98 (d, *J* = 10.8 Hz, 1H), 2.83 (d, *J* = 10.8Hz, 1H), 2.64-2.55 (m, 2H), 2.42-2.34 (m, 2H), 2.23-2.09 (m, 3H), 1.74-1.71 (m, 2H), 1.62-1.59 (m, 2H), 1.42-1.35 (m, 4H), 1.23-

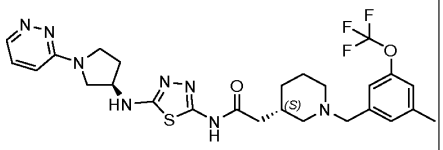
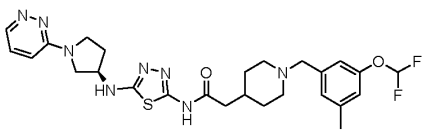
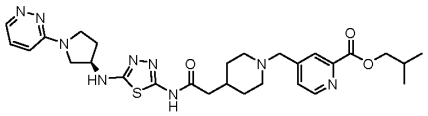
	One of isomers A and B is 2-((R)-4-(4,4-diethylcyclohexyl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((S)-4-(4,4-diethylcyclohexyl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1.17 (m, 2H), 0.80-0.74 (m, 6H). LCMS (A analogous method to Method 21, ESI) 529.2 $[M+H]^+$, RT 1.55 minutes. Chiral SFC (General Procedure 5E), RT 2.301 minutes. 1H NMR (400 MHz, CD3OD) δ 8.43-8.42 (m, 1H), 7.38 (dd, *J* = 9.2 Hz, 4.4Hz, 1H), 6.98-6.95 (m, 1H), 4.51-4.47 (m, 1H), 3.99-3.96 (m, 1H), 3.87-3.83 (m, 2H), 3.68-3.57 (m, 4H), 2.98 (d, *J* = 10.8 Hz, 1H), 2.83 (d, *J* = 10.8Hz, 1H), 2.64-2.55 (m, 2H), 2.42-2.34 (m, 2H), 2.23-2.09 (m, 3H), 1.74-1.71 (m, 2H), 1.62-1.59 (m, 2H), 1.42-1.35 (m, 4H), 1.23-1.17 (m, 2H), 0.80-0.74 (m, 6H). LCMS (A analogous method to Method 21, ESI) 529.2 $[M+H]^+$, RT 1.55 minutes. Chiral SFC (General Procedure 5E), RT 3.346 minutes.
Example 149	 *N*-(5-(((*R*)-1-(1,2,4-triazin-6-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(4,4-dimethylcyclohexyl)morpholin-2-yl)acetamide	1H NMR (400 MHz, MeOD-d4) δ 8.88 (s, 1H), 8.27 (s, 1H), 3.99-3.93 (m, 1H), 3.91-3.84 (m, 2H), 3.73-3.60 (m, 4H), 2.93 (d, *J* =10.8 Hz, 1H), 2.82-2.78 (m, 1H), 2.38-2.06 (m, 6H), 1.75-1.72 (m, 2H), 1.33-1.23 (m, 7H), 0.909 (d, *J* =2.8 Hz, 1H). LCMS (A analogous method to Method 21, ESI) 502.3$[M+H]^+$, RT 10.41 minutes.
Example 150	 *N*-(5-{[(3*R*)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*S*)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (s, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.48 (d, *J* = 9.5 Hz, 1H), 7.11 – 6.93 (m, 4H), 4.41 – 4.32 (m, 1H), 3.74 (dd, *J* = 11.2, 5.7 Hz, 1H), 3.61 – 3.39 (m, 5H), 2.71 – 2.55 (m, 2H), 2.35 – 2.20 (m, 3H), 2.12 – 1.90 (m, 3H), 1.78 (t, *J* = 10.1 Hz, 1H), 1.70 – 1.54 (m, 2H), 1.53 – 1.37 (m, 1H), 1.04 – 0.89 (m, 1H). LCMS (A analogous method to Method 7, ESI) 549.34 [MH]+, RT 2.17 min.

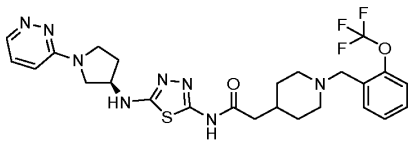
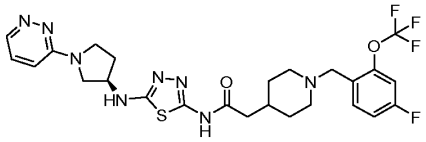
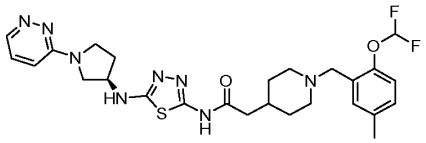
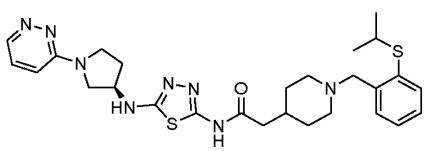
Example 151	 2-[4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.43 – 4.33 (m, 1H), 3.80 – 3.70 (m, 3H), 3.61 – 3.46 (m, 3H), 3.43 – 3.36 (m, 1H), 2.79 – 2.72 (m, 1H), 2.63 – 2.56 (m, 1H), 2.56 – 2.52 (m, 2H), 2.35 – 2.25 (m, 1H), 2.21 – 2.11 (m, 1H), 2.11 – 2.01 (m, 1H), 1.96 – 1.87 (m, 1H), 1.83 – 1.67 (m, 4H), 1.65 – 1.57 (m, 1H), 1.47 – 1.35 (m, 1H), 1.24 – 1.02 (m, 3H), 0.96 – 0.84 (m, 2H), 0.82 (s, 6H). LCMS (Method 1, ESI) 515.37 [MH]+, RT 2.85. Chiral HPLC (A analogous method to Method 11, 254 nm) RT_1 7.22 min; RT_2 8.80 min; d.r.= 47.99:52.01.
Example 152 and Example 153 Isomers A and B	  One of isomers A and B is 2-[(*R*)-4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-[(*S*)-4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.48 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.62 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.1, 1.4 Hz, 1H), 4.41 – 4.34 (m, 1H), 3.80 – 3.71 (m, 3H), 3.60 – 3.53 (m, 2H), 3.52 – 3.47 (m, 1H), 3.41 – 3.34 (m, 1H), 2.78 – 2.72 (m, 1H), 2.62 – 2.57 (m, 1H), 2.55 – 2.52 (m, 2H), 2.32 – 2.25 (m, 1H), 2.20 – 2.12 (m, 1H), 2.11 – 2.03 (m, 1H), 1.95 – 1.88 (m, 1H), 1.80 – 1.70 (m, 4H), 1.65 – 1.58 (m, 1H), 1.45 – 1.36 (m, 1H), 1.21 – 1.05 (m, 3H), 0.94 – 0.84 (m, 2H), 0.82 (s, 6H). LCMS (Method 41, ESI) 515.08 [MH]+, RT 2.82. Chiral HPLC (A analogous method to Method 11, 254 nm) RT_1 7.17 min; d.r.= 100:0 ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.62 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.41 – 4.34 (m, 1H), 3.80 – 3.70 (m, 3H), 3.60 – 3.53 (m, 2H), 3.52 – 3.47 (m, 1H), 3.41 – 3.34 (m, 1H), 2.78 – 2.72 (m, 1H),

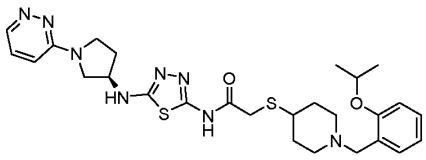
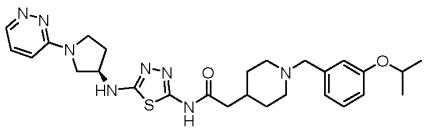
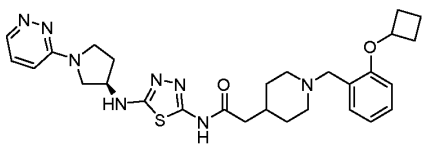
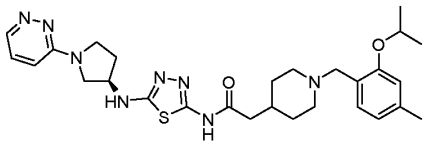
		2.62 – 2.57 (m, 1H), 2.56 – 2.52 (m, 2H), 2.31 – 2.24 (m, 1H), 2.20 – 2.12 (m, 1H), 2.12 – 2.03 (m, 1H), 1.95 – 1.88 (m, 1H), 1.82 – 1.68 (m, 4H), 1.65 – 1.57 (m, 1H), 1.45 – 1.37 (m, 1H), 1.21 – 1.03 (m, 3H), 0.94 – 0.86 (m, 2H), 0.82 (s, 6H). LCMS (Method 41, ESI) 514.86 [MH]+, RT 2.80. Chiral HPLC (A analogous method to Method 11, 254 nm) RT_1 7.21 min; RT_2 8.74 min; d.r.= 0.66:99.34.
Example 154	 2-(1-cycloheptyl-4,4-difluoropiperidin-3-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.64 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.43 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.60 – 3.54 (m, 2H), 3.54 – 3.48 (m, 1H), 2.73 – 2.64 (m, 3H), 2.60 – 2.53 (m, 1H), 2.45 – 2.36 (m, 3H), 2.31 – 2.26 (m, 1H), 2.26 – 2.17 (m, 1H), 2.13 – 2.03 (m, 1H), 2.03 – 1.96 (m, 1H), 1.73 – 1.65 (m, 2H), 1.64 – 1.56 (m, 2H), 1.53 – 1.28 (m, 9H). LCMS (Method 7, ESI) 521.09 [MH]+, RT 3.52 min, 521.21 [MH]+, RT 3.59 min.
Example 155	 isopropyl (*R*)-4-((4-(2-oxo-2-((5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)piperidin-1-yl)methyl)benzoate	^{1}H NMR (400 MHz, DMSO-d_6): δ 11.93 (br s, 1 H), 8.48 (dd, *J* =4.4 Hz, 1.2 Hz, 1 H), 7.89 (d, *J* =8.0 Hz, 2 H), 7.57 (d, *J* =6.0 Hz, 1 H), 7.43 (d, *J* =8.4 Hz, 2 H), 7.33 (dd, *J* =9.2 Hz, 4.8 Hz, 1 H), 6.86 (dd, *J* =8.8 Hz, 0.8 Hz, 1 H), 5.09-5.16 (m, 1 H), 4.36-4.39 (m, 1 H), 3.73-3.77 (m, 1 H), 3.59-3.50 (m, 5 H), 2.73-2.76 (m, 2 H), 2.07-2.31 (m, 3 H), 2.07-2.08 (m, 1 H), 1.90-1.95 (m, 2 H), 1.71-1.73 (m, 1 H), 1.57-1.60 (m, 2 H), 1.31 (d, *J* =6.0 Hz, 6 H), 1.13-1.26 (m, 2 H). LCMS (Method 13, ESI): 565.5 $[M+H]^+$, RT 5.910 minutes.

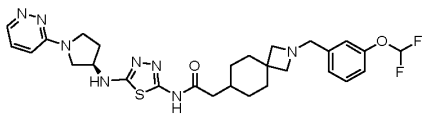
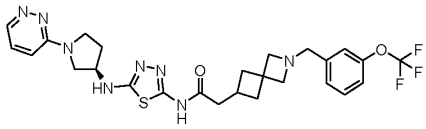
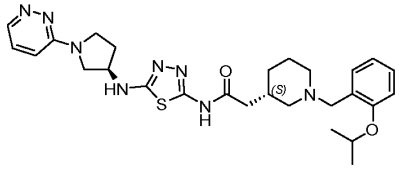
Example 156	 isopropyl (*R*)-3-((4-(2-oxo-2-((5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)piperidin-1-yl)methyl)benzoate	1H NMR (400 MHz, DMSO-d_6): δ 11.79 (br s, 1 H), 8.47 (dd, *J* =4.4 Hz, 1.2 Hz, 1 H), 7.81-7.85 (m, 2 H), 7.55 (d, *J* =7.6 Hz, 1 H), 7.40-7.47 (m, 2 H), 7.32 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 6.86 (dd, *J* =9.2 Hz, 1.2 Hz, 1 H), 5.10-5.16 (m, 1 H), 4.34-4.38 (m, 1 H), 3.72-3.76 (m, 1 H), 3.46-3.59 (m, 5 H), 2.73-2.76 (m, 2 H), 2.27-2.30 (m, 3 H), 2.07-2.24 (m, 1 H), 1.90-2.07 (m, 2 H), 1.71-1.74 (m, 1 H), 1.58-1.61 (m, 2 H), 1.32 (d, *J* =6.0 Hz, 6 H), 1.10-1.23 (m, 2 H). LCMS (Method 13, ESI): 565.6 $[M+H]^+$, RT 5.911 minutes.
Example 157	 (*R*)-2-(1-(3-methyl-5-(trifluoromethoxy)benzyl)piperidin-4-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.90 (s, 1 H), 8.47 (dd, *J* =4.8 Hz, 1.2 Hz, 1 H), 7.60 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 7.13 (s, 1 H), 7.04 (s, 2 H), 6.87 (dd, *J* =8.8 Hz, 0.8 Hz, 1 H), 4.36-4.39 (m, 1 H), 3.73-3.77 (m, 1 H), 3.48-3.58 (m, 3 H), 3.44 (s, 2 H), 2.67-2.76 (m, 2 H), 2.25-2.47 (m, 6 H), 2.05-2.11 (m, 1 H), 1.89-1.94 (m, 2 H), 1.67-1.74 (m, 1 H), 1.57-1.60 (m, 2 H), 1.15-1.25 (m, 2 H). 19F NMR (376 MHz, DMSO-d6): δ -56.53. LCMS (Method 13, ESI): 577.6 $[M+H]^+$, RT 6.273 minutes.
Example 158	 (*R*)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(2,4,6-trimethylbenzyl)piperidin-4-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.88 (s, 1 H), 8.48 (dd, *J* =4.4 Hz, 0.8 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 6.87 (dd, *J* =9.2 Hz, 1.2 Hz, 1 H), 6.78 (s, 2 H), 4.37-4.38 (m, 1 H), 3.73-3.77 (m, 1 H), 3.48-3.58 (m, 3 H), 3.34-3.48 (m, 2 H), 2.67-2.69 (m, 2 H), 2.27-2.33 (m, 9 H), 2.18 (s, 3 H), 2.06-2.09 (m, 1 H), 1.95-2.00 (m, 2 H), 1.67-1.74 (m, 1 H), 1.54-1.57 (m, 2 H), 1.04-1.15 (m, 2 H). LCMS (Method 13, ESI): 521.5 $[M+H]^+$, RT 5.835 minutes.
Example 159		1H NMR (400 MHz, DMSO-d_6): δ 11.90 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.31-7.34 (m, 2 H), 7.15

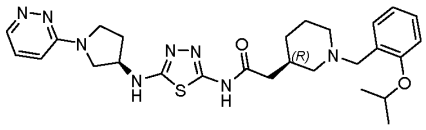
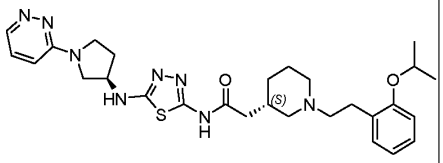
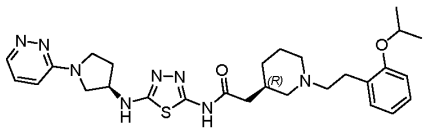
	(*R*)-2-(1-(2-methyl-4-(trifluoromethoxy)benzyl)piperidin-4-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	(s, 1 H), 7.11 (d, *J* =8.4 Hz, 1 H), 6.87 (d, *J* =8.4 Hz, 1 H), 4.36-4.40 (m, 1 H), 3.73-3.77 (m, 1 H), 3.48-3.59 (m, 3 H), 3.39 (s, 2 H), 2.73-2.75 (m, 2 H), 2.25-2.33 (m, 6 H), 2.05-2.11 (m, 1 H), 1.93-2.04 (m, 2 H), 1.73-1.76 (m, 1 H), 1.57-1.60 (m, 2 H), 1.09-1.26 (m, 2 H). 19F NMR (376 MHz, DMSO-d_6): δ -56.62. LCMS (Method 14, ESI): 577.2 $[M+H]^+$, RT 1.158 minutes.
Example 160	 (*R*)-2-(1-(3-methyl-4-(trifluoromethyl)benzyl)piperidin-4-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.90 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.31-7.34 (m, 1 H), 7.28 (s, 1 H), 7.22 (s, 2 H), 6.87 (d, *J* =8.4 Hz, 1 H), 4.36-4.40 (m, 1 H), 3.73-3.74 (m, 1 H), 3.52-3.57 (m, 3 H), 3.40 (s, 2 H), 2.73-2.76 (m, 2 H), 2.26-2.32 (m, 6 H), 2.04-2.11 (m, 1 H), 1.88-2.07 (m, 2 H), 1.69-1.73 (m, 1 H), 1.57-1.60 (m, 2 H), 1.19-1.22 (m, 2 H). 19F NMR (376 MHz, DMSO-d_6): δ -56.41. LCMS (Method 14, ESI): 561.5 $[M+H]^+$, RT 6.156 minutes.
Example 161	 (*R*)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-((5-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)acetamide	1H NMR (400 MHz, DMSO-d6): δ 11.90 (s, 1 H), 8.86 (s, 1 H), 8.79 (s, 1 H), 8.48 (d, *J* =3.6 Hz, 1 H), 8.06 (s, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H),7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 6.87 (dd, *J* =9.2 Hz, 0.8 Hz, 1 H), 4.36-4.40 (m, 1 H), 3.73-3.77 (m, 1 H), 3.51-3.59 (m, 4 H), 3.48-3.51 (m, 1 H), 2.74-2.77 (m, 2 H), 2.27-2.32 (m, 3 H), 2.05-2.11 (m, 1 H), 1.95-2.01 (m, 2 H), 1.70-1.74 (m, 1 H), 1.58-1.61 (m, 2 H), 1.17-1.25 (m, 2 H). 19F NMR (376 MHz, DMSO-d_6): δ -60.85. LCMS (Method 13, ESI): 548.5 $[M+H]^+$, RT 4.989 minutes.
Example 162		1H NMR (400 MHz, DMSO-d6): δ 11.92 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.70-7.78 (m, 2 H), 7.62 (d, *J* =6.0 Hz, 1 H),7.33 (dd, *J* =8.8 Hz, 4.4 Hz, 1 H), 6.87 (dd, *J* =9.2 Hz, 1.2 Hz, 1 H), 4.34-4.43 (m,

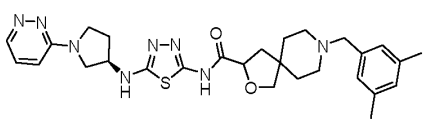
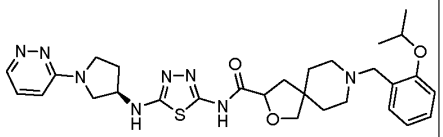
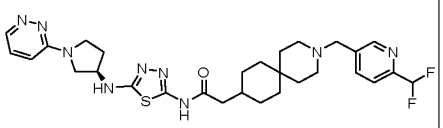
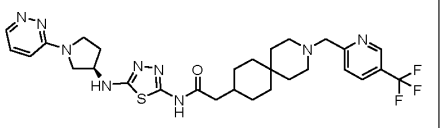
	(*R*)-2-(1-((5-methoxy-6-(trifluoromethyl)pyridin-2-yl)methyl)piperidin-4-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1 H), 3.93 (s, 3 H), 3.73-3.77 (m, 1 H), 3.48-3.59 (m, 5 H), 2.68-2.84 (m, 2 H), 2.27-2.33 (m, 3 H), 1.99-2.10 (m, 3 H), 1.68-1.83 (m, 1 H), 1.54-1.66 (m, 2 H), 1.15-1.34 (m, 2 H). 19F NMR (376 MHz, DMSO-d6): δ -64.49. LCMS (Method 13, ESI): 578.5 $[M+H]^+$, RT 5.637 minutes.
Example 163	 2-((*S*)-1-(3-methyl-5-(trifluoromethoxy)benzyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.90 (s, 1 H), 8.47 (d, *J* =4.4 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.32-7.35 (m, 1 H), 7.13 (s, 1 H), 7.04 (s, 2 H), 6.86 (d, *J* =8.8 Hz, 1 H), 4.34-4.41 (m, 1 H), 3.73-3.77 (m, 1 H), 3.42-3.59 (m, 5 H), 2.58-2.71 (m, 2 H), 2.27-2.32 (m, 6 H), 1.91-2.11 (m, 3 H), 1.57-1.77 (m, 3 H), 1.41-1.48 (m, 1 H), 0.92-1.05 (m, 1 H). LCMS (Method 15, ESI): 577.3 $[M+H]^+$, RT 1.165 minutes.
Example 164	 (*R*)-2-(1-(3-(difluoromethoxy)-5-methylbenzyl)piperidin-4-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.91 (s, 1 H), 8.47 (dd, *J* =4.8 Hz, 1.2 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7-7.00.7.62 (m, 2 H), 6.97 (s, 1 H), 6.86-6.88 (m, 3 H), 4.36-4.41 (m, 1 H), 3.73-3.77 (m, 1 H), 3.48-3.58 (m, 3 H), 3.40 (s, 2 H), 2.74-2.77 (m, 2 H), 2.27-2.32 (m, 6 H), 2.04-2.11 (m, 1 H), 1.88-1.94 (m, 2 H), 1.70-1.76 (m, 1 H), 1.57-1.60 (m, 2 H), 1.16-1.26 (m, 2 H). LCMS (Method 13, ES-API): 558.8 $[M+H]^+$, RT 5.891 minutes.
Example 165	 isobutyl (*R*)-4-((4-(2-oxo-2-((5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)piperidin-1-yl)methyl)picolinate	1H NMR (400 MHz, DMSO-d_6): δ 11.92 (s, 1 H), 8.65 (d, *J* =4.0 Hz, 1 H), 8.48 (dd, *J* =4.4 Hz, 0.8 Hz, 1 H), 8.01 (s, 1 H), 7.57-7.63 (m, 2 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 6.86 (dd, *J* =9.2 Hz, 1.2 Hz, 1 H), 4.35-4.41 (m, 1 H), 4.10 (d, *J* =6.4 Hz, 2 H), 3.73-3.77 (m, 1 H), 3.48-3.59 (m, 4 H), 3.27-3.32 (m, 2 H), 2.71-2.85 (m, 2 H), 2.25-2.34 (m, 3 H), 1.97-2.11 (m, 3 H), 1.61-1.79 (m, 3 H), 1.18-1.33 (m, 2 H), 0.96-0.98 (m, 6 H). LCMS

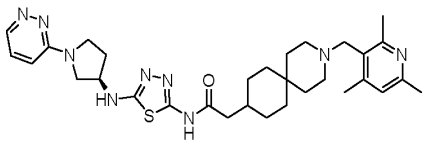
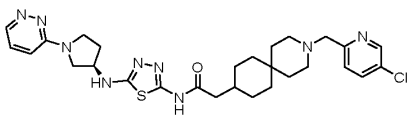
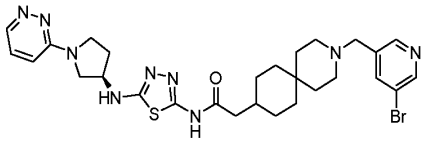
		(Method 16, ESI): 580.1 $[M+H]^+$, RT 1.258 minutes.
Example 166	 (*R*)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(2-(trifluoromethoxy)benzyl)piperidin-4-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.89 (s, 1 H), 8.47 (d, *J* =4.4 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.53-7.56 (m, 1 H), 7.31-7.41 (m, 4 H), 6.86 (d, *J* =9.2 Hz, 1 H), 4.35-4.41 (m, 1 H), 3.73-3.77 (m, 1 H), 3.49-3.59 (m, 5 H), 2.73-2.76 (m, 2 H), 2.25-2.32 (m, 3 H), 1.94-2.11 (m, 3 H), 1.58-1.77 (m, 3 H), 1.15-1.24 (m, 2 H). LCMS (Method 17, ESI): 563.3 $[M+H]^+$, RT 0.872 minutes.
Example 167	 (*R*)-2-(1-(4-fluoro-2-(trifluoromethoxy)benzyl)piperidin-4-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.77 (br s, 1 H), 8.48 (dd, *J* =4.4 Hz, 0.8 Hz, 1 H), 7.56-7.62 (m, 2 H), 7.25-7.35 (m, 3 H), 6.86 (dd, *J* =9.2 Hz, 1.2 Hz, 1 H), 4.35-4.41 (m, 1 H), 3.73-3.77 (m, 1 H), 3.45-3.59 (m, 5 H), 2.71-2.85 (m, 2 H), 2.27-2.34 (m, 3 H), 1.94-2.11 (m, 3 H), 1.57-1.77 (m, 3 H), 1.17-1.24 (m, 2 H). LCMS (Method 18, ESI): 581.0 $[M+H]^+$, RT 0.642 minutes.
Example 168	 (*R*)-2-(1-(2-(difluoromethoxy)-5-methylbenzyl)piperidin-4-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.90 (br s, 1 H), 8.47 (d, *J* =4.4 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =13.6 Hz, 4.4 Hz, 1 H), 7.05-7.23 (m, 4 H), 6.87 (d, *J* =8.8 Hz, 1 H), 4.35-4.41 (m, 1 H), 3.73-3.77 (m, 1 H), 3.48-3.59 (m, 3 H), 3.40 (s, 2 H), 2.71-2.80 (m, 2 H), 2.27-2.32 (m, 6 H), 1.90-2.11 (m, 3 H), 1.57-1.77 (m, 3 H), 1.13-1.25 (m, 2 H). LCMS (Method 19, ESI): 559.1 $[M+H]^+$, RT 1.089 minutes.
Example 169	 (*R*)-2-(1-(2-(isopropylthio)benzyl)piperidin-4-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-	1H NMR (400 MHz, DMSO-d_6): δ 11.90 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.31-7.43 (m, 3 H), 7.21-7.24 (m, 2 H), 6.87 (d, *J* =8.8 Hz, 1 H), 4.36-4.40 (m, 1 H), 3.73-3.77 (m, 1 H), 3.45-3.59 (m, 6 H), 2.67-2.77 (m, 2 H), 2.27-2.32 (m, 3 H), 2.05-2.10 (m, 1 H), 1.94-1.99 (m, 2 H), 1.56-1.73 (m, 3 H),

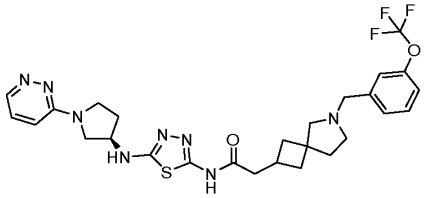
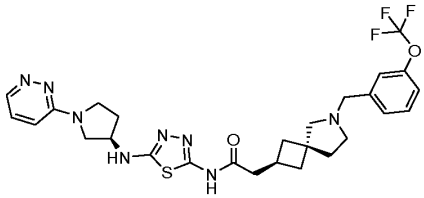
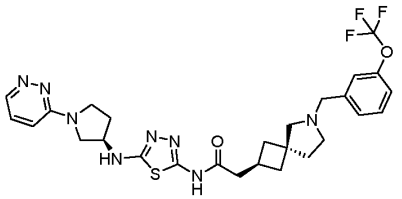
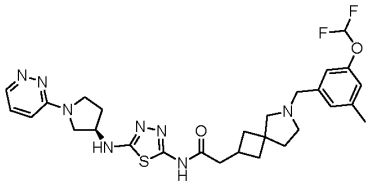
	yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1.16-1.22 (m, 8 H). LCMS (Method 15, ESI): 553.1 $[M+H]^+$, RT 1.153 minutes.
Example 170	 (*R*)-2-((1-(2-isopropoxybenzyl)piperidin-4-yl)thio)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 12.08 (s, 1 H), 8.48 (d, *J* = 3.6 Hz, 1 H), 7.67 (d, *J* = 6.0 Hz, 1 H), 7.18-7.35 (m, 3 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 9.2 Hz, 2 H), 4.57-4.59 (m, 1 H), 4.38-4.39 (m, 1 H), 3.74-3.78 (m, 1 H), 3.40-3.59 (m, 7 H), 2.67-2.77 (m, 3 H), 2.27-2.33 (m, 1 H), 2.03-2.10 (m, 3 H), 1.89-1.92 (m, 2 H), 1.43-1.46 (m, 2 H), 1.25 (d, *J* = 6.0 Hz, 6 H). LCMS (Method 16, ESI): 569.2 $[M+H]^+$, RT 1.267 minutes.
Example 171	 (*R*)-2-(1-(3-isopropoxybenzyl)piperidin-4-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.91 (s, 1 H), 8.48 (dd, *J* =4.4 Hz, 1.2 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 7.18 (t, *J* =8.0 Hz, 1 H), 6.76-6.88 (m, 4 H), 4.54-4.60 (m, 1 H), 4.36-4.39 (m, 1 H), 3.73-3.77 (m, 1 H), 3.32-3.58 (m, 5 H), 2.67-2.77 (m, 2 H), 2.27-2.33 (m, 3 H), 2.05-2.09 (m, 1 H), 1.70-1.73 (m, 1 H), 1.57-1.60 (m, 2 H), 1.19-1.57 (m, 8 H). LCMS (Method 16, ESI): 537.7 $[M+H]^+$, RT 1.450 minutes.
Example 172	 (*R*)-2-(1-(2-cyclobutoxybenzyl)piperidin-4-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.91 (s, 1 H), 8.48 (d, *J* =3.6 Hz, 1 H), 7.61 (d, *J* =6.4 Hz, 1 H), 7.33 (dd, *J* =8.8 Hz, 4.4 Hz, 1 H), 7.28 (d, *J* =7.2 Hz, 1 H), 7.15 (t, *J* =8.4 Hz, 1 H), 6.86-6.90 (m, 2 H), 6.77 (d, *J* =8.0 Hz, 1 H), 4.63-4.70 (m, 1 H), 4.34-4.41 (m, 1 H), 3.73-3.77 (m, 1 H), 3.42-3.58 (m, 5 H), 2.78-2.81 (m, 2 H), 2.37-2.44 (m, 2 H), 2.27-2.32 (m, 3 H), 1.93-2.10 (m, 5 H), 1.57-1.80 (m, 5 H), 1.16-1.25 (m, 2 H). LCMS (Method 16, ESI): 549.4 $[M+H]^+$, RT 1.500 minutes.
Example 173		1H NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 7.14 (d, *J* =7.6 Hz, 1 H), 6.87 (d, *J* =7.6 Hz, 1 H), 6.77 (s, 1 H), 6.68 (d, *J*

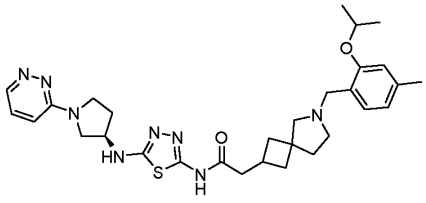
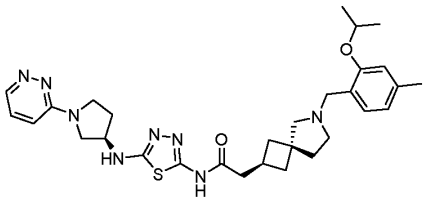
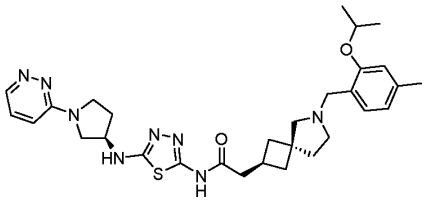
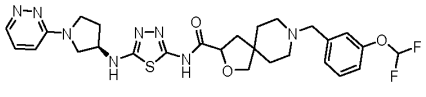
	(*R*)-2-(1-(2-isopropoxy-4-methylbenzyl)piperidin-4-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	=7.6 Hz, 1 H), 4.52-4.58 (m, 1 H), 4.36-4.40 (m, 1 H), 3.73-3.77 (m, 1 H), 3.48-3.59 (m, 3 H), 3.34 (d, *J* =12.0 Hz, 2 H), 2.75-2.78 (m, 2 H), 2.26-2.31 (m, 6 H), 2.04-2.11 (m, 1 H), 1.91 (t, *J* =11.2 Hz, 2 H), 1.66-1.73 (m, 1 H), 1.55-1.58 (m, 2 H), 1.13-1.25 (m, 8 H). LCMS (Method 18, ESI): 551.2 $[M+H]^+$, RT 0.671 minutes.
Example 174	 (*R*)-2-(2-(3-(difluoromethoxy)benzyl)-2-azaspiro[3.5]nonan-7-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.87 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.03-7.40 (m, 6 H), 6.87 (dd, *J* =9.2 Hz, 1.2 Hz, 1 H), 4.35-4.41 (m, 1 H), 3.73-3.77 (m, 1 H), 3.49-3.58 (m, 5 H), 2.81-2.99 (m, 4 H), 2.28-2.33 (m, 1 H), 2.23 (d, *J* =7.2 Hz, 2 H), 2.04-2.11 (m, 1 H), 1.82-1.86 (m, 2 H), 1.62-1.67 (m, 1 H), 1.52-1.55 (m, 2 H), 1.33-1.39 (m, 2 H), 0.91-1.00 (m, 2 H). LCMS (Method 16, ESI): 585.7 $[M+H]^+$, RT 1.467 minutes.
Example 175	 (*R*)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(2-(3-(trifluoromethoxy)benzyl)-2-azaspiro[3.3]heptan-6-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.87 (s, 1 H), 8.48 (d, *J* =3.6 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H),7.45-7.41 (m, 1 H),7.33 (dd, *J* =8.8 Hz, 4.4 Hz, 1 H),7.28 (d, *J* =7.6 Hz, 1 H),7.22-7.21 (m, 2 H), 6.87 (d, *J* =9.2 Hz, 1 H), 4.39-4.353 (m, 1 H), 3.77-3.73 (m, 1 H), 3.61-3.48 (m, 5 H), 3.18 (s, 2 H), 3.09 (s, 2 H), 2.44 (s, 3H), 2.33-2.18 (m, 3 H), 2.09-2.05 (m, 1 H), 1.81-1.77 (m, 2 H).LCMS (Method 15, ESI): 575.1 $[M+H]^+$, RT 1.124 minutes.
Example 176	 2-((*S*)-1-(2-isopropoxybenzyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.89 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.60 (d, *J* =4.8 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H),7.27 (d, *J* =7.6 Hz, 1 H), 7.15 (t, *J* =7.2 Hz, 1 H), 6.93 (d, *J* =8.0 Hz, 1 H), 6.88-6.83 (m, 2 H), 4.57-4.54 (m, 1 H), 4.38-4.36 (m, 1 H), 3.77-3.73 (m, 1 H), 3.59-3.48 (m, 3 H), 3.40 (d, *J* =3.6 Hz, 2 H), 2.72-2.65 (m, 2 H), 2.33-2.25 (m, 3

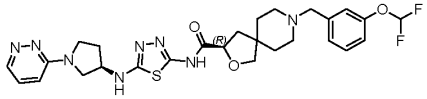
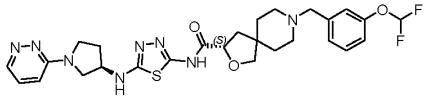
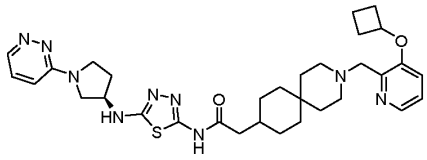
		H), 2.11-2.04 (m, 1 H), 1.99-1.95 (m, 2 H), 1.77-1.73 (m, 1 H), 1.64-1.57 (m, 2 H), 1.45-1.42 (m, 1 H), 1.24-1.22 (m, 6 H), 0.95-0.93 (m, 1 H).LCMS (Method 16, ESI): 537.5 $[M+H]^+$, RT 1.467 minutes.
Example 177	 2-((*R*)-1-(2-isopropoxybenzyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.87 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.60 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.8 Hz, 1 H),7.27 (d, *J* =7.6 Hz, 1 H), 7.18-7.13 (m, 1 H), 6.94 (d, *J* =8.4Hz, 1 H), 6.88-6.83 (m, 2 H), 4.59-4.53 (m, 1 H), 4.40-4.36 (m, 1 H), 3.77-3.73 (m, 1 H), 3.59-3.48 (m, 3 H), 3.41-3.39 (m, 2 H), 2.72-2.65 (m, 2 H), 2.33-2.24 (m, 3 H), 2.11-2.04 (m, 1 H), 2.01-1.93 (m, 2 H), 1.77-1.73 (m, 1 H), 1.63-1.57 (m, 2 H), 1.44-1.42 (m, 1 H), 1.24-1.22 (m, 6 H), 0.95-0.92 (m, 1 H).LCMS (Method 20, ESI): 537.1 $[M+H]^+$, RT 1.167 minutes.
Example 178	 2-((*S*)-1-(2-isopropoxyphenethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.91 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.60 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.8 Hz, 1 H), 7.12-7.10 (m, 2 H), 6.92-6.85 (m, 2 H), 6.81-6.77 (m, 1 H), 4.59-4.53 (m, 1 H), 4.40-4.36 (m, 1 H), 3.77-3.73 (m, 1 H), 3.59-3.48 (m, 3 H), 2.83-2.64 (m, 4 H), 2.42-2.40 (m, 1 H), 2.31-2.25 (m, 3 H), 2.11-2.04 (m, 3 H), 1.79-1.77 (m, 1 H), 1.65-1.59 (m, 2 H), 1.46-1.43 (m, 1 H), 1.24-1.22 (m, 6 H), 0.96-0.93 (m, 1 H). LCMS (Method 15, ESI): 551.1 $[M+H]^+$, RT 1.113 minutes.
Example 179	 2-((*R*)-1-(2-isopropoxyphenethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.91 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.8 Hz, 1 H), 7.13-7.10 (m, 2 H), 6.91 (d, *J* =8.8 Hz, 1 H), 6.87 (d, *J* =8.8 Hz, 1 H), 4.60-4.54 (m, 1 H), 4.40-4.37 (m, 1 H), 3.77-3.73 (m, 1 H), 3.61-3.49 (m, 3 H), 2.80-2.79 (m, 2 H), 2.69-2.63 (m, 2 H), 2.44-2.42 (m, 2 H), 2.36-2.33 (m, 3 H),

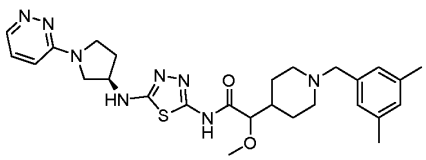
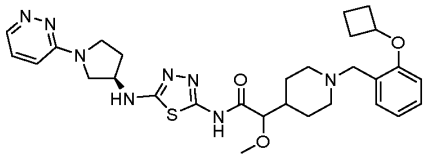
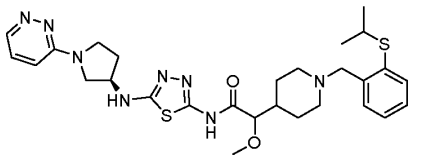
		2.11-2.05 (m, 1H), 1.98-1.97 (m, 2 H), 1.80-1.73 (m, 1 H), 1.65-1.59 (m, 2 H), 1.45-1.39 (m, 1 H), 1.25-1.22 (m, 6 H), 0.98-0.92 (m, 1 H). LCMS (Method 16, ESI): 551.3 $[M+H]^+$, RT 1.500 minutes.
Example 180	 8-(3,5-dimethylbenzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide	1H NMR (400 MHz, DMSO-d_6): δ 11.79 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.67 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.8 Hz, 1 H), 6.88-6.85 (m, 4 H), 4.57-4.53 (m, 1 H), 4.41-4.37(m, 1 H), 3.77-3.73 (m, 1 H), 3.65 (s, 2 H), 3.61-3.48 (m, 3 H), 2.39-2.21 (m, 11 H), 2.20-2.04 (m, 2 H), 1.75-1.70 (m, 1 H), 1.52 (s, 4 H). LCMS (Method 13, ESI): 549.5 $[M+H]^+$, RT 5.838 minutes.
Example 181	 8-(2-isopropoxybenzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide	1H NMR (400 MHz, DMSO-d_6): δ 11.79 (s, 1 H), 8.80 (d, *J* =4.4 Hz, 1 H), 7.67 (d, *J* =6.0 Hz, 1 H), 7.35-7.28 (m, 2 H), 7.19-7.15 (m, 1 H), 6.97-6.95 (m, 2 H), 4.62-4.54 (m, 2 H), 4.39-4.37 (m, 1 H), 3.77-3.71 (m, 1 H), 3.65 (s, 2 H), 3.59-3.550 (m, 2 H), 3.52-3.47 (m, 1 H), 3.43 (s, 2 H), 2.45-2.25 (m, 5 H), 2.17-2.09 (m, 2 H), 1.75-1.70 (m, 1H),1.53 (s, 4 H), 1.25 (d, *J* =6.0 Hz, 6 H). LCMS (Method 15, ESI): 579.2 $[M+H]^+$, RT 1.124 minutes.
Example 182	 (*R*)-2-(3-((6-(difluoromethyl)pyridin-3-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.86 (s, 1 H), 8.57 (s, 1 H), 8.48 (d, *J* =3.6 Hz, 1 H), 7.89 (d, *J* =7.6 Hz, 1 H), 7.65 (d, *J* =8.0 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.35-7.31 (m, 1 H), 7.07-6.79 (m, 2 H), 4.41-4.34 (m, 1 H), 3.77-3.73 (m, 1 H), 3.61-3.48 (m, 5 H), 2.33-2.25 (m, 7 H), 2.11-2.03 (m, 1 H), 1.75-1.58 (m, 3 H), 1.45-1.43 (m, 4 H), 1.37-1.36 (m, 2 H), 1.15-1.01 (m, 4 H). LCMS (Method 15, ESI): 598.3 $[M+H]^+$, RT 1.066 minutes.
Example 183		1H NMR (400 MHz, DMSO-d_6): δ 11.86 (s, 1 H), 8.87 (s, 1 H), 8.48 (d, *J* =3.2 Hz, 1 H), 8.16 (d, *J* =8.0 Hz, 1 H), 7.67-7.59 (m, 2 H), 7.34-7.31 (m, 1 H), 6.87 (d, *J*

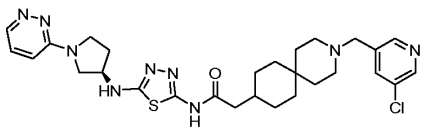
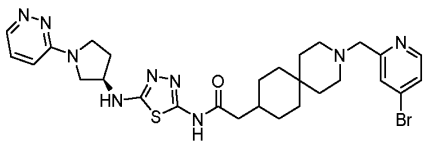
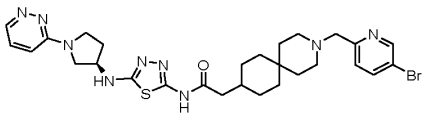
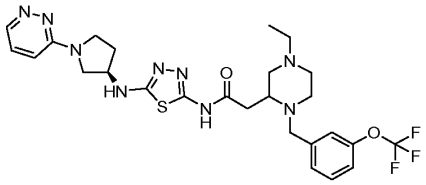
	(*R*)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(3-((5-(trifluoromethyl)pyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)acetamide	=8.0 Hz, 1 H), 4.39-4.36 (m, 1 H), 3.77-3.73(m, 1 H), 3.67 (s, 2 H), 3.58-3.48 (m, 3 H), 2.49-2.38 (m, 4 H), 2.33-2.27 (m, 3 H), 2.11-2.05 (m, 1 H), 1.70-1.61 (m, 3 H), 1.47-1.44 (m, 4 H), 1.33 (s, 2 H), 1.16-1.02 (m, 4 H). LCMS (Method 15, ESI): 616.3 $[M+H]^+$, RT 1.136 minutes.
Example 184	 (*R*)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(3-((2,4,6-trimethylpyridin-3-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.86(s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.35-7.31 (m, 1 H), 6.88-6.85 (m, 2 H), 4.41-4.34 (m, 1 H), 3.77-3.73(m, 1 H), 3.59-3.48 (m, 3 H), 3.39 (s, 2 H), 2.45 (s, 3 H), 2.32-2.28 (m, 13 H), 2.11-2.03 (m, 1 H), 1.74-1.58 (m, 3 H), 1.45-1.38 (m, 4 H), 1.26-1.23 (m, 2 H), 1.19-1.02 (m, 4 H). LCMS (Method 16, ESI): 590.2 $[M+H]^+$, RT 1.610 minutes.
Example 185	 (*R*)-2-(3-((5-chloropyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.86 (s, 1 H), 8.57 (s, 1 H), 8.48 (d, *J* =3.6 Hz, 1 H), 7.88-7.86 (m, 1 H), 7.62-7.60 (m, 1 H), 7.46-7.44 (m, 1 H), 7.36-7.30 (m, 1 H), 6.87 (d, *J* =8.8 Hz, 1 H), 4.42-4.33 (m, 1 H), 3.79-3.72 (m, 1 H), 3.63-3.52 (m, 5 H), 2.28-2.10 (m, 7 H), 1.76-1.68 (m, 1 H), 1.67-1.51 (m, 3 H), 1.46-1.36 (m, 4 H), 1.31-1.26 (m, 2 H), 1.18-0.97 (m, 4 H). LCMS (Method 20, ESI): 582.0 $[M+H]^+$, RT 1.117 minutes.
Example 186	 (*R*)-2-(3-((5-bromopyridin-3-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.87 (s, 1 H), 8.59 (s, 1 H), 8.50-8.44 (m, 2 H), 7.93 (s, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.35-7.31 (m, 1 H), 6.87 (d, *J* =9.2 Hz, 1 H),4.42-4.33 (m, 1 H), 3.79-3.71 (m, 1 H),3.62-3.443 (m, 5 H), 2.38-2.22 (m, 7 H), 2.12-2.02 (m, 7 H), 1.75-1.51 (m, 3 H), 1.45-1.43 (m, 4 H), 1.38-1.30(m, 2 H), 1.25-1.06 (m, 4 H). LCMS (Method 20, ESI): 627.9 $[M+H]^+$, RT 1.092 minutes.

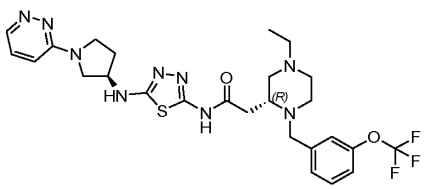
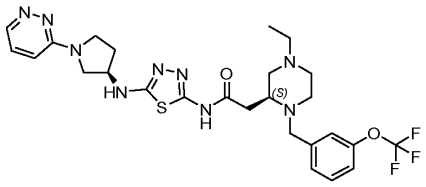
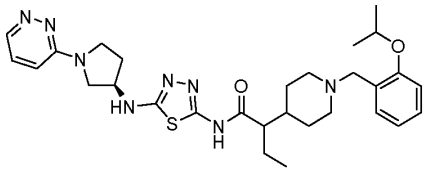
Example 187	 (*R*)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(6-(3-(trifluoromethoxy)benzyl)-6-azaspiro[3.4]octan-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.85 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.60 (d, *J* =6.0 Hz, 1 H), 7.46-7.43 (m, 2 H), 7.36-7.25 (m, 2 H), 7.23-7.19 (m, 2 H), 6.87 (d, *J* =10.0 Hz, 1 H),4.42-4.33 (m, 1 H), 3.79-3.71 (m, 1 H), 3.64-3.46 (m, 5 H), 2.59-2.53 (m, 2 H), 2.51-2.35 (m, 5 H), 2.30-2.28 (m, 1 H), 2.30-2.28 (m, 1 H), 2.23-1.92 (m, 3H), 1.88-1.72 (m, 1 H), 1.65-1.55 (m, 3 H). LCMS (Method 19, ESI): 589.2 $[M+H]^+$, RT 1.118 minutes.
Example 188 and Example 189 Isomers A and B	  One of isomers A and B is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((2*r*,4*R*)-6-(3-(trifluoromethoxy)benzyl)-6-azaspiro[3.4]octan-2-yl)acetamide and *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((2*s*,4*S*)-6-(3-(trifluoromethoxy)benzyl)-6-azaspiro[3.4]octan-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.85 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.60 (d, *J* =6.0 Hz, 1 H), 7.50-7.45 (m, 1 H),7.41-7.37 (m, 2 H), 7.33-7.18 (m, 2 H), 6.87 (d, *J* =9.2 Hz, 1 H), 4.40-4.32 (m, 1 H), 3.78-3.71 (m, 1 H), 3.62-3.46 (m, 5 H), 2.59-2.55 (m, 2 H), 2.45-2.41 (m, 5 H), 2.30-2.24 (m, 1 H), 2.12-1.83 (m, 3 H), 1.78-1.72 (m, 2 H), 1.70-1.67 (m, 2 H). LCMS (Method 13, ESI): 589.4 $[M+H]^+$, RT 6.074 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 11.85 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.60 (d, *J* =6.0 Hz, 1 H), 7.47-7.43 (m, 1 H), 7.38-7.19 (m, 4 H), 6.87 (d, *J* =8.8 Hz, 1 H), 4.42-4.32 (m, 1 H), 3.79-3.67 (m, 1 H), 3.61-3.45 (m, 5 H), 2.63-2.50 (m, 2 H), 2.48-2.30 (m, 5 H), 2.28-2.23 (m, 1 H), 2.12-2.02 (m, 3 H), 1.81-1.64 (m, 4 H). LCMS (Method 13, ESI): 589.4 $[M+H]^+$, RT 6.098 minutes.
Example 190	 (*R*)-2-(6-(3-(difluoromethoxy)-5-methylbenzyl)-6-azaspiro[3.4]octan-2-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-	1H NMR (400 MHz, DMSO-d_6): δ 11.85 (s, 1 H), 8.48 (d, *J* =3.6 Hz, 1 H), 7.60 (d, *J* =6.0 Hz, 1 H), 7.37-7.31 (m, 2 H), 7.01-6.98 (m, 1 H), 6.88-6.86 (m, 3 H), 4.38-4.37 (m, 1 H), 3.77-3.73 (m, 1 H), 3.58-3.48 (m, 5 H), 2.50-2.43 (m, 6 H), 2.33-2.270 (m, 5 H), 2.09-2.00 (m, 3 H), 1.87-1.80 (m, 1 H), 1.76-1.69 (m, 3 H). LCMS

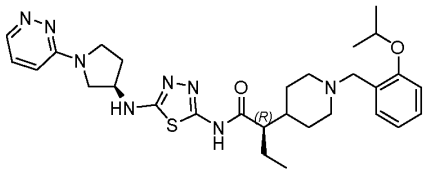
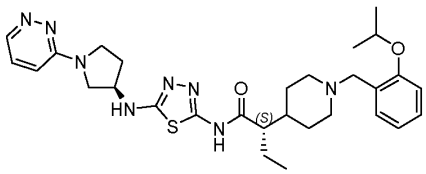
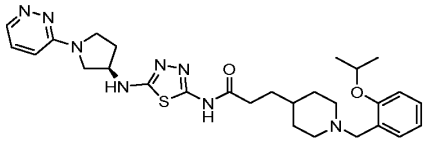
	yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	(Method 16, ESI): 587.5 $[M+H]^+$, RT 1.533 minutes.
Example 191	 (*R*)-2-(6-(2-isopropoxy-4-methylbenzyl)-6-azaspiro[3.4]octan-2-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.85 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.60 (d, *J* =6.0 Hz, 1 H), 7.35-7.31 (m, 1 H), 7.16-7.13 (m, 1 H), 6.88-6.86 (m, 1 H), 6.77 (s, 1 H), 6.69 (d, *J* =7.6 Hz, 1 H), 4.56-4.54 (m, 1 H), 4.38-4.37 (m, 1 H), 3.77-3.73 (m, 1 H), 3.58-3.55 (m, 2 H), 3.51-3.47 (m, 3 H), 2.45-2.43 (m, 6 H), 2.33-2.26 (m, 5 H), 2.09-1.99 (m, 3 H), 1.86-1.83 (m, 1 H), 1.74-1.68 (m, 3H), 1.25-1.23 (m, 6 H). LCMS (Method 19, ESI): 577.3 $[M+H]^+$, RT 1.188 minutes.
Example 192 and Example 193 Isomers A and B	  One of isomers A and B 2-((2*r*,4*R*)-6-(2-isopropoxy-4-methylbenzyl)-6-azaspiro[3.4]octan-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and 2-((2*s*,4*S*)-6-(2-isopropoxy-4-methylbenzyl)-6-azaspiro[3.4]octan-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, *J* =5.6 Hz, 1 H), 7.39-7.36 (m, 1 H), 7.16 (d, *J* =7.6 Hz, 1 H), 6.96 (d, *J* =9.2 Hz, 1 H), 6.78 (s, 1 H), 6.72-6.70 (m, 1 H), 4.64-4.57 (m, 1 H), 4.50-4.45 (m, 1 H), 3.87-3.83 (m, 1 H), 3.68-3.63 (m, 4 H), 3.59-3.56 (m, 1 H), 2.76 (s, 2 H), 2.64-2.61 (m, 2 H), 2.56-2.49 (m, 3 H), 2.44-2.37 (m, 1 H), 2.30-2.22 (m, 3 H), 2.20-2.16 (m, 3 H), 1.85-1.78 (m, 4H), 1.35-1.25 (m, 6 H). LCMS (Method 16, ESI): 577.1 $[M+H]^+$, RT 1.725 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, *J* =4.4 Hz, 1 H), 7.39-7.36 (m, 1 H), 7.14 (d, *J* =7.6 Hz, 1 H), 6.96 (d, *J* =9.2 Hz, 1 H), 6.77 (s, 1 H), 6.71 (d, *J* =8.0 Hz, 1 H), 4.63-4.57 (m, 1 H), 4.50-4.45 (m, 1 H), 3.87-3.83 (m, 1 H), 3.68-3.58 (m, 4 H), 3.57-3.55 (m, 1 H), 2.70-2.61 (m, 5 H), 2.49-2.47 (m, 2 H), 2.42-2.38 (m, 1 H), 2.30 (s, 3 H), 2.20-2.16 (m, 3 H), 2.15-2.10 (m, 2H), 1.99-1.80 (m, 2 H), 1.35-1.25 (m, 6 H). LCMS (Method 16, ESI): 577.1 $[M+H]^+$, RT 1.742 minutes.
Example 194		1H NMR (400 MHz, DMSO-d_6): δ 11.79 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.67 (d, *J* =6.0 Hz, 1 H), 7.42-7.35 (m, 2 H), 7.29-

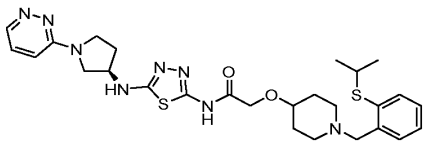
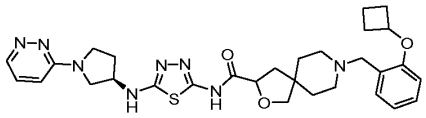
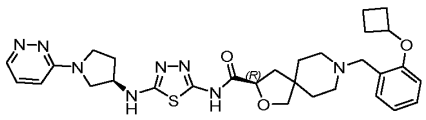
	8-(3-(difluoromethoxy)benzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide	7.01 (m, 4 H), 6.87 (d, *J* =9.2 Hz, 1 H), 4.60-4.52 (m, 1 H), 4.43-4.34 (m, 1 H), 3.79-3.75 (m, 1 H), 3.72 (s, 2 H), 3.66-3.48 (m, 5 H), 2.42-2.34 (m, 5 H), 2.22-2.02 (m, 2 H), 1.78-1.70 (m, 1 H), 1.54-1.47 (m, 4 H). LCMS (Method 13, ESI): 587.4 $[M+H]^+$, RT 5.596 minutes.
Example 195 and Example 196 Isomers A and B	  One of isomers A and B is (*R*)-8-(3-(difluoromethoxy)benzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide and the other is (*S*)-8-(3-(difluoromethoxy)benzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide	1H NMR (400 MHz, DMSO-d_6): δ 11.79 (s, 1 H), 8.48 (dd, *J* =4.4 Hz, 0.8 Hz, 1 H), 7.67 (d, *J* =6.0 Hz, 1 H), 7.22-7.43 (m, 3 H), 7.16 (d, *J* =8.0 Hz, 1 H), 7.09 (s, 1 H), 7.03-7.05 (m, 1 H), 6.87 (dd, *J* =9.2 Hz, 1.2 Hz, 1 H), 4.54-4.58 (m, 1 H), 4.34-4.44 (m, 1 H), 3.73-3.78 (m, 1 H), 3.66 (s, 2 H), 3.44-3.62 (m, 5 H), 2.23-2.42 (m, 5 H), 2.02-2.20 (m, 2 H), 1.71-1.76 (m, 1 H), 1.45-1.62 (m, 4 H). ^{19}F NMR (376 MHz, DMSO-d_6): δ -81.64. LCMS (Method 15, ESI): 587.1 $[M+H]^+$, RT 1.089 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 11.79 (s, 1 H), 8.48 (dd, *J* =4.4 Hz, 1.2 Hz, 1 H), 7.67 (d, *J* =6.0 Hz, 1 H), 7.21-7.42 (m, 3 H), 7.16 (d, *J* =7.6 Hz, 1 H), 7.09 (s, 1 H), 7.04-7.05 (m, 1 H), 6.87 (dd, *J* =9.2 Hz, 1.2 Hz, 1 H), 4.54-4.58 (m, 1 H), 4.35-4.43 (m, 1 H), 3.73-3.78 (m, 1 H), 3.66 (s, 2 H), 3.43-3.61 (m, 5 H), 2.23-2.40 (m, 5 H), 2.03-2.19 (m, 2 H), 1.69-1.79 (m, 1 H), 1.23-1.60 (m, 4 H). 19F NMR (376 MHz, DMSO-d_6): δ -81.64. LCMS (Method 19, ESI): 587.1 $[M+H]^+$, RT 1.060 minutes.
Example 197	 (*R*)-2-(3-((3-cyclobutoxypyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-	1H NMR (400 MHz, DMSO-d_6): δ 11.86 (s, 1 H), 8.48 (d, *J* =4.8 Hz, 1 H), 8.03-8.09 (m, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 7.20 (d, *J* =2.8 Hz, 2 H), 6.87 (d, *J* =9.2 Hz, 1 H), 4.68-4.77 (m, 1 H), 4.33-4.42 (m, 1 H), 3.71-3.79 (m, 1 H), 3.46-3.64 (m, 5 H), 2.36-2.47 (m, 5 H), 2.23-2.35 (m, 3 H),

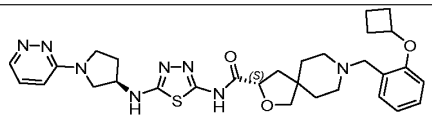
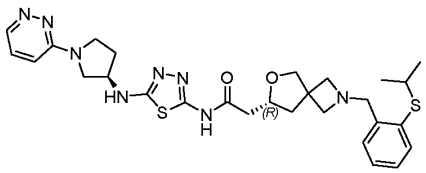
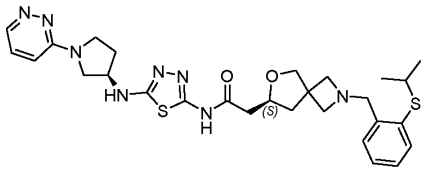
	yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1.95-2.12 (m, 3 H), 1.51-1.85 (m, 6 H), 1.37-1.47 (m, 4 H), 1.22-1.31 (m, 2 H), 0.95-1.16 (m, 4 H). LCMS (Method 13, ESI): 618.5 $[M+H]^+$, RT 6.080 minutes.
Example 198	 2-(1-(3,5-dimethylbenzyl)piperidin-4-yl)-2-methoxy-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, *J* =3.2 Hz, 1 H), 7.38 (dd, *J* =9.2 Hz, 4.8 Hz, 1 H), 6.96 (dd, *J* =8.8 Hz, 0.8 Hz, 1 H), 6.91 (s, 3 H), 4.47-4.52 (m, 1 H), 3.83-3.87 (m, 1 H), 3.57-3.67 (m, 4 H), 3.43 (s, 2 H), 3.39 (s, 3 H), 2.91-2.94 (m, 2 H), 2.37-2.45 (m, 1 H), 2.27 (s, 6 H), 2.16-2.23 (m, 1 H), 1.94-2.03 (m, 2 H), 1.68-1.79 (m, 2 H), 1.49-1.58 (m, 3 H). LCMS (Method 15, ESI): 537.2 $[M+H]^+$, RT 1.136 minutes.
Example 199	 2-(1-(2-cyclobutoxybenzyl)piperidin-4-yl)-2-methoxy-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 12.03 (s, 1 H), 8.48 (d, *J* =3.6 Hz, 1 H), 7.70 (d, *J* =6.4 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 7.27 (d, *J* =7.2 Hz, 1 H), 7.13-7.18 (m, 1 H), 6.84-7.13 (m, 2 H), 6.77 (d, *J* =8.4 Hz, 1 H), 4.61-4.70 (m, 1 H), 4.35-4.44 (m, 1 H), 3.72-3.80 (m, 1 H), 3.69 (d, *J* =6.4 Hz, 1 H), 3.47-3.61 (m, 3 H), 3.41 (s, 2 H), 3.23 (s, 3 H), 2.77-2.87 (m, 2 H), 2.24-2.53 (m, 3 H), 1.84-2.14 (m, 5 H), 1.59-1.80 (m, 4 H), 1.22-1.42 (m, 3 H). LCMS (Method 13, ESI):579.4 $[M+H]^+$, RT 6.127 minutes.
Example 200	 2-(1-(2-(isopropylthio)benzyl)piperidin-4-yl)-2-methoxy-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 12.03 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.70 (d, *J* =6.0 Hz, 1 H), 7.32-7.43 (m, 3 H), 7.18-7.25 (m, 2 H), 6.87 (d, *J* =9.2 Hz, 1 H), 4.36-4.43 (m, 1 H), 3.69-3.78 (m, 2 H), 3.46-3.59 (m, 6 H), 3.23 (s, 3 H), 2.74-2.83 (m, 2 H), 2.25-2.34 (m, 1 H), 2.05-2.12 (m, 1 H), 1.85-1.95 (m, 2 H), 1.62-1.70 (m, 2 H), 1.20-1.40 (m, 9 H). LCMS (Method 16, ESI): 583.2 $[M+H]^+$, RT 1.383 minutes.

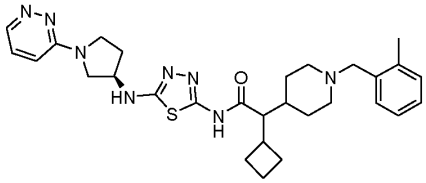
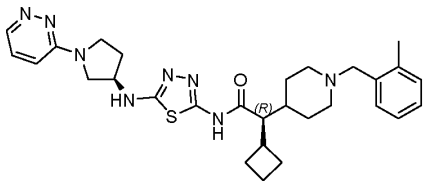
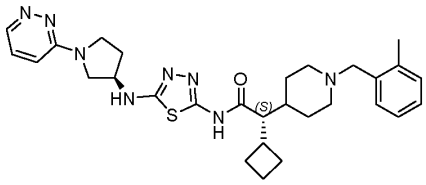
Example 201	 (*R*)-2-(3-((5-chloropyridin-3-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1 H), 8.43-8.50 (m, 3 H), 7.80 (s, 1 H), 7.59 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 6.86 (d, *J* =9.2 Hz, 1 H), 4.36-4.40 (m, 1 H), 3.73-3.77 (m, 1 H), 3.50-3.59 (m, 5 H), 2.25-2.32 (m, 7 H), 2.05-2.10 (m, 1 H), 1.58-1.69 (m, 3 H), 1.31-1.45 (m, 4 H), 1.29-1.30 (m, 2 H), 1.00-1.13 (m, 4 H). LCMS (Method 16, ESI): 582.2 $[M+H]^+$, RT 1.505 minutes.
Example 202	 (*R*)-2-(3-((4-bromopyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.85 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 8.37 (d, *J* =5.2 Hz, 1 H), 7.63 (s, 1 H), 7.60 (d, *J* =6.4 Hz, 1 H), 7.54 (d, *J* =4.8 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 6.87 (d, *J* =9.2 Hz, 1 H), 4.34-4.42 (m, 1 H), 3.73-3.79 (m, 1 H), 3.46-3.72 (m, 5 H), 2.24-2.43 (m, 7 H), 2.02-2.12 (m, 1 H), 1.57-1.76 (m, 3 H), 1.40-1.51 (m, 4 H), 1.28-1.36 (m, 2 H), 0.98-1.18 (m, 4 H). LCMS (Method 15, ESI): 626.1 $[M+H]^+$, RT 1.083 minutes.
Example 203	 (*R*)-2-(3-((5-bromopyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1 H), 8.59 (d, *J* =2.0 Hz, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.99 (dd, *J* =8.4 Hz, 2.4 Hz, 1 H), 7.59 (d, *J* =6.0 Hz, 1 H), 7.40 (d, *J* =8.4 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 6.87 (d, *J* =8.8 Hz, 1 H), 4.36-4.40 (m, 1 H), 3.73-3.78 (m, 1 H), 3.48-3.59 (m, 5 H), 2.25-2.35 (m, 7 H), 2.05-2.10 (m, 1 H), 1.59-1.69 (m, 3 H), 1.43-1.56 (m, 4 H), 1.29-1.32 (m, 2 H), 1.01-1.16 (m, 4 H). LCMS (Method 16, ESI): 626.1 $[M+H]^+$, RT 1.523 minutes.
Example 204	 2-(4-ethyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-	1H NMR (400 MHz, DMSO-d_6): δ 12.00 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.62 (d, *J* =6.0 Hz, 1 H), 7.43 (t, *J* =8.0 Hz, 1 H), 7.31-7.35 (m, 2 H), 7.26 (s, 1 H), 7.21 (d, *J* =7.6 Hz, 1 H), 6.87 (d, *J* =9.2 Hz, 1 H), 4.35-4.42 (m, 1 H), 3.83-3.86 (m, 1 H), 3.74-3.76 (m, 1 H), 3.41-3.59 (m, 4 H),

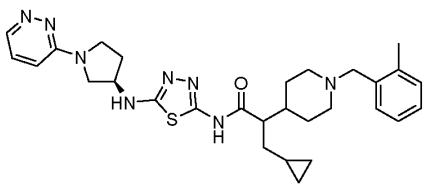
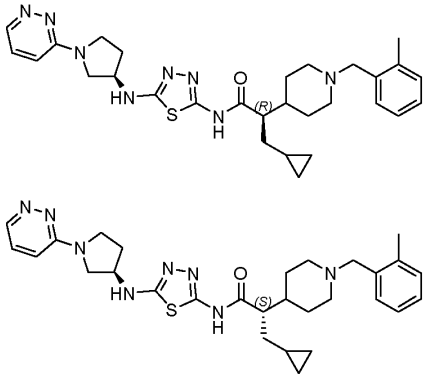
	N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	2.95-3.04 (m, 1 H), 2.76-2.81 (m, 1 H), 2.57-2.67 (m, 2 H), 2.37-2.50 (m, 1 H), 2.21-2.34 (m, 7 H), 2.04-2.12 (m, 1 H), 0.95 (t, *J* =6.8 Hz, 3 H). LCMS (Method 15, ESI): 592.1 $[M+H]^+$, RT 1.247 minutes.
Example 205 and Example 206 Isomers A and B	  One of isomers A and B is 2-((*R*)-4-ethyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((*S*)-4-ethyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 12.00 (s, 1 H), 8.48 (dd, *J* =4.4 Hz, 1.2 Hz, 1 H), 7.62 (d, *J* =6.0 Hz, 1 H), 7.43 (t, *J* =8.0 Hz, 1 H), 7.31-7.35 (m, 2 H), 7.26 (s, 1 H), 7.22 (d, *J* =7.2 Hz, 1 H), 6.87 (dd, *J* =9.2 Hz, 1.6 Hz, 1 H), 4.35-4.41 (m, 1 H), 3.83-3.86 (m, 1 H), 3.73-3.76 (m, 1 H), 3.41-3.59 (m, 4 H), 2.96-3.01 (m, 1 H), 2.76-2.80 (m, 1 H), 2.56-2.67 (m, 2 H), 2.35-2.46 (m, 1 H), 2.22-2.29 (m, 7 H), 2.04-2.11 (m, 1 H), 0.95 (t, *J* =7.2 Hz, 3 H). LCMS (Method 15, ESI): 592.1 $[M+H]^+$, RT 1.171 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 11.98 (s, 1 H), 8.48 (dd, *J* =4.4 Hz, 1.2 Hz, 1 H), 7.62 (d, *J* =6.0 Hz, 1 H), 7.43 (t, *J* =7.6 Hz, 1 H), 7.31-7.35 (m, 2 H), 7.26 (s, 1 H), 7.21 (d, *J* =8.4 Hz, 1 H), 6.87 (dd, *J* =9.2 Hz, 1.2 Hz, 1 H), 4.35-4.41 (m, 1 H), 3.83-3.86 (m, 1 H), 3.73-3.76 (m, 1 H), 3.41-3.59 (m, 4 H), 2.94-3.02 (m, 1 H), 2.75-2.80 (m, 1 H), 2.56-2.67 (m, 2 H), 2.37-2.46 (m, 1 H), 2.22-2.29 (m, 7 H), 2.04-2.10 (m, 1 H), 0.95 (t, *J* =7.2 Hz, 3 H). LCMS (Method 15, ESI): 592.1 $[M+H]^+$, RT 1.159 minutes.
Example 207	 2-(1-(2-isopropoxybenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide	1H NMR (400 MHz, DMSO-d_6): δ 11.94 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.64 (d, *J* =6.4 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.4 Hz, 1 H), 7.27 (d, *J* =7.6 Hz, 1 H), 7.16 (t, *J* =7.6 Hz, 1 H), 6.95 (d, *J* =8.0 Hz, 1 H), 6.85-6.88 (m, 2 H), 4.53-4.60 (m, 1 H), 4.35-4.42 (m, 1 H), 3.73-3.77 (m, 1 H), 3.49-3.59 (m, 3 H), 3.38 (s, 2 H), 2.77-2.86 (m, 2 H), 2.24-2.33 (m, 2 H), 2.04-

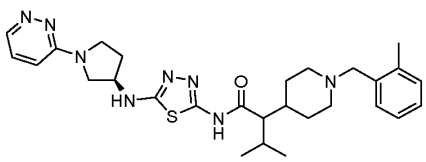
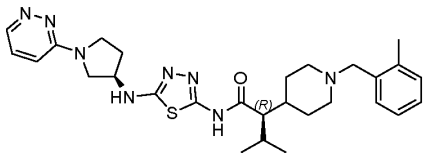
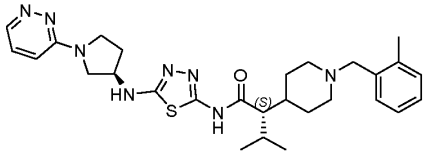
		2.12 (m, 1 H), 1.83-1.94 (m, 2 H), 1.69-1.72 (m, 1 H), 1.41-1.58 (m, 4 H), 1.24-1.36 (m, 7 H), 1.10-1.16 (m, 1 H), 0.75-1.06 (m, 3 H). LCMS (Method 13, ESI): 565.4 $[M+H]^+$, RT 6.226 minutes.
Example 208 and Example 209 Isomers A and B	  One of isomers A and B is (*R*)-2-(1-(2-isopropoxybenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide and the other is (*S*)-2-(1-(2-isopropoxybenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide	1H NMR (400 MHz, DMSO-d_6): δ 11.94 (s, 1 H), 8.48 (dd, *J* =4.4 Hz, 1.2 Hz, 1 H), 7.64 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =10.0 Hz, 4.4 Hz, 1 H), 7.26 (dd, *J* =7.6 Hz, 1.6 Hz, 1 H), 7.14-7.18 (m, 2 H), 6.95 (d, *J* =8.0 Hz, 1 H), 6.83-6.90 (m, 2 H), 4.52-4.61 (m, 1 H), 4.34-4.42 (m, 1 H), 3.71-3.79 (m, 1 H), 3.47-3.62 (m, 3 H), 3.38 (s, 2 H), 2.74-2.87 (m, 2 H), 2.22-2.34 (m, 2 H), 2.02-2.13 (m, 1 H), 1.81-1.94 (m, 2 H), 1.69-1.75 (m, 1 H), 1.40-1.66 (m, 4 H), 1.23-1.39 (m, 7 H), 1.09-1.13 (m, 1 H), 0.77 (t, *J* =7.2 Hz, 3 H). LCMS (Method 15, ESI): 565.2 $[M+H]^+$, RT 1.153 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 11.95 (s, 1 H), 8.48 (dd, *J* =4.4 Hz, 1.2 Hz, 1 H), 7.64 (d, *J* =6.0 Hz, 1 H), 7.33 (dd, *J* =9.2 Hz, 4.8 Hz, 1 H), 7.27 (d, *J* =6.0 Hz, 1 H), 7.17 (t, *J* =8.0 Hz, 1 H), 6.95 (d, *J* =8.0 Hz, 1 H), 6.83-6.90 (m, 2 H), 4.53-4.62 (m, 1 H), 4.35-4.42 (m, 1 H), 3.73-3.77 (m, 1 H), 3.47-3.62 (m, 3 H), 3.40 (s, 2 H), 2.76-2.89 (m, 2 H), 2.23-2.35 (m, 2 H), 2.03-2.13 (m, 1 H), 1.82-1.99 (m, 2 H), 1.70-1.76 (m, 1 H), 1.37-1.67 (m, 4 H), 1.17-1.30 (m, 7 H), 1.11-1.17 (m, 1 H), 0.76 (t, *J* =7.2 Hz, 3 H). LCMS (Method 19, ESI): 565.2 $[M+H]^+$, RT 1.165 minutes.
Example 210	 (*R*)-3-(1-(2-isopropoxybenzyl)piperidin-4-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-	1H NMR (400 MHz, DMSO-d_6): δ 11.90 (s, 1 H), 8.48 (dd, *J* = 4.8 Hz, 1.2 Hz, 1 H), 7.61 (d, *J* = 6.0 Hz, 1 H), 7.33 (dd, *J* = 9.2 Hz, 4.4 Hz, 1 H), 7.28 (dd, *J* = 7.2 Hz, 1.2 Hz, 1 H), 7.14-7.19 (m, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 6.86-6.89 (m, 2 H),

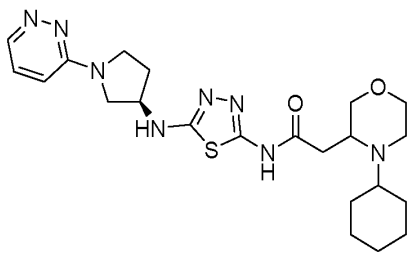
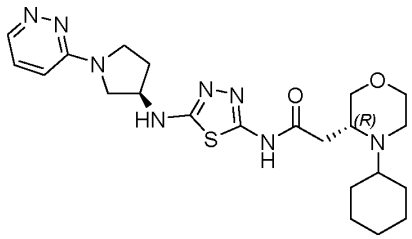
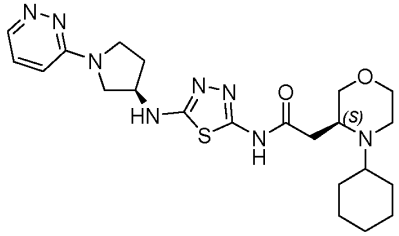
	yl)amino)-1,3,4-thiadiazol-2-yl)propanamide	4.39-4.58 (m, 1 H), 4.36-4.37 (m, 1 H), 3.73-3.77 (m, 1 H), 3.48-3.59 (m, 3 H), 3.40 (s, 2 H), 2.78-2.81 (m, 2 H), 2.37-2.40 (m, 2 H), 2.27-2.32 (m, 1 H), 2.07-2.10 (m, 1 H), 1.88-1.93 (m, 2 H), 1.59-1.61 (m, 2 H), 1.47-1.52 (m, 2 H), 1.25 (d, *J* = 6.0 Hz, 6 H), 1.10-1.15 (m, 2 H). LCMS (Method 19, ESI): 551.3 $[M+H]^+$, RT 1.149 minutes.
Example 211	 (*R*)-2-((1-(2-(isopropylthio)benzyl)piperidin-4-yl)oxy)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.79 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.67 (d, *J* =6.0 Hz, 1 H), 7.43 (d, *J* =8.8 Hz, 1 H), 7.38 (dd, *J* =7.2 Hz, 1.6 Hz, 1 H), 7.33 (dd, *J* =7.2 Hz, 4.4 Hz, 1 H), 7.20-7.26 (m, 2 H), 6.87 (d, *J* =9.2 Hz, 1 H), 4.36-4.44 (m, 1 H), 4.16 (s, 2 H), 3.74-3.78 (m, 1 H), 3.47-3.59 (m, 7 H), 2.62-2.71 (m, 2 H), 2.26-2.33 (m, 1 H), 2.05-2.13 (m, 3 H), 1.81-2.11 (m, 2 H), 1.43-1.52 (m, 2 H), 1.22 (d, *J* =6.8 Hz, 6 H). LCMS (Method 15, ESI): 569.1 $[M+H]^+$, RT 1.159 minutes.
Example 212	 8-(2-cyclobutoxybenzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide	1H NMR (400 MHz, DMSO-d_6): δ 11.80 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.67 (d, *J* =6.0 Hz, 1 H), 7.29-7.35 (m, 2 H), 7.16 (t, *J* =8.0 Hz, 1 H), 6.86-6.90 (m, 2 H), 6.78 (d, *J* =8.4 Hz, 1 H), 4.65-4.69 (m, 1 H), 4.54-4.58 (m, 1 H), 4.36-4.42 (m, 1 H), 3.73-3.78 (m, 1 H), 3.66 (s, 2 H), 3.46-3.59 (m, 5 H), 2.27-2.44 (m, 7 H), 1.97-2.17 (m, 4 H), 1.71-1.78 (m, 2 H), 1.59-1.66 (m, 1 H), 1.48-1.54 (m, 4 H). LCMS (Method 13, ESI): 591.4 $[M+H]^+$, RT 6.051 minutes.
Example 213 and Example 214 Isomers A and B		1H NMR (400 MHz, DMSO-d6): δ 11.79 (s, 1 H), 8.48 (d, *J* =3.6 Hz, 1 H), 7.68 (d, *J* =6.0 Hz, 1 H), 7.29-7.35 (m, 2 H), 7.17 (t, *J* =8.0 Hz, 1 H), 6.86-6.93 (m, 2 H), 6.80 (d, *J* =8.0 Hz, 1 H), 4.66-4.69 (m, 1 H), 4.54-4.58 (m, 1 H), 4.35-4.44 (m, 1 H), 3.73-3.78 (m, 1 H), 3.66 (s, 2 H), 3.41-

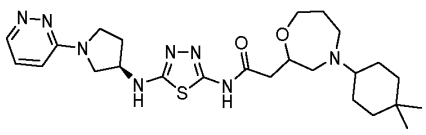
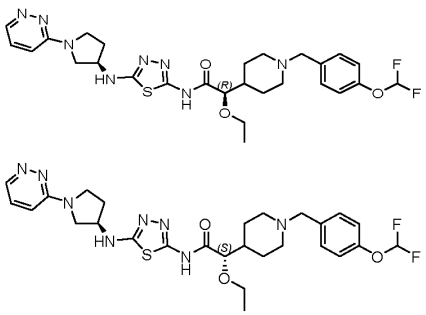
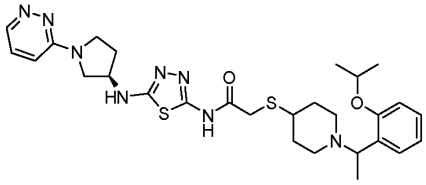
	 One of isomers A and B is (*R*)-8-(2-cyclobutoxybenzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide and the other is (*S*)-8-(2-cyclobutoxybenzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide	3.61 (m, 5 H), 2.31-2.46 (m, 7 H), 1.94-2.24 (m, 4 H), 1.73-1.84 (m, 2 H), 1.60-1.70 (m, 1 H), 1.47-1.54 (m, 4 H). LCMS (Method 15, ESI): 591.2 $[M+H]^+$, RT 1.165 minutes. Chiral SFC (General Procedure 5C): RT 1.765 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 11.81 (s, 1 H), 8.48 (d, *J* =3.6 Hz, 1 H), 7.68 (d, *J* =6.4 Hz, 1 H), 7.27-7.37 (m, 2 H), 7.17 (t, *J* =7.6 Hz, 1 H), 6.84-6.93 (m, 2 H), 6.79 (d, *J* =8.0 Hz, 1 H), 4.63-4.72 (m, 1 H), 4.54-4.60 (m, 1 H), 4.35-4.52 (m, 1 H), 3.73-3.78 (m, 1 H), 3.66 (s, 2 H), 3.43-3.64 (m, 5 H), 2.31-2.49 (m, 7 H), 1.95-2.24 (m, 4 H), 1.76-1.83 (m, 2 H), 1.60-1.71 (m, 1 H), 1.47-1.54 (m, 4 H). LCMS (Method 15, ESI): 591.2 $[M+H]^+$, RT 1.165 minutes. Chiral SFC (General Procedure 5C): RT 3.132 minutes.
Example 215 and Example 216 Isomers A and B	  One of isomers A and B is 2-((*R*)-2-(2-(isopropylthio)benzyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((*S*)-2-(2-(isopropylthio)benzyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.92 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.62 (d, *J* =6.0 Hz, 1 H), 7.41-7.34 (m, 1 H), 7.32-7.31 (m, 2 H), 7.25-7.18 (m, 2 H), 6.88-6.86 (m, 1 H), 4.40-4.36 (m, 1 H), 4.19-4.16 (m, 1 H), 3.88-3.85 (m, 1 H), 3.77-3.69 (m, 2 H), 3.63 (s, 2 H), 3.59-3.44 (m, 4 H), 3.22-3.13 (m, 4 H), 2.61-2.50 (m, 2 H), 2.34-2.19 (m, 2 H), 2.11-2.07 (m, 1 H), 2.04-1.75 (m, 1 H), 1.26-1.22 (m, 6 H). LCMS (Method 15, ESI): 581.1 $[M+H]^+$, RT 1.142 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 11.91 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.62 (d, *J* =6.0 Hz, 1 H), 7.40-7.34 (m, 1 H), 7.32-7.31 (m, 2 H), 7.25-7.18 (m, 2 H), 6.88-6.86 (m, 1 H), 4.42-4.37 (m, 1 H), 4.20-4.14 (m, 1 H), 3.87-3.85 (m, 1 H), 3.77-3.68 (m, 2 H), 3.63 (s, 2 H), 3.59-3.44 (m, 4 H), 3.22-3.13 (m, 4 H), 2.61-2.51 (m, 2 H), 2.33-2.19 (m, 2 H), 2.11-2.07 (m, 1 H), 2.04-1.74 (m, 1 H), 1.23-1.22 (m, 6

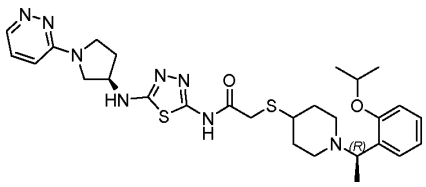
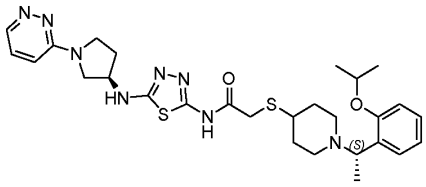
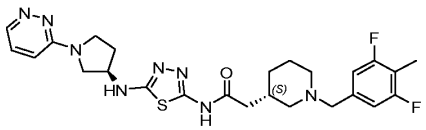
		H). LCMS (Method 15, ESI): 581.1 $[M+H]^+$, RT 1.153 minutes.
Example 217	 2-cyclobutyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 8.49-8.47 (m, 1 H), 7.36-7.33 (m, 1 H), 7.21-7.15 (m, 1 H), 7.12-7.07 (m, 3 H), 6.89-6.87 (m, 1 H), 4.41-4.34 (m, 1 H), 3.77-3.72 (m, 1 H), 3.61-3.52 (m, 3 H), 3.39-3.28 (m, 2 H), 2.80-2.70 (m, 2 H), 2.54-2.51 (m, 1 H), 2.42-2.35 (m, 1 H), 2.32-2.23 (m, 4 H), 2.07-1.93 (m, 2 H), 1.87-1.56 (m, 8 H), 1.50-1.43 (m, 1H), 1.38-1.35 (m, 1 H), 1.28-1.15 (m, 2 H). LCMS (Method 13, ESI): 547.4 $[M+H]^+$, RT 6.028 minutes.
Example 218 and Example 219 Isomers A and B	  One of isomers A and B is (*R*)-2-cyclobutyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is (*S*)-2-cyclobutyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, *J* =3.6 Hz, 1 H), 7.39-7.36 (m, 1 H), 7.24-7.19 (m, 1 H), 7.15-7.07 (m, 3 H), 6.97-6.95 (m, 1 H), 4.52-4.45 (m, 1 H), 3.87-3.83 (m, 1 H), 3.68-3.62 (m, 2 H), 3.59-3.56 (m, 1 H), 3.46 (s, 2 H), 2.98-2.85 (m, 2 H), 2.70-2.60 (m, 1 H), 2.40-2.30 (m, 5 H), 2.24-2.17 (m, 2 H), 2.13-1.88 (m, 2 H), 1.85-1.62 (m, 6 H), 1.58-1.49 (m, 1H), 1.46-1.43 (m, 1 H), 1.38-1.34 (m, 2 H). LCMS (Method 15, ESI): 547.2 $[M+H]^+$, RT 1.153 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, *J* =3.6 Hz, 1 H), 7.39-7.36 (m, 1 H), 7.23-7.22 (m, 1 H), 7.17-7.07 (m, 3 H), 6.97-6.95 (m, 1 H), 4.52-4.44 (m, 1 H), 3.87-3.83 (m, 1 H), 3.71-3.62 (m, 2 H), 3.59-3.56 (m, 1 H), 3.50-3.44 (m, 2 H), 2.99-2.87 (m, 2 H), 2.73-2.60 (m, 1 H), 2.44-2.30 (m, 5 H), 2.24-2.03 (m, 4 H), 1.95-1.68 (m, 6 H), 1.64-1.52 (m, 1H), 1.50-1.43 (m, 1 H), 1.35-1.30 (m, 2 H). LCMS (Method 15, ESI): 547.2 $[M+H]^+$, RT 1.142 minutes.

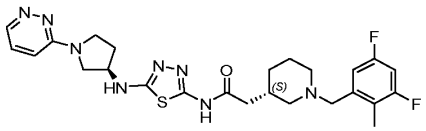
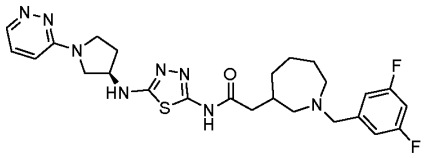
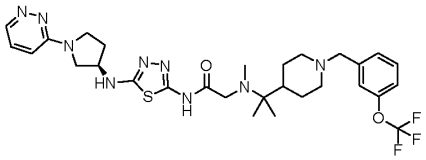
Example 220	 3-cyclopropyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide	1H NMR (400 MHz, DMSO-d_6): δ 11.96 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.62 (d, *J* =6.0 Hz, 1 H), 7.35-7.31 (m, 1 H), 7.21-7.06 (m, 4 H), 6.87 (d, *J* =9.2 Hz, 1 H), 4.42-3.79 (m, 1 H), 3.77-3.72 (m, 1 H), 3.62-3.47 (m, 3 H), 3.39-3.34 (m, 2 H), 2.82-2.70 (m, 1 H), 2.49-2.41 (m, 1 H), 2.36-2.28 (m, 4 H), 2.13-2.03 (m, 1 H), 1.92-1.79 (m, 2 H), 1.73-1.63 (m, 1 H), 1.49-1.41 (m, 4H), 1.40-1.34 (m, 1 H), 0.62-0.55 (m, 1 H), 0.42-0.35 (m, 2 H), 0.10-0.02 (m, 2 H). LCMS (Method 13, ESI): 547.4 $[M+H]^+$, RT 5.946 minutes.
Example 221 and Example 222 **Isomers A and B**	 One of isomers A and B is (*R*)-3-cyclopropyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide and the other is (*S*)-3-cyclopropyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide	1H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, *J* =4.0 Hz, 1 H), 7.40-7.36 (m, 1 H), 7.23-7.22 (m, 1 H), 7.16-7.08 (m, 3 H), 6.98-6.95 (m, 1 H), 4.52-4.44 (m, 1 H), 3.83-3.66 (m, 1 H), 3.62-3.60 (m, 2 H), 3.58-3.56 (m, 1 H), 3.52-3.45 (m, 2 H), 3.01-2.87 (m, 1 H), 2.45-2.42 (m, 2 H), 2.39-2.33 (m, 3 H), 2.25-2.19 (m, 1 H), 2.16-2.01 (m, 2 H), 1.82-1.78 (m, 1 H), 1.61-1.52 (m, 4 H),1.44-1.38 (m, 1 H), 1.35-1.32 (m, 1 H), 0.64-0.59 (m, 1 H), 0.45-0.38 (m, 2 H), 0.10-0.01 (m, 2 H). LCMS (Method 15, ESI): 547.2 $[M+H]^+$, RT 1.142 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, *J* =4.4 Hz, 1 H), 7.40-7.36 (m, 1 H), 7.24-7.23 (m, 1 H), 7.17-7.09 (m, 3 H), 6.98-6.96 (m, 1 H), 4.52-4.45 (m, 1 H), 3.87-3.70 (m, 1 H), 3.65-3.60 (m, 2 H), 3.57-3.56 (m, 1 H), 3.53-3.46 (m, 2 H), 3.01-2.90 (m, 1 H), 2.45-2.42 (m, 2 H), 2.39-2.34 (m, 3 H), 2.24-2.20 (m, 1 H), 2.14-2.07 (m, 2 H), 1.82-1.78 (m, 1 H), 1.62-1.52 (m, 4 H), 1.47-1.38 (m, 1 H), 1.37-1.32 (m, 1 H), 0.63-0.54 (m, 1 H), 0.44-0.39 (m, 2 H), 0.12-0.03 (m, 2 H). LCMS (Method 15, ESI): 547.2 $[M+H]^+$, RT 1.136 minutes.

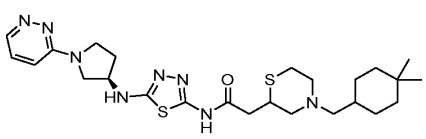
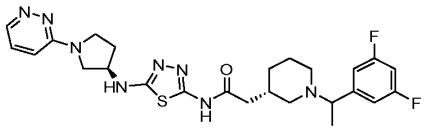
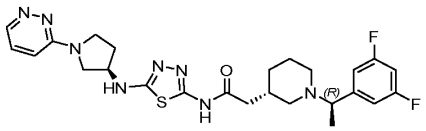
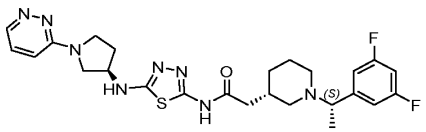
Example 223	 3-methyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide	1H NMR (400 MHz, DMSO-d_6): δ 11.89 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.63 (d, *J* =6.0 Hz, 1 H), 7.35-7.31 (m, 1 H), 7.19-7.09 (m, 4 H), 6.88-6.86 (m, 1 H), 4.40-4.36 (m, 1 H), 3.77-3.73 (m, 1 H), 3.59-3.49 (m, 3 H), 3.35-3.32 (m, 2 H), 2.77-2.72 (m, 2 H), 2.31-2.22 (m, 5 H), 2.12-2.06 (m, 1 H), 1.98-1.84 (m, 3 H), 1.66-1.61 (m, 1 H), 1.28-1.25 (m, 1 H), 1.09-1.03 (m, 1 H), 0.89-0.83 (m, 6 H). LCMS (Method 16, ESI): 535.2 $[M+H]^+$, RT 1.700 minutes.
Example 224 and Example 225 Isomers A and B	  One of the isomers A and B is (*R*)-3-methyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide and the other is (*S*)-3-methyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide	1H NMR (400 MHz, DMSO-d_6): δ 11.89 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.63 (d, *J* =6.0 Hz, 1 H), 7.35-7.31 (m, 1 H), 7.18-7.09 (m, 4 H), 6.88-6.86 (m, 1 H), 4.40-4.36 (m, 1 H), 3.77-3.73 (m, 1 H), 3.59-3.49 (m, 3 H), 3.35-3.32 (m, 2 H), 2.79-2.74 (m, 2 H), 2.31-2.22 (m, 5 H), 2.10-2.06 (m, 1 H), 1.98-1.84 (m, 3 H), 1.66-1.61 (m, 2 H), 1.43-1.40 (m, 1 H), 1.28-1.25 (m, 1 H), 1.06-1.03 (m, 1 H), 0.89-0.84 (m, 6 H). LCMS (Method 15, ESI): 535.2 $[M+H]^+$, RT 1.130 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 11.89 (s, 1 H), 8.48 (d, *J* =4.4 Hz, 1 H), 7.63 (d, *J* =6.0 Hz, 1 H), 7.35-7.31 (m, 1 H), 7.19-7.10 (m, 4 H), 6.88-6.86 (m, 1 H), 4.40-4.36 (m, 1 H), 3.77-3.73 (m, 1 H), 3.59-3.49 (m, 3 H), 3.35-3.32 (m, 2 H), 2.77-2.75 (m, 2 H), 2.31-2.24 (m, 5 H), 2.11-2.06 (m, 1 H), 1.98-1.85 (m, 3 H), 1.66-1.61 (m, 2 H), 1.44-1.41 (m, 1 H), 1.28-1.25 (m, 1 H), 1.06-1.03 (m, 1 H), 0.89-0.83 (m, 6 H). LCMS (Method 13, ESI): 535.2 $[M+H]^+$, RT 1.113 minutes.

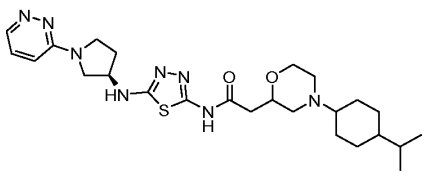
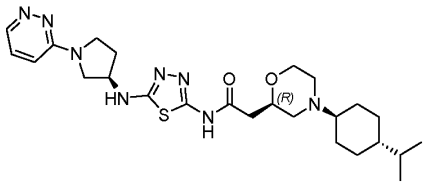
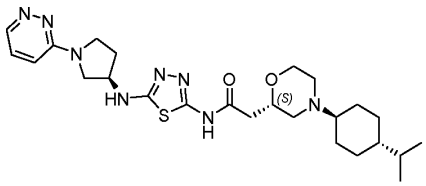
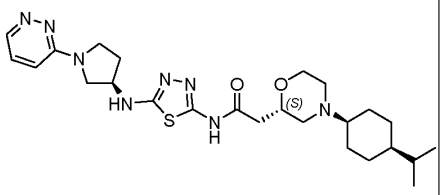
Example 226	 2-(4-cyclohexylmorpholin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 12.10 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.63 (d, *J* =6.0 Hz, 1 H), 7.35-7.31 (m, 1 H), 6.84 (d, *J* =9.2 Hz, 1 H),4.42-4.34 (m, 1 H), 3.78-3.73 (m, 1 H), 3.58-3.49 (m, 6 H), 3.32-3.28 (m, 1 H), 3.19-3.11 (m, 1 H), 2.58-2.57 (m, 3 H), 2.53-2.34 (m, 2 H), 2.29-2.25 (m, 1 H), 2.11-2.04 (m, 1 H), 1.81-1.65 (m, 4 H), 1.53-1.48 (m, 1 H), 1.28-1.22 (m, 2 H), 1.15-1.06 (m, 3 H). LCMS (Method 15, ESI): 473.2 $[M+H]^+$, RT 0.984 minutes.
Example 227 and Example 228 Isomers A and B	  One of isomers A and B is 2-((*R*)-4-cyclohexylmorpholin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((*S*)-4-cyclohexylmorpholin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 12.10 (s, 1 H), 8.49-8.47 (m, 1 H), 7.63 (d, *J* =6.0 Hz, 1 H), 7.35-7.32 (m, 1 H), 6.89-6.86 (m, 1 H), 4.42-4.35 (m, 1 H), 3.78-3.74 (m, 1 H), 3.58-3.49 (m, 6 H), 3.32-3.25 (m, 1 H), 3.20-3.11 (m, 1 H), 2.58-2.54 (m, 3 H), 2.50-2.34 (m, 2 H), 2.30-2.25 (m, 1 H), 2.10-2.04 (m, 1 H), 1.80-1.68 (m, 4 H), 1.53-1.50 (m, 1 H), 1.30-1.23 (m, 2 H), 1.17-1.05 (m, 3 H). LCMS (Method 19, ESI): 473.2 $[M+H]^+$, RT 0.998 minutes. Chiral SFC (General Procedure 5C): RT 1.167 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 12.11 (s, 1 H), 8.49-8.47 (m, 1 H), 7.64 (d, *J* =6.0 Hz, 1 H), 7.35-7.32 (m, 1 H), 6.88-6.86 (m, 1 H), 4.42-4.35 (m, 1 H), 3.78-3.73 (m, 1 H), 3.58-3.49 (m, 6 H), 3.34-3.30 (m, 1 H), 3.20-3.11 (m, 1 H), 2.59-2.54 (m, 3 H), 2.50-2.34 (m, 2 H), 2.30-2.25 (m, 1 H), 2.10-2.06 (m, 1 H), 1.76-1.65 (m, 4 H), 1.53-1.48 (m, 1 H), 1.30-1.23 (m, 2 H), 1.18-1.00 (m, 3 H). LCMS (Method 19, ESI): 473.1 $[M+H]^+$, RT 0.998 minutes. Chiral SFC (General Procedure 5C): RT 2.287 minutes.

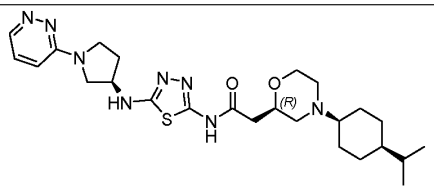
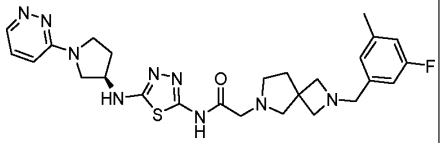
Example 229	 2-[4-(4,4-dimethylcyclohexyl)-1,4-oxazepan-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.61 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.44 – 4.32 (m, 1H), 3.90 (s, 1H), 3.79 – 3.66 (m, 2H), 3.61 – 3.46 (m, 4H), 2.91 – 2.75 (m, 2H), 2.68 – 2.54 (m, 2H), 2.46 – 2.27 (m, 4H), 2.13 – 2.01 (m, 1H), 1.70 (s, 2H), 1.52 (s, 2H), 1.40 – 1.27 (m, 4H), 1.21 – 1.09 (m, 2H), 0.85 (d, *J* = 2.0 Hz, 6H). LCMS (Method 5, ESI) 514.77 [MH]+, RT 1.43. Chiral SFC (Method 25, 210-400 nm) RT_1 11.72 min; RT_2 13.20 min; d.r.= 48.84:51.16.
Example 230 and Example 231 Isomers A and B	 One of isomers A and B is (*R*)-2-(1-(4-(difluoromethoxy)benzyl)piperidin-4-yl)-2-ethoxy-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is (*S*)-2-(1-(4-(difluoromethoxy)benzyl)piperidin-4-yl)-2-ethoxy-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 8.48 (d, *J* =4.4 Hz, 1 H), 7.37-7.10 (m, 6 H), 6.90-6.88 (m, 1 H), 4.43-4.37 (m, 1 H), 3.77-3.73 (m, 1 H), 3.79-3.73 (m, 2 H), 3.65-3.53 (m, 4 H), 3.49-3.41 (m, 2 H), 3.36-3.30 (m, 1 H), 2.80-2.76 (m, 2 H), 2.35-2.26 (m, 1 H), 2.13-2.05 (m, 1 H), 1.89-1.83 (m, 2 H), 1.67-1.60 (m, 2 H), 1.40-1.25 (m, 3 H), 1.13-1.10 (m, 3 H). LCMS (Method 15, ESI): 589.1 $[M+H]^+$, RT 1.124 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 8.48 (d, *J* =4.4 Hz, 1 H), 7.36-6.99 (m, 6 H), 6.89-6.87 (m, 1 H), 4.42-4.37 (m, 1 H), 3.79-3.73 (m, 2 H), 3.79-3.73 (m, 2 H), 3.60-3.53 (m, 4 H), 3.50-3.42 (m, 2 H), 3.36-3.31 (m, 1 H), 2.84-2.75 (m, 2 H), 2.35-2.26 (m, 1 H), 2.12-2.06 (m, 1 H), 1.88-1.83 (m, 2 H), 1.70-1.60 (m, 2 H), 1.40-1.24 (m, 3 H), 1.13-1.12 (m, 3 H). LCMS (Method 15, ESI): 589.1 $[M+H]^+$, RT 1.130 minutes.
Example 232		1H NMR (400 MHz, DMSO-d_6): δ 12.06 (s, 1 H), 8.48 (d, *J* =4.8 Hz, 1 H), 7.66 (d, *J* =6.0 Hz, 1 H), 7.35-7.30 (m, 2 H), 7.17-7.12 (m, 1 H), 6.97-6.95 (m, 1 H), 6.89-6.86 (m, 2 H), 4.61-4.55 (m, 1 H), 4.40-

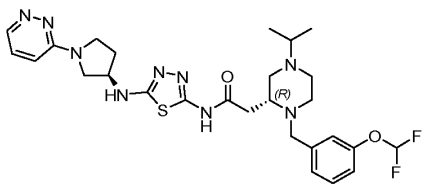
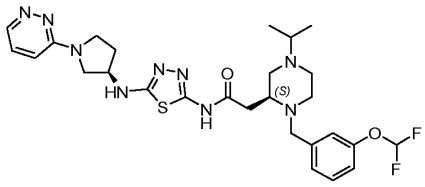
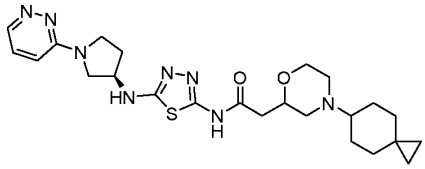
	2-((1-(1-(2-isopropoxyphenyl)ethyl)piperidin-4-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	4.36 (m, 1 H), 3.90-3.88 (m, 1 H), 3.77-3.73 (m, 1 H), 3.59-3.49 (m, 3 H), 3.37-3.32 (m, 2 H), 2.95-2.92 (m, 1 H), 2.74-2.67 (m, 2 H), 2.32-2.27 (m, 1 H), 2.10-2.05 (m, 1 H), 1.98-1.81 (m, 4 H), 1.45-1.34 (m, 2 H), 1.26-1.24 (m, 6 H), 1.19-1.17 (m, 3 H). LCMS (Method 19, ESI): 583.1 $[M+H]^+$, RT 1.148 minutes.
Example 233 and Example 234 Isomers A and B	  One of isomers A and B is 2-((1-((*R*)-1-(2-isopropoxyphenyl)ethyl)piperidin-4-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((1-((*S*)-1-(2-isopropoxyphenyl)ethyl)piperidin-4-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 12.06 (s, 1 H), 8.48 (d, *J* =4.8 Hz, 1 H), 7.66 (d, *J* =6.0 Hz, 1 H), 7.35-7.30 (m, 2 H), 7.17-7.12 (m, 1 H), 6.97-6.95 (m, 1 H), 6.90-6.86 (m, 2 H), 4.61-4.55 (m, 1 H), 4.40-4.36 (m, 1 H), 3.90-3.88 (m, 1 H), 3.77-3.73 (m, 1 H), 3.59-3.49 (m, 3 H), 3.37-3.32 (m, 2 H), 2.95-2.92 (m, 1 H), 2.72-2.67 (m, 2 H), 2.32-2.27 (m, 1 H), 2.10-2.07 (m, 1 H), 2.01-1.82 (m, 4 H), 1.48-1.34 (m, 2 H), 1.26-1.24 (m, 6 H), 1.19-1.17 (m, 3 H). LCMS (Method 15, ESI): 583.1 $[M+H]^+$, RT 1.171 minutes. 1H NMR (400 MHz, DMSO-d_6): δ 12.05 (s, 1 H), 8.48 (d, *J* =4.8 Hz, 1 H), 7.66 (d, *J* =6.0 Hz, 1 H), 7.35-7.30 (m, 2 H), 7.17-7.12 (m, 1 H), 6.97-6.95 (m, 1 H), 6.90-6.86 (m, 2 H), 4.59-4.56 (m, 1 H), 4.39-4.36 (m, 1 H), 3.90-3.88 (m, 1 H), 3.77-3.73 (m, 1 H), 3.59-3.48 (m, 3 H), 3.37-3.32 (m, 2 H), 2.94-2.92 (m, 1 H), 2.72-2.67 (m, 2 H), 2.32-2.27 (m, 1 H), 2.10-2.07 (m, 1 H), 1.98-1.81 (m, 4 H), 1.46-1.33 (m, 2 H), 1.26-1.24 (m, 6 H), 1.19-1.17 (m, 3 H). LCMS (Method 15, ESI): 583.1 $[M+H]^+$, RT 1.165 minutes.
Example 235	 2-((*S*)-1-(3,5-difluoro-4-methylbenzyl)piperidin-3-yl)-*N*-(5-(((*R*)-	1H NMR (400 MHz, DMSO-d_6): δ 11.89 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.61 (d, *J* =6.4 Hz, 1 H), 7.35-7.31 (m, 1 H), 6.96-6.94 (m, 2 H), 6.88-6.86 (m, 1 H), 4.41-4.35 (m, 1 H), 3.77-3.73 (m, 1 H), 3.59-3.40 (m, 5 H), 2.65-2.58 (m, 2 H), 2.36-2.26 (m, 3 H), 2.10-2.04 (m, 4 H), 1.99-

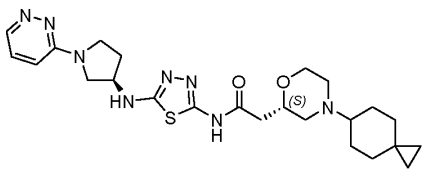
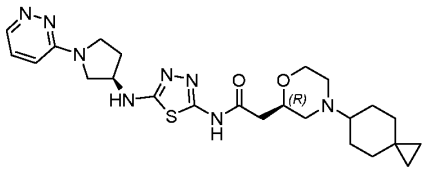
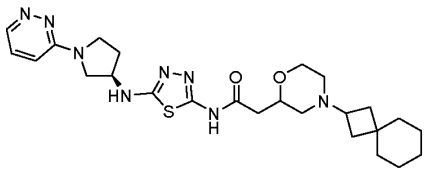
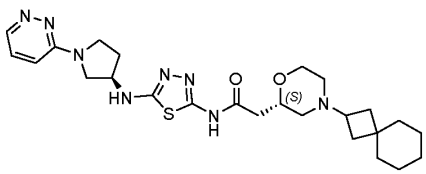
	1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1.93 (m, 2 H), 1.79-1.74 (m, 1 H), 1.64-1.57 (m, 2 H), 1.48-1.40 (m, 1 H), 1.02-0.92 (m, 1 H). LCMS (Method 16, ESI): 529.1 $[M+H]^+$, RT 1.425 minutes.
Example 236	 2-((*S*)-1-(3,5-difluoro-2-methylbenzyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.82 (s, 1 H), 8.48 (d, *J* =5.6 Hz, 1 H), 7.61 (d, *J* =6.0 Hz, 1 H), 7.35-7.29 (m, 1 H), 7.09-6.93 (m, 2 H), 6.87 (d, *J* =10.4 Hz, 1 H), 4.44-4.33 (m, 1 H), 3.81-3.71 (m, 1 H), 3.63-3.40 (m, 3 H), 3.33-3.30 (m, 2 H), 2.71-2.60 (m, 1 H), 2.54-2.50 (m, 1 H), 2.36-2.25 (m, 3 H), 2.01-1.83 (m, 3 H), 1.78-1.70 (m, 1 H), 1.61-1.53 (m, 2 H), 1.44-1.34 (m, 1 H), 1.07-0.89 (m, 1 H). LCMS (Method 13, ESI): 529.3 $[M+H]^+$, RT 5.514 minutes.
Example 237	 2-(1-(3,5-difluorobenzyl)azepan-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.88 (s, 1 H), 8.48 (d, *J* =4.8 Hz, 1 H), 7.59 (d, *J* =6.0 Hz, 1 H), 7.35-7.31 (m, 1 H), 7.03-6.98 (m, 3 H), 6.88-6.86 (m, 1 H), 4.41-4.35 (m, 1 H), 3.78-3.73 (m, 1 H), 3.66-3.49 (m, 5 H), 2.65-2.62 (m, 1 H), 2.55-2.50 (m, 2 H), 2.41-2.26 (m, 4 H), 2.16-2.04 (m, 2 H), 1.67-1.61 (m, 3 H), 1.55-1.51 (m, 2 H), 1.45-1.23 (m, 1 H). LCMS (Method 15, ESI): 529.2 $[M+H]^+$, RT 1.037 minutes.
Example 238	 (*R*)-2-(methyl(2-(1-(3-(trifluoromethoxy)benzyl)piperidin-4-yl)propan-2-yl)amino)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6): δ 11.15 (s, 1 H), 8.48 (d, *J* =4.0 Hz, 1 H), 7.67 (d, *J* =6.0 Hz, 1 H), 7.47-7.43 (m, 1 H), 7.36-7.30 (m, 2 H), 7.28-7.20 (m, 2 H), 6.87 (d, *J* =8.8 Hz, 1 H), 4.43-4.35 (m, 1 H), 3.78-3.72 (m, 1 H), 3.60-3.46 (m, 5 H), 3.26-3.25 (m, 2 H), 2.89-2.81 (m, 2 H), 2.35-2.29 (m, 1 H), 2.12-2.03 (m, 1 H), 1.95-1.84 (m, 2 H), 1.71-1.61 (m, 2 H), 1.53-1.46 (m, 1 H), 1.25-1.17 (m, 2 H), 0.92-0.82 (s, 6 H). LCMS (Method 16, ESI): 634.2 $[M+H]^+$, RT 1.767 minutes.

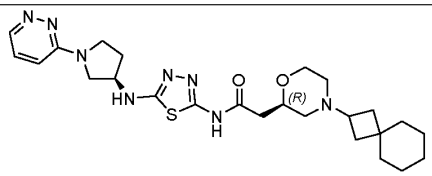
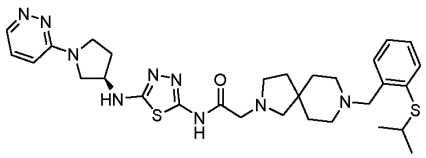
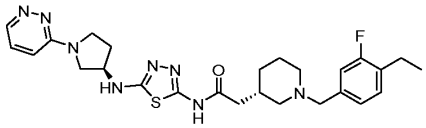
Example 239	 2-(4-((4,4-dimethylcyclohexyl)methyl)thiomorpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.48 (d, *J* = 3.6 Hz, 1H), 7.63 (d, *J* = 6.2 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.02 – 6.77 (m, 1H), 4.38 (d, *J* = 5.4 Hz, 1H), 3.75 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.58 – 3.49 (m, 3H), 3.17 (d, *J* = 5.2 Hz, 1H), 2.84 – 2.61 (m, 4H), 2.60 – 2.52 (m, 2H), 2.43 – 2.25 (m, 3H), 2.14 – 1.97 (m, 3H), 1.52 (t, *J* = 10.8 Hz, 2H), 1.33 – 1.24 (m, 3H), 1.13 – 0.91 (m, 4H), 0.84 (dd, *J* = 8.9, 3.3 Hz, 6H). LCMS (Method 13, ESI): 531.4 [M+H]$^+$, RT 1.152 minutes
Example 240	 2-((3*S*)-1-(1-(3,5-difluorophenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.86 (s, 1H), 8.47 (dd, *J* =4.4, 1.2 Hz, 1H), 7.45 (brs, 1H), 7.33 (dd, *J* =9.2, 4.4 Hz, 1H), 7.05 – 6.98 (m, 3H), 6.86 (d, *J* =9.2 Hz, 1H), 4.45 – 4.31 (m, 1H), 3.75 (dd, *J* =10.8, 5.6 Hz, 1H), 3.60 – 3.45 (m, 4H), 2.78 – 2.57 (m, 2H), 2.36 – 2.15 (m, 3H), 2.10 – 2.03 (m, 1H), 2.01 – 1.90 (m, 2H), 1.82 – 1.70 (m, 1H), 1.63 – 1.52 (m, 2H), 1.49 – 1.27 (m, 1H), 1.25-1.22 (m, 3H), 0.97 – 0.86 (m, 1H). ^{19}F NMR (376 MHz, DMSO-*d6*): δ -110.39. LCMS (Method 21, ESI): 529.4 [M+H]$^+$, RT 1.550 minutes.
Example 241 and Example 242 Isomers A and B	  One of isomers A and B is 2-((*S*)-1-((*S*)-1-(3,5-difluorophenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((*S*)-1-((*R*)-1-(3,5-difluorophenyl)ethyl)piperidin-3-yl)-*N*-(5-	^{1}H NMR (400 MHz, DMSO-*d6*) δ11.85 (s, 1H), 8.48 (dd, *J* =4.4, 1.2 Hz, 1H), 7.60 (d, *J* =6.0 Hz, 1H), 7.33 (dd, *J* =9.2, 4.4 Hz, 1H), 7.12 – 6.98 (m, 3H), 6.87 (dd, *J* =9.2, 1.2 Hz, 1H), 4.43 – 4.32 (m, 1H), 3.77 – 3.71 (m, 1H), 3.63 – 3.45 (m, 4H), 2.72 – 2.57 (m, 2H), 2.33 – 2.20 (m, 3H), 2.14 – 2.02 (m, 1H), 2.02 – 1.87 (m, 2H), 1.79 – 1.71 (m, 1H), 1.60 (d, *J* =10.4 Hz, 2H), 1.48 – 1.36 (m, 1H), 1.25-1.22 (m, 3H), 0.99 – 0.85 (m, 1H). ^{19}F NMR (376 MHz, DMSO-*d6*): δ -110.38. LCMS (Method 13, ESI): 529.3 [M+H]$^+$, RT 1.078 minutes.

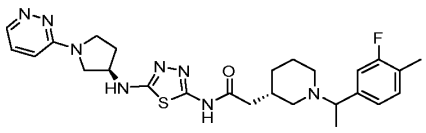
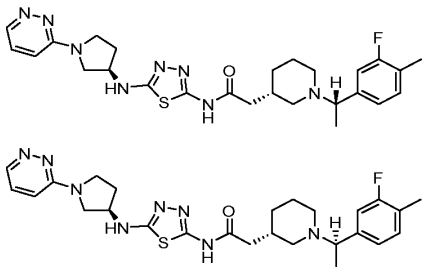
	(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-*d6*) δ11.90 (s, 1H), 8.48 (d, *J* =4.4 Hz, 1H), 7.61 (d, *J* =6.0 Hz, 1H), 7.33 (dd, *J* =9.2, 4.4 Hz, 1H), 7.11 – 6.95 (m, 3H), 6.87 (dd, *J* =9.2, 1.2Hz, 1H), 4.45 – 4.34 (m, 1H), 3.75 (dd, *J* =11.0, 5.8 Hz, 1H), 3.59 – 3.47 (m, 4H), 2.76 – 2.64 (m, 1H), 2.63 – 2.56 (m, 1H), 2.35 – 2.24 (m, 3H), 2.13 – 1.90 (m, 3H), 1.81 – 1.71 (m, 1H), 1.64 – 1.51 (m, 2H), 1.43 – 1.37 (m, 1H), 1.25 – 1.23 (m, 3H), 0.97 – 0.92 (m, 1H). ^{19}F NMR (376 MHz, DMSO-*d6*): δ -110.36. LCMS (Method 13, ESI): 529.3 $[M+H]^+$, RT 1.083 minutes.
Example 243	 2-(4-(4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-*d6*) δ11.93 (s, 1H), 8.48 (dd, *J* =4.4, 1.2 Hz, 1H), 7.63 (d, *J* =6.0 Hz, 1H), 7.33 (dd, *J* =9.2, 4.4 Hz, 1H), 6.87 (dd, *J* =9.2, 1.2 Hz, 1H), 4.46 – 4.30 (m, 1H), 3.87 – 3.65 (m, 3H), 3.59 – 3.40 (m, 4H), 2.89 – 2.74 (m, 1H), 2.76 – 2.51 (m, 4H), 2.33 – 2.19 (m, 1H), 2.15 – 1.82 (m, 3H), 1.86 – 1.64 (m, 3H), 1.55 – 1.18 (m, 5H), 1.21 – 0.97 (m, 2H), 0.83 (t, *J* =6.8 Hz, 6H). LCMS (Method 21, ESI): 515.4 $[M+H]^+$, RT 1.617 minutes.
Example 244, Example 245, Example 246 and Example 247 Isomers A, B, C and D	  	^{1}H NMR (400 MHz, DMSO-*d6*) δ11.95 (s, 1H), 8.48 (dd, *J* =4.4, 1.2 Hz, 1H), 7.63 (d, *J* =6.0 Hz, 1H), 7.33 (dd, *J* =9.2, 4.4 Hz, 1H), 6.87 (dd, *J* =9.2, 1.2 Hz, 1H), 4.46 – 4.30 (m, 1H), 3.87 – 3.65 (m, 3H), 3.59 – 3.40 (m, 4H), 2.72 – 2.67 (m, 1H), 2.63 – 2.51 (m, 4H), 2.32 – 2.22 (m, 2H), 2.14 – 2.02 (m, 3H), 1.88 – 1.68 (m, 4H), 1.35 – 1.23 (m, 1H), 1.21 – 1.15 (m, 2H), 0.99 – 0.95 (m, 2H), 0.83 (t, *J* =6.8 Hz, 6H). LCMS (Method 13, ESI): 515.5 $[M+H]^+$, RT 1.114 minutes. ^{1}H NMR (400 MHz, DMSO-*d6*) δ11.91 (s, 1H), 8.48 (dd, *J* =4.4, 1.2 Hz, 1H), 7.63 (d, *J* =6.0 Hz, 1H), 7.33 (dd, *J* =9.2, 4.4

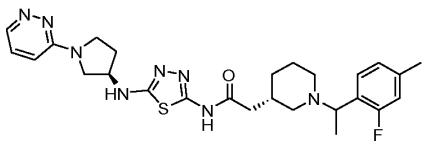
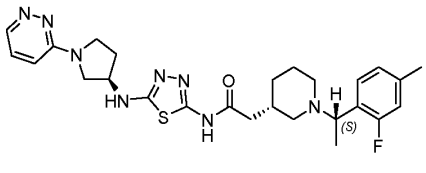
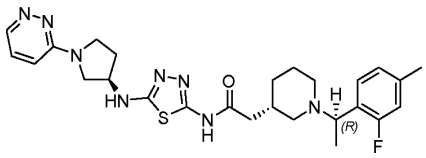
	 Each of Isomers A, B, C and D is one of the following: 2-((*S*)-4-((1*r*,4*S*)-4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide; 2-((*R*)-4-((1*r*,4*R*)-4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide; 2-((*S*)-4-((1*s*,4*R*)-4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide; 2-((*R*)-4-((1*s*,4*S*)-4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	Hz, 1H), 6.87 (dd, *J* =9.2, 1.2 Hz, 1H), 4.46 – 4.30 (m, 1H), 3.87 – 3.65 (m, 3H), 3.59 – 3.40 (m, 4H), 2.72 – 2.67 (m, 1H), 2.63 – 2.51 (m, 4H), 2.32 – 2.22 (m, 2H), 2.14 – 2.02 (m, 3H), 1.81 (d, *J* = 11.1 Hz, 2H), 1.73-1.67 (m, 2H), 1.35 – 1.23 (m, 1H), 1.21 – 1.15 (m, 2H), 0.99 – 0.95 (m, 2H), 0.83 (t, *J* =6.8 Hz, 6H). LCMS (Method 13, ESI): 515.4 $[M+H]^+$, RT 1.152 minutes. ^{1}H NMR (400 MHz, DMSO-*d6*) δ11.93 (s, 1H), 8.48 (dd, *J* =4.4, 1.2 Hz, 1H), 7.63 (d, *J* =6.0 Hz, 1H), 7.33 (dd, *J* =9.2, 4.4 Hz, 1H), 6.87 (dd, *J* =9.2, 1.2 Hz, 1H), 4.46 – 4.30 (m, 1H), 3.87 – 3.65 (m, 3H), 3.59 – 3.40 (m, 4H), 2.89 – 2.74 (m, 1H), 2.76 – 2.51 (m, 4H), 2.30 – 2.27 (m, 1H), 2.15 – 1.82 (m, 3H), 1.86 – 1.64 (m, 3H), 1.55 – 1.30 (m, 6H), 1.09 – 1.07 (m, 1H), 0.83 (t, *J* =6.8 Hz, 6H). LCMS (Method 21, ESI): 515.4 $[M+H]^+$, RT 1.617 minutes. ^{1}H NMR (400 MHz, DMSO-*d6*) δ11.94 (s, 1H), 8.48 (dd, *J* =4.4, 1.2 Hz, 1H), 7.63 (d, *J* =6.0 Hz, 1H), 7.33 (dd, *J* =9.2, 4.4 Hz, 1H), 6.87 (dd, *J* =9.2, 1.2 Hz, 1H), 4.46 – 4.30 (m, 1H), 3.87 – 3.65 (m, 3H), 3.59 – 3.40 (m, 4H), 2.86 – 2.75 (m, 1H), 2.69 – 2.53 (m, 4H), 2.30 – 2.27 (m, 1H), 2.15 – 1.82 (m, 3H), 1.86 – 1.64 (m, 3H), 1.50 – 1.33 (m, 6H), 1.09 – 1.07 (m, 1H), 0.83 (t, *J* =6.8 Hz, 6H). LCMS (Method 13, ESI): 515.4 $[M+H]^+$, RT 1.108 minutes.
Example 248	 (*R*)-2-(2-(3-fluoro-5-methylbenzyl)-2,6-diazaspiro[3.4]octan-6-yl)-*N*-(5-((1-	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.67 (s, 1H), 8.48 (dd, *J* = 4.4, 1.1 Hz, 1H), 7.63 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.92 – 6.81 (m, 4H), 4.38 (dd, *J* = 9.6, 4.5 Hz, 1H), 3.75 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.60 – 3.47 (m, 5H), 3.31 (s, 2H), 3.08 (dd, *J* = 29.1, 6.9 Hz, 4H), 2.75 (s,

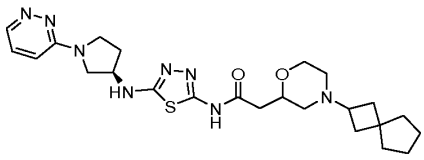
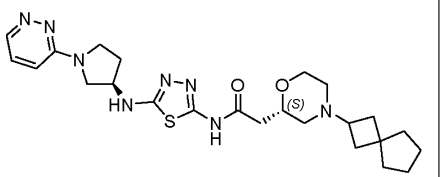
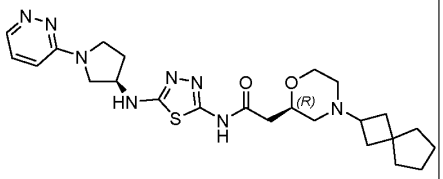
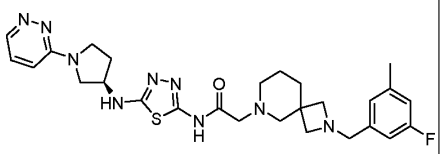
	(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	2H), 2.56 (t, *J* = 7.0 Hz, 2H), 2.34 – 2.26 (m, 4H), 2.08 (td, *J* = 11.9, 5.0 Hz, 1H), 1.92 (t, *J* = 6.9 Hz, 2H). LCMS (Method 21, ESI): 538.4 $[M+H]^+$, RT 1.400 minutes.
Example 249 and Example 250 Isomer A and Isomer B	  One of isomers A or B is 2-((*R*)-1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((*S*)-1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.00 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.38-7.31 (m, 2H), 7.19-7.01 (m, 4H), 6.87 (dd, *J* = 9.2, 0.8 Hz, 1H), 4.43-4.33 (m, 1H), 3.80-3.73 (m, 2H), 3.62-3.48 (m, 3H), 3.40-3.37 (m, 1H), 3.01-2.93 (m, 1H), 2.77-2.62 (m, 3H), 2.57-2.54 (m, 2H), 2.46-2.42 (m, 1H), 2.37-2.20 (m, 4H), 2.11-2.05 (m, 1H), 0.92 (d, *J* = 12.4 Hz, 6H). LCMS (Method 13, ESI): 588.3 $[M+H]^+$, RT 1.091 minutes. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.98 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.38-7.31 (m, 2H), 7.20-7.01 (m, 4H), 6.87 (dd, *J* = 9.2, 0.8 Hz, 1H), 4.41-4.34 (m, 1H), 3.80-3.73 (m, 2H), 3.59-3.48 (m, 3H), 3.40-3.37 (m, 1H), 3.02-2.93 (m, 1H), 2.77-2.62 (m, 5H), 2.46-2.41 (m, 1H), 2.36-2.20 (m, 4H), 2.12-2.03 (m, 1H), 0.92 (d, *J* = 12.0 Hz, 6H). LCMS (Method 13, ESI): 588.3 $[M+H]^+$, RT 1.097 minutes.
Example 251	 *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[2.5]octan-6-yl)morpholin-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-*d6*) δ11.93 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.39-4.36 (m, 1H), 3.81-3.74 (m, 3H), 3.55-3.40 (m, 4H), 2.77 (d, *J* = 10.8 Hz, 1H), 2.63-2.60 (m, 3H), 2.35-2.20 (m, 3H), 2.11-2.00 (m, 2H), 1.71-1.66 (m, 4H), 1.31-1.23 (m, 2H), 0.94 (d, *J* = 12.4 Hz, 2H), 0.27-0.25 (m, 2H), 0.16-0.14 (m, 2H). LCMS (Method 15, ESI): 499.0 $[M+H]^+$, RT 0.838 minutes.

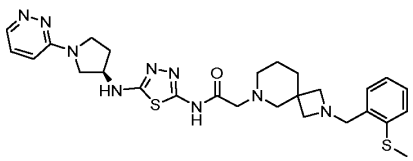
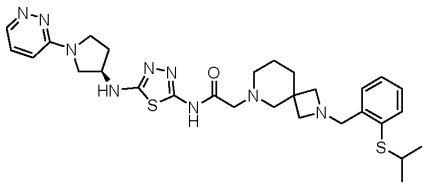
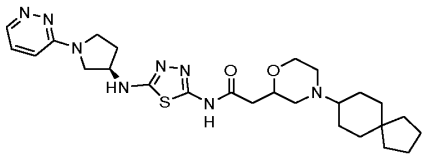
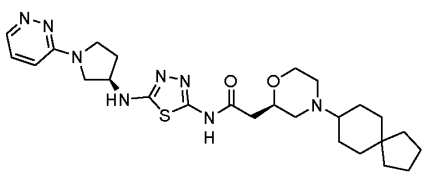
Example 252 and Example 253 Isomers A and B	  One of isomers A and B is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((S)-4-(spiro[2.5]octan-6-yl)morpholin-2-yl)acetamide and the other is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-4-(spiro[2.5]octan-6-yl)morpholin-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-*d6*) δ11.94 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.39-4.36 (m, 1H), 3.80-3.74 (m, 3H), 3.55-3.38 (m, 4H), 2.77 (d, *J* = 10.8 Hz, 1H), 2.63-2.60 (m, 3H), 2.35-2.20 (m, 3H), 2.11-2.00 (m, 2H), 1.71-1.66 (m, 4H), 1.35-1.32 (m, 2H), 0.95 (d, *J* = 12.4 Hz, 2H), 0.27-0.25 (m, 2H), 0.17-0.15 (m, 2H). LCMS (Method 15, ESI): 499.2 [M+H]$^+$, RT 0.832 minutes. ^{1}H NMR (400 MHz, DMSO-*d6*) δ11.93 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.38-4.37 (m, 1H), 3.80-3.73 (m, 3H), 3.58-3.48 (m, 4H), 2.77 (d, *J* = 10.8 Hz, 1H), 2.63-2.60 (m, 3H), 2.35-2.20 (m, 3H), 2.08-1.99 (m, 2H), 1.71-1.59 (m, 4H), 1.35-1.32 (m, 2H), 0.94 (d, *J* = 12.4 Hz, 2H), 0.27-0.25 (m, 2H), 0.17-0.15 (m, 2H). LCMS (Method 15, ESI): 499.1 [M+H]$^+$, RT 0.826 minutes.
Example 254	 *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[3.5]nonan-2-yl)morpholin-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-*d6*) δ11.92 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.86 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.39-4.37 (m, 1H), 3.80-3.73 (m, 3H), 3.58-3.45 (m, 4H), 2.69 (d, *J* = 10.8 Hz, 1H), 2.61-2.50 (m, 4H), 2.32-2.31 (m, 1H), 2.08-2.06 (m, 1H), 1.85-1.77 (m, 3H), 1.56 (t, *J* = 10.8 Hz, 1H), 1.46-1.30 (m, 12H). LCMS (Method 13, ESI): 513.1 [M+H]$^+$, RT 0.890 minutes.
Example 255 and Example 256 Isomers A and B		^{1}H NMR (400 MHz, DMSO-*d6*) δ11.89 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.58 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.86 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.39-4.34 (m, 1H), 3.82-3.71 (m, 3H), 3.59-3.40 (m, 4H), 2.68 (d, *J* = 10.8 Hz,

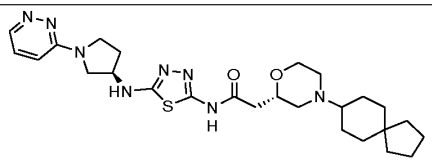
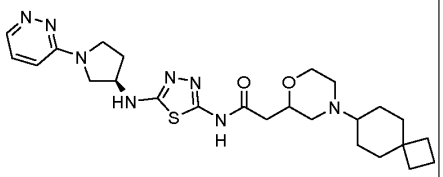
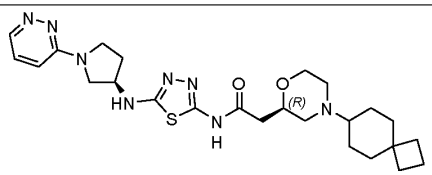
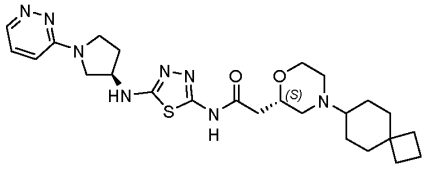
	 One of isomers A and B is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-4-(spiro[3.5]nonan-2-yl)morpholin-2-yl)acetamide and the other is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-4-(spiro[3.5]nonan-2-yl)morpholin-2-yl)acetamide	1H), 2.59-2.55 (m, 4H), 2.33-2.27 (m, 1H), 2.09-2.04 (m, 1H), 1.85-1.74 (m, 3H), 1.56 (t, *J* = 10.8 Hz, 1H), 1.46-1.30 (m, 12H). LCMS (Method 13, ESI): 513.5 $[M+H]^+$, RT 1.108 minutes. ^{1}H NMR (400 MHz, DMSO-*d6*) δ11.86 (s, 1H), 8.47 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.60 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.86 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.39-4.34 (m, 1H), 3.82-3.71 (m, 3H), 3.59-3.40 (m, 4H), 2.68 (d, *J* = 10.8 Hz, 1H), 2.59-2.55 (m, 4H), 2.33-2.27 (m, 1H), 2.09-2.04 (m, 1H), 1.85-1.74 (m, 3H), 1.56 (t, *J* = 10.8 Hz, 1H), 1.46-1.30 (m, 12H). LCMS (Method 13, ESI): 513.4 $[M+H]^+$, RT 1.103 minutes.
Example 257	 (*R*)-2-(8-(2-(isopropylthio)benzyl)-2,8-diazaspiro[4.5]decan-2-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, MeOD-d_4) δ 8.42 (d, *J* = 4.8 Hz, 1H), 7.47-7.36 (m, 3H), 7.25-7.19 (m, 2H), 6.92 (d, *J* = 9.2 Hz, 1H), 4.52-4.45 (m, 1H), 3.87-3.83 (m, 1H), 3.68-3.65 (m, 4H), 3.61-3.57 (m, 1H), 3.43-3.39 (m, 3H), 2.78-2.74 (m, 2H), 2.58 (s, 2H), 2.47-2.36 (m, 5H), 2.24-2.16 (m, 1H), 1.73-1.59 (m, 6H), 1.24 (d, *J* = 6.4 Hz, 6H). LCMS (Method 13, ESI): 608.4 $[M+H]^+$, RT 1.056 minutes.
Example 258	 2-((*S*)-1-(4-ethyl-3-fluorobenzyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.35-7.31 (m, 1H), 7.20-7.16 (m, 1H), 7.03-7.00 (m, 2H), 6.87 (d, *J* = 9.2 Hz, 1H), 4.38-4.36 (m, 1H), 3.77-3.73 (m, 1H), 3.59-3.48 (m, 3H), 3.44 – 3.37 (m, 2H), 2.65-2.59 (m, 2H), 2.57-2.53 (m, 2H), 2.36-2.25 (m, 3H), 2.11-2.04 (m, 1H), 2.01-1.92 (m, 2H), 1.77-1.71 (m, 1H), 1.64-1.57 (m, 2H), 1.45-1.42 (m, 1H), 1.13 (t, *J* =7.6 Hz, 3H), 1.01-0.93 (m, 1H). LCMS (Method 13, ESI): 525.4 $[M+H]^+$, RT 1.108 minutes.

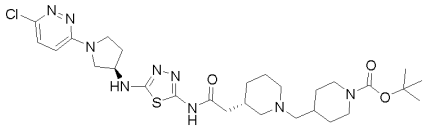
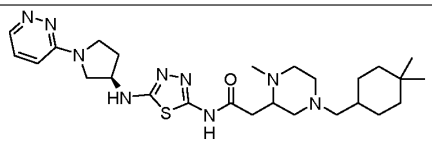
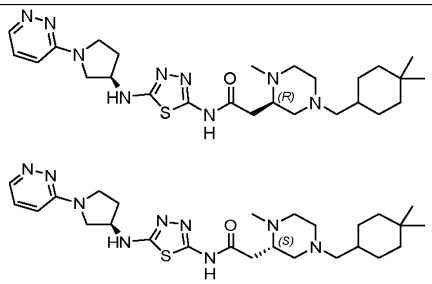
Example 259	 2-((3*S*)-1-(1-(3-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.48 (d, *J* = 4.0 Hz, 1H), 7.60 (d, *J* = 5.6 Hz, 1H), 7.35-7.31 (m, 1H), 7.18-7.13 (m, 1H), 7.03-6.98 (m, 2H), 6.87 (d, *J* = 9.2 Hz, 1H), 4.42-4.34 (m, 1H), 3.77-3.73 (m, 1H), 3.59-3.40 (m, 4H), 2.68-2.56 (m, 2H), 2.37-2.20 (m, 3H), 2.17 (s, 3H), 2.11-2.05 (m, 1H), 1.96-1.91 (m, 2H), 1.76-1.69 (m, 1H), 1.60-1.57 (m, 2H), 1.42-1.37 (m, 1H), 1.23 (dd, *J* = 6.8, 2.8 Hz, 3H), 0.96-0.89 (m, 1H). LCMS (Method 13, ESI): 525.4 $[M+H]^+$, RT 1.097 minutes.
Example 260 and Example 261 Isomers A and B	 One of isomers A and B is 2-((*S*)-1-((*S*)-1-(3-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((*S*)-1-((*R*)-1-(3-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 8.48 (d, *J* = 4.8 Hz, 1H), 7.60 (d, *J* = 6.4 Hz, 1H), 7.35-7.31 (m, 1H), 7.16 (t, *J* =8.0 Hz, 1H), 7.03-6.99 (m, 2H), 6.86 (dd, *J* = 8.8, 0.8 Hz, 1H), 4.40-4.36 (m, 1H), 3.77-3.73 (m, 1H), 3.59-3.43 (m, 4H), 2.68-2.60 (m, 2H), 2.34-2.20 (m, 3H), 2.17 (s, 3H), 2.11-2.04 (m, 1H), 1.95-1.91 (m, 2H), 1.72-1.67 (m, 1H), 1.60-1.57 (m, 2H), 1.45-1.36 (m, 1H), 1.23 (d, *J* = 6.4 Hz, 3H), 0.91-0.85 (m, 1H). LCMS (Method 13, ESI): 525.4 $[M+H]^+$, RT 1.124 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.48 (d, *J* = 3.2 Hz, 1H), 7.57 (d, *J* = 3.2 Hz, 1H), 7.35-7.31 (m, 1H), 7.18-7.14 (m, 1H), 7.02-6.98 (m, 2H), 6.87 (d, *J* = 9.2 Hz, 1H), 4.41-4.34 (m, 1H), 3.77-3.73 (m, 1H), 3.61-3.56 (m, 1H), 3.49-3.40 (m, 3H), 2.68-2.66 (m, 1H), 2.62-2.57 (m, 1H), 2.35-2.22 (m, 3H), 2.17 (s, 3H), 2.10-2.07 (m, 1H), 1.99-1.89 (m, 2H), 1.75-1.70 (m, 1H), 1.61-1.51 (m, 2H), 1.42-1.35 (m, 1H), 1.23 (d, *J* = 5.6 Hz, 3H), 0.96-0.87 (m, 1H). LCMS (Method 13, ESI): 525.4 $[M+H]^+$, RT 1.085 minutes.

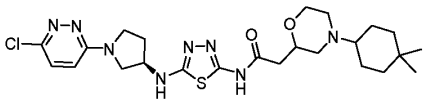
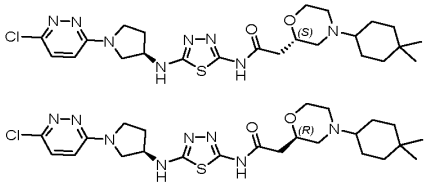
Example 262	 2-((3*S*)-1-(1-(2-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (d, *J* = 14.4 Hz, 1H), 8.48 (d, *J* = 3.6 Hz, 1H), 7.61-7.58 (m, 1H), 7.34-7.31 (m, 1H), 7.24 (t, *J* = 15.6 Hz, 1H), 6.96-6.86 (m, 3H), 4.42-4.34 (m, 1H), 3.78-3.74 (m, 2H), 3.59-3.49 (m, 3H), 2.76-2.54 (m, 2H), 2.39-2.17 (m, 6H), 2.10-2.06 (m, 1H), 1.99-1.85 (m, 2H), 1.77-1.52 (m, 3H), 1.43-1.34 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 3H), 0.93-0.86 (m, 1H). LCMS (Method 13, ESI): 525.4 [M+H]$^+$, RT 1.068 minutes.
Example 263 and Example 264 Isomers A and B	  One of isomers A and B is 2-((*S*)-1-((*S*)-1-(2-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((*S*)-1-((*R*)-1-(2-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.35-7.31 (m, 1H), 7.24 (t, *J* = 15.6 Hz, 1H), 6.96-6.86 (m, 3H), 4.40-4.35 (m, 1H), 3.79-3.73 (m, 2H), 3.61-3.49 (m, 3H), 2.75-2.64 (m, 2H), 2.34-2.16 (m, 6H), 2.11-2.04 (m, 1H), 1.94-1.85 (m, 2H), 1.63-1.56 (m, 3H), 1.43-1.40 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 3H), 0.90-0.83 (m, 1H). LCMS (Method 13, ESI): 525.4 [M+H]$^+$, RT 1.056 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.35-7.31 (m, 1H), 7.24 (t, *J* = 16.0 Hz, 1H), 6.94-6.86 (m, 3H), 4.41-4.35 (m, 1H), 3.78-3.72 (m, 2H), 3.59-3.49 (m, 3H), 2.70-2.67 (m, 1H), 2.60-2.56 (m, 2H), 2.39-2.22 (m, 6H), 2.11-2.04 (m, 1H), 2.00-1.85 (m, 2H), 1.76-1.71 (m, 1H), 1.59-1.52 (m, 2H), 1.41-1.33 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 3H), 0.95-0.85 (m, 1H). LCMS (Method 13, ESI): 525.4 [M+H]$^+$, RT 1.073 minutes.

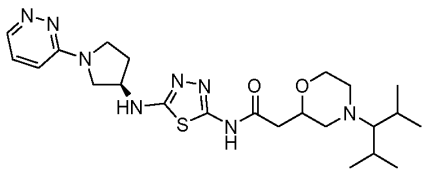
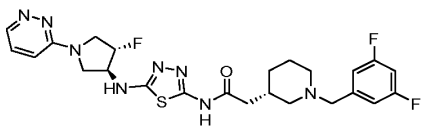
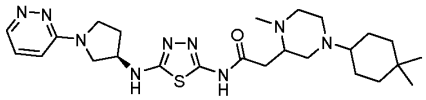
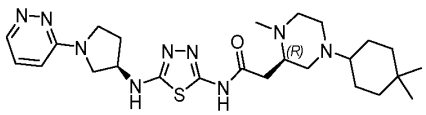
Example 265	 *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[3.4]octan-2-yl)morpholin-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (d, *J* =3.6 Hz, 1H), 7.64 (d, *J* =2.0 Hz, 1H), 7.33 (dd, *J* =9.2, 4.4 Hz, 1H), 6.87 (d, *J* =9.2 Hz, 1H), 4.41-4.35 (m, 1H), 3.82-3.72 (m, 3H), 3.59-3.40 (m, 4H), 2.69-2.52 (m, 5H), 2.34-2.25 (m, 1H), 2.11-2.04 (m, 1H), 1.91-1.86 (m, 2H), 1.82-1.70 (m, 1H) 1.70-1.64 (m, 2H) 1.60-1.48 (m, 9H). LCMS (Method 13, ESI): 499.4 [M+H]$^+$, RT 1.050 minutes.
Example 266 and Example 267 Isomers A and B	  One of isomers A and B is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-4-(spiro[3.4]octan-2-yl)morpholin-2-yl)acetamide and the other is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-4-(spiro[3.4]octan-2-yl)morpholin-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (d, *J* =4.0 Hz, 1H), 7.63 (d, *J* =6.0 Hz, 1H), 7.33 (dd, *J* =8.8, 4.4 Hz, 1H), 6.87 (d, *J* =8.8 Hz, 1H), 4.41-4.35 (m, 1H), 3.83-3.72 (m, 3H), 3.61-3.40 (m, 4H), 2.69-2.52 (m, 5H), 2.34-2.25 (m, 1H), 2.11-2.04 (m, 1H), 1.91-1.86 (m, 2H), 1.82-1.77 (m, 1H) 1.70-1.64 (m, 2H) 1.60-1.48 (m, 9H). LCMS (Method 13, ESI):499.4 [M+H]$^+$, RT 1.050 minutes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.48 (d, *J* =4.0 Hz, 1H), 7.63 (d, *J* =6.0 Hz, 1H), 7.33 (dd, *J* =8.8, 4.4 Hz, 1H), 6.87 (d, *J* =8.8 Hz, 1H), 4.41-4.35 (m, 1H), 3.83-3.72 (m, 3H), 3.60-3.40 (m, 4H), 2.69-2.54 (m, 5H), 2.34-2.25 (m, 1H), 2.13-2.03 (m, 1H), 1.91-1.86 (m, 2H), 1.82-1.75 (m, 1H) 1.70-1.64 (m, 2H) 1.60-1.48 (m, 9H). LCMS (Method 13, ESI): 499.4 [M+H]$^+$, RT 1.044 minutes.
Example 268	 (*R*)-2-(2-(3-fluoro-5-methylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.65 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* =8.8, 4.4 Hz, 1H), 6.89-6.82 (m, 4H), 4.43-4.36 (m, 1H), 3.78-3.74 (m, 1H), 3.59-3.49 (m, 5H), 3.22 (s, 2H), 3.00 (d, *J* = 7.2 Hz, 2H), 2.82 (d, *J* = 6.8 Hz, 2H), 2.55 (s, 2H), 2.38-2.26 (m, 6H), 2.12-2.04 (m, 1H), 1.54-1.42 (m, 4H). LCMS (Method 13, ESI): 552.4 [M+H]$^+$, RT 1.003 minutes.

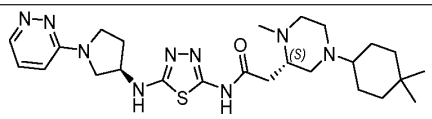
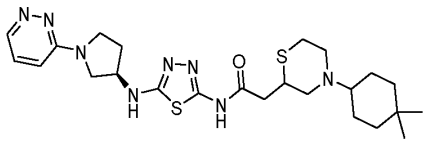
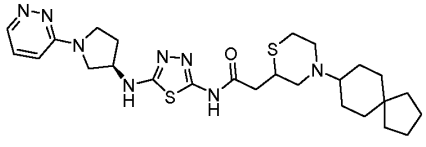
Example 269	 (*R*)-2-(2-(2-(methylthio)benzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* =8.8, 4.4 Hz, 1H), 7.27-7.22 (m, 3H), 7.13-7.08 (m, 1H), 6.87 (d, *J* = 9.6 Hz, 1H), 4.43-4.36 (m, 1H), 3.78-3.74 (m, 1H), 3.56-3.49 (m, 5H), 3.23 (s, 2H), 3.04 (d, *J* = 6.8 Hz, 2H), 2.85 (d, *J* = 6.8 Hz, 2H), 2.56 (s, 2H), 2.42-2.38 (m, 5H), 2.35-2.26 (m, 1H), 2.12-2.04 (m, 1H), 1.55-1.42 (m, 4H). LCMS (Method 13, ESI): 566.4 $[M+H]^+$, RT 1.003 minutes.
Example 270	 (*R*)-2-(2-(2-(isopropylthio)benzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 7.67 (d, *J* = 6.4 Hz, 1H), 7.40-7.31 (m, 3H), 7.24-7.18 (m, 2H), 6.87 (d, *J* = 10.4 Hz, 1H), 4.42-4.36 (m, 1H), 3.78-3.74 (m, 1H), 3.65 (s, 2H), 3.59-3.42 (m, 4H), 3.23 (s, 2H), 3.04 (d, *J* = 6.4 Hz, 2H), 2.85 (d, *J* = 6.4 Hz, 2H), 2.55 (s, 2H), 2.38 (s, 2H), 2.34-2.25 (m, 1H), 2.13-2.04 (m, 1H), 1.50-1.46 (m, 4H), 1.21 (d, *J* = 6.8 Hz, 6H). LCMS (Method 13, ESI): 594.3 $[M+H]^+$, RT 1.171 minutes.
Example 271	 *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[4.5]decan-8-yl)morpholin-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.48 (s, 1H), 7.64 (d, *J* = 1.2 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 1H), 4.38 (s, 1H), 3.77-3.71 (m, 3H), 3.56-3.37 (m, 5H), 2.76 (d, *J* = 10.8 Hz, 1H), 2.64-2.62 (m, 1H), 2.28 (s, 1H), 2.18-2.09 (m, 2H), 1.98-1.93 (m, 1H), 1.62 (s, 2H), 1.53-1.48 (m, 6H), 1.38-1.23 (m, 10H). LCMS (An analogous method to Method 21, ESI) 527.2 $[M+H]^+$, RT 1.68 minutes.
Example 272 and Example 273 Isomers A and B		1H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.47 (s, 1H), 7.62 (d, *J* = 0.4 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 1H), 4.38 (s, 1H), 3.81-3.74 (m, 3H), 3.71-3.42 (m, 5H), 2.77-2.74 (m, 1H), 2.67-2.61 (m, 1H), 2.47-2.41 (m,

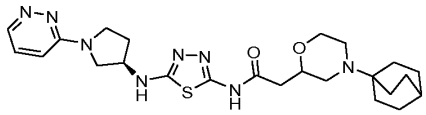
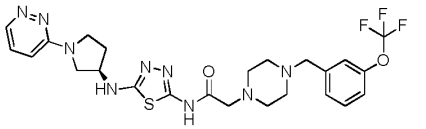
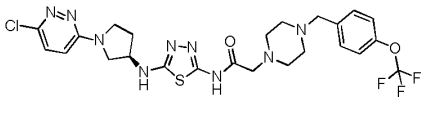
	 One of isomers A and B is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-4-(spiro[4.5]decan-8-yl)morpholin-2-yl)acetamide and the other is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-4-(spiro[4.5]decan-8-yl)morpholin-2-yl)acetamide	1H), 2.37-2.31 (m, 3H), 2.08-1.97 (m, 1H), 1.75-1.62 (m, 2H), 1.61-1.48 (m, 6H), 1.46-1.24 (m, 9H). LCMS (An analogous method to Method 21, ESI) 527.2 $[M+H]^+$, RT 1.67 minutes. 1H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.47 (d, *J* = 0.4 Hz, 1H), 7.62 (d, *J* = 0.4 Hz, 1H), 7.31 (d, *J* = 0.8 Hz, 1H), 6.86 (d, *J* = 0.8 Hz, 1H), 4.37 (d, *J* = 0.8 Hz, 1H), 3.81-3.73 (m, 3H), 3.71-3.55 (m, 5H), 2.75-2.71 (S, 1H), 2.65 (m, 1H), 2.41-2.37 (m, 1H), 2.27-2.03 (m, 3H), 1.98-1.94 (m, 1H), 1.75-1.71 (m, 2H), 1.62-1.46 (m, 6H), 1.45-1.24 (m, 9H). LCMS (An analogous method to Method 21, ESI) 527.2$[M+H]^+$, RT 1.676 minutes.
Example 274	 *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[3.5]nonan-7-yl)morpholin-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 7.30 (d, *J* = 0.8 Hz, 1H), 7.03 (s, 1H), 6.83 (d, *J* = 0.8 Hz, 1H), 4.32 (s, 1H), 3.76-3.71 (m, 3H), 3.51-3.48 (m, 2H), 3.43-3.32 (m, 2H), 2.85-2.71 (d, *J* = 4.3Hz, 1H), 2.61 (d, *J* = 4.0 Hz, 1H), 2.41-2.38 (m, 1H), 2.35-2.31 (m, 2H), 2.30-2.18 (m, 1H), 2.18-2.07 (m, 2H), 1.96-1.91 (m, 1H), 1.79-1.73 (m, 4H), 1.68-1.63 (m, 4H), 1.62-1.60 (m, 2H), 1.23-1.14 (m, 4H). LCMS (An analogous method to Method 21, ESI) 513.2$[M+H]^+$, RT 1.61 minutes.
Example 275 and Example 276 Isomers A and B	  One of isomers A and B is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-4-	1H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.47 (d, *J* = 0.4 Hz, 1H), 7.62 (d, *J* = 0.8 Hz, 1H), 7.33-7.31 (m, 1H), 6.86 (d, *J* = 0.8 Hz, 1H), 4.38 (s, 1H), 3.77-3.73 (m, 3H), 3.71-3.61 (m, 3H), 3.47-3.38 (m, 1H), 2.67-2.61 (m, 1H), 2.60-2.57 (m, 1H), 2.41-1.98 (m, 4H), 1.97-1.92 (m, 1H), 1.79-1.50 (m, 12H), 1.24-1.18 (m, 4H), . LCMS (An analogous method to Method 21, ESI): 513.1$[M+H]^+$, RT 1.60 minutes.

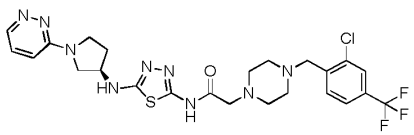
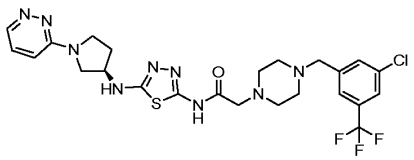
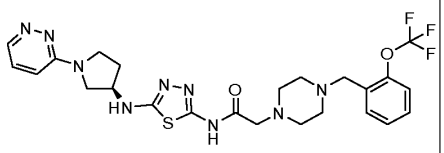
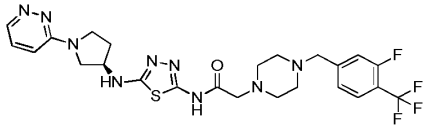
	(spiro[3.5]nonan-7-yl)morpholin-2-yl)acetamide and the other is *N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-4-(spiro[3.5]nonan-7-yl)morpholin-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.48 (s, 1H), 7.63 (s, 1H), 7.32 (s, 1H), 6.86 (s, 1H), 4.38 (s, 1H), 3.76-3.32 (m, 7H), 2.73-2.59 (m, 2H), 2.27-1.95 (m, 4H), 1.79-1.58 (m, 12H), 1.18 (s, 5H). LCMS (An analogous method to Method 21, ESI) 513.2 $[M+H]^+$, RT 1.60 minutes.
Example 277	 *tert*-butyl 4-(((*S*)-3-(2-((5-(((*R*)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)-2-oxoethyl)piperidin-1-yl)methyl)piperidine-1-carboxylate	1H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 7.61(d, *J* =6.0, 1H), 7.47 (d, *J* =9.2, 1H), 7.01 (d, *J* =9.6 1H), 4.40-4.36 (m, 1H), 3.91-3.88 (m, 2H), 3.77-3.73 (m, 1H), 3.58-3.47 (m, 3H), 2.70-2.64 (m, 3H), 2.31-2.25 (m, 3H), 2.11-2.04 (m, 3H), 1.96-1.86 (m, 2H), 1.72-1.60 (m, 6H), 1.38 (s, 9H), 0.93-0.88 (m, 3H). LCMS (An analogous method to Method 15, ESI) 620.2$[M+H]^+$, RT 1.04 minutes.
Example 278	 2-(4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6) δ 12.1 (s, 1H), 8.48 (s, 1H), 7.61 (s, 1H), 7.34-7.31 (m, 1H), 6.85 (s, 1H), 4.40-4.35 (m, 1H), 3.77-3.48 (m,4H), 2.67-1.89 (m, 15H), 1.50-1.09 (m, 9H), 0.84-0.82 (m, 6H), LCMS (Method 15, ESI): 528.4$[M+H]^+$, RT 1.29 minutes.
Example 279 and Example 280 Isomers A and B	 One of isomers A and B is 2-((*R*)-4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-((*S*)-4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)-*N*-(5-(((*R*)-1-	1H NMR (400 MHz, DMSO-d_6) δ 12.1 (s, 1H), 8.48-8.47 (m, 1H), 7.61 (d, *J* =6.0Hz, 1H), 7.34-7.31 (m, 1H), 6.88-6.85 (m, 1H), 4.40-4.35 (m, 1H), 3.77-3.48 (m,4H), 2.67-1.89 (m, 15H), 1.55-0.94 (m, 9H), 0.85-0.84 (m, 6H). LCMS (Method 15, ESI) 528.4$[M+H]^+$, RT 1.121 minutes. 1H NMR (400 MHz, DMSO-d_6) δ 12.1 (s, 1H), 8.48-8.47 (m, 1H), 7.61 (d, *J* = 6.0Hz, 1H), 7.34-7.31 (m, 1H), 6.88-6.85 (m, 1H), 4.40-4.35 (m, 1H), 3.77-3.48 (m,4H), 2.67-1.89 (m, 15H), 1.55-0.94 (m, 9H), 0.85-0.84 (m, 6H). LCMS (An analogous method to Method 21, ESI) 528.4$[M+H]^+$, RT 1.605 minutes.

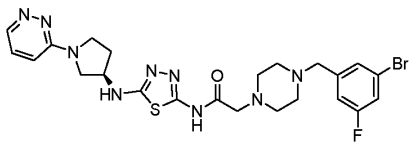
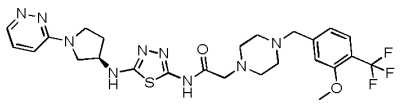
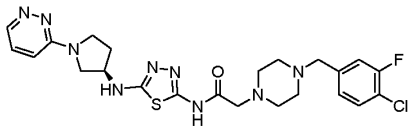
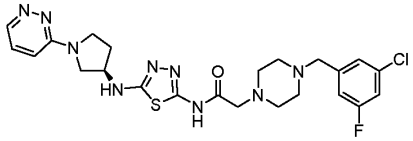
	(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	
Example 281	 N-(5-(((R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(4,4-dimethylcyclohexyl)morpholin-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 7.01 (d, *J* = 9.6 Hz, 1H), 4.39-4.36 (m, 1H), 3.80-3.71 (m, 3H), 3.58-3.42 (m, 4H), 2.77 (d, *J* = 10.8 Hz, 1H), 2.62 (d, *J* = 10.8 Hz, 1H), 2.57-2.54 (m, 1H), 2.31-2.17 (m, 2H), 2.11-2.05 (m, 2H), 1.97 (t, *J* = 10.8 Hz, 1H), 1.58-1.55 (m, 2H), 1.39-1.28 (m, 4H), 1.17-1.11 (m, 2H), 0.85 (d, *J* = 10.4 Hz, 6H). LCMS (An analogous method to Method 15, ESI) 535.0[M+H]$^+$, RT 0.822 minutes.
Example 282 and Example 283 Isomers A and B	 One of isomers A and B is N-(5-(((R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((S)-4-(4,4-dimethylcyclohexyl)morpholin-2-yl)acetamide and the other is *N*-(5-(((*R*)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-4-(4,4-dimethylcyclohexyl)morpholin-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 7.62 (d, *J* =6.0 Hz, 1H), 7.47 (d, *J* =9.2 Hz, 1H), 7.01 (d, *J* =9.6 Hz, 1H), 4.39-4.36 (m, 1H), 3.80-3.71 (m, 3H), 3.58-3.42 (m, 4H), 2.77 (d, *J* =10.8 Hz, 1H), 2.62 (d, *J* =10.8 Hz, 1H), , 2.57-2.54 (m, 1H), 2.31-2.17 (m, 2H), 2.11-2.05 (m, 2H), 1.97 (t, *J* =10.8 Hz, 1H), 1.58-1.55 (m, 2H), 1.39-1.28 (m, 4H), 1.17-1.11 (m, 2H), 0.85 (d, *J* =10.4 Hz, 6H). LCMS (An analogous method to Method 15, ESI) 535.0[M+H]$^+$, RT 0.822 minutes. 1H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 7.62 (d, *J* =6.0 Hz, 1H), 7.47 (d, *J* =9.2 Hz, 1H), 7.01 (d, *J* =9.6 Hz, 1H), 4.39-4.36 (m, 1H), 3.80-3.71 (m, 3H), 3.58-3.42 (m, 4H), 2.77 (d, *J* =10.8 Hz, 1H), 2.62 (d, *J* =10.8 Hz, 1H), , 2.57-2.54 (m, 1H), 2.31-2.17 (m, 2H), 2.11-2.05 (m, 2H), 1.97 (t, *J* =10.8 Hz, 1H), 1.58-1.55 (m, 2H), 1.39-1.28 (m, 4H), 1.17-1.11 (m, 2H), 0.85 (d, *J* =10.4 Hz, 6H). LCMS (An analogous method to Method 15, ESI) 535.2[M+H]$^+$, RT 1.01 minutes

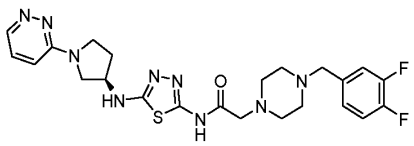
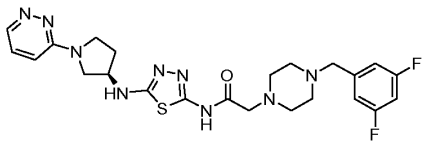
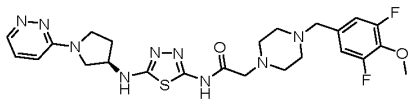
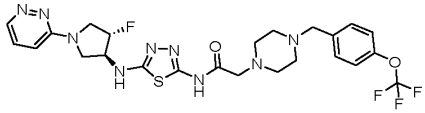
Example 284	 2-(4-(2,4-dimethylpentan-3-yl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	1H NMR (400 MHz, DMSO-d_6) δ 8.48-8.47 (m, 1H), 7.60 (d, *J* =6.0Hz, 1H), 7.34-7.31 (m, 1H), 6.88-6.85 (m, 1H), 4.39-4.36 (m, 1H), 3.82-3.73 (m, 2H), 3.65 (d, *J* =11.2 Hz, 1H), 3.59-3.37 (m, 4H), 2.62 (d, *J* =10.8 Hz, 1H) , 2.70-2.53 (m, 3H), 2.46-2.25 (m, 4H), 2.09-2.05 (m, 1H), 1.86 (s, 3H), 0.90-087 (m, 12H). LCMS (An analogous method to Method 15, ESI) 489.3$[M+H]^+$, RT 0.60 minutes.
Example 285	 2-((*S*)-1-(3,5-difluorobenzyl)piperidin-3-yl)-N-(5-(((3*S*,4*S*)-4-fluoro-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.55 (dd, J = 4.5, 1.3 Hz, 1H), 7.71 (d, J = 5.8 Hz, 1H), 7.40 (dd, J = 9.1, 4.5 Hz, 1H), 7.14 – 6.93 (m, 4H), 5.38 (d, J = 50.8 Hz, 1H), 4.57 – 4.39 (m, 1H), 4.01 – 3.77 (m, 2H), 3.77 – 3.68 (m, 2H), 3.45 (d, J = 4.8 Hz, 2H), 2.68 – 2.56 (m, 2H), 2.36 – 2.27 (m, 2H), 2.08 – 1.89 (m, 2H), 1.89 – 1.72 (m, 1H), 1.72 – 1.55 (m, 2H), 1.54 – 1.38 (m, 1H), 1.03 – 0.90 (m, 1H). LCMS (An analogous method to Method 20, ESI) 533.38 [MH]+, RT 2.64.
Example 286	 2-[4-(4,4-dimethylcyclohexyl)-1-methylpiperazin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.48 (dd, J = 4.5, 1.3 Hz, 1H), 7.62 (d, J = 6.0 Hz, 1H), 7.33 (dd, J = 9.1, 4.5 Hz, 1H), 6.87 (dd, J = 9.2, 1.3 Hz, 1H), 4.43 – 4.33 (m, 1H), 3.75 (dd, J = 11.1, 5.8 Hz, 1H), 3.61 – 3.46 (m, 4H), 2.69 – 2.57 (m, 4H), 2.47 – 2.36 (m, 3H), 2.33 – 2.24 (m, 2H), 2.15 (s, 3H), 2.13 – 2.01 (m, 3H), 1.59 – 1.47 (m, 2H), 1.41 – 1.25 (m, 5H), 1.18 – 1.09 (m, 2H), 0.87 – 0.82 (m, 6H). LCMS (Method 8, ESI) 513.99 [MH]+, RT 2.57. Chiral SFC (Method 24, 210-400 nm) RT_1 8.41 min; RT_2 10.24 min; d.r.= 47.70:52.30.
Example 287 and Example 288		^{1}H NMR (300 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.42 – 4.33 (m, 1H), 3.75 (dd, *J* = 11.1,

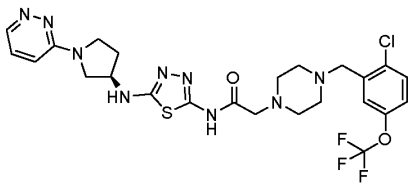
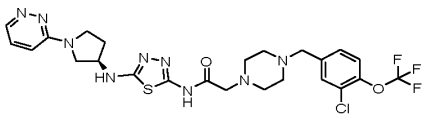
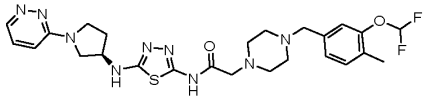
Isomers A and B	 One of examples A and B is 2-[(R)-4-(4,4-dimethylcyclohexyl)-1-methylpiperazin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide and the other is 2-[(S)-4-(4,4-dimethylcyclohexyl)-1-methylpiperazin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	5.8 Hz, 1H), 3.64 – 3.46 (m, 4H), 2.67 – 2.59 (m, 4H), 2.44 – 2.36 (m, 2H), 2.33 – 2.25 (m, 2H), 2.15 (s, 3H), 2.14 – 1.99 (m, 3H), 1.64 – 1.45 (m, 2H), 1.43 – 1.26 (m, 4H), 1.20 – 0.99 (m, 2H), 0.89 – 0.78 (m, 6H). LCMS (Method 8, ESI) 514.10 [MH]+, RT 2.57. Chiral SFC (Method 24, 210-400 nm) RT_1 8.36 min; d.r.= 100:0 ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.63 (d, *J* = 6.1 Hz, 1H), 7.33 (dd, *J* = 9.1, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.45 – 4.31 (m, 1H), 3.75 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.61 – 3.53 (m, 2H), 3.53 – 3.46 (m, 3H), 2.69 – 2.61 (m, 3H), 2.46 – 2.37 (m, 2H), 2.35 – 2.25 (m, 2H), 2.23 – 2.13 (m, 4H), 2.13 – 2.02 (m, 2H), 1.58 – 1.48 (m, 2H), 1.43 – 1.29 (m, 4H), 1.19 – 1.10 (m, 2H), 0.88 – 0.81 (m, 6H). LCMS (Method 7, ESI) 514.28 [MH]+, RT 2.58. Chiral SFC (Method 24, 210-400 nm) RT_1 8.52 min; RT_2 10.22 min; d.r.= 1.45:98.55.
Example 289	 2-[4-(4,4-dimethylcyclohexyl)thiomorpholin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.48 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.42 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.59 – 3.46 (m, 3H), 3.20 – 3.09 (m, 1H), 2.96 – 2.88 (m, 1H), 2.87 – 2.78 (m, 1H), 2.71 – 2.53 (m, 6H), 2.35 – 2.20 (m, 2H), 2.13 – 2.02 (m, 1H), 1.52 – 1.29 (m, 6H), 1.22 – 1.07 (m, 2H), 0.85 (d, *J* = 4.6 Hz, 6H). LCMS (Method 7, ESI) 514.77 [MH]+, RT 1.43.
Example 290		^{1}H NMR (300 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.48 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.42 – 4.34 (m, 1H), 3.75 (dd, *J* = 11.1,

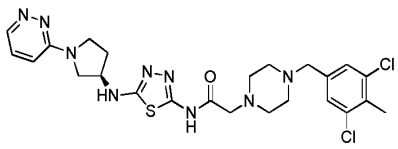
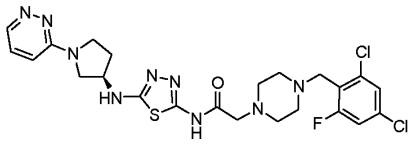
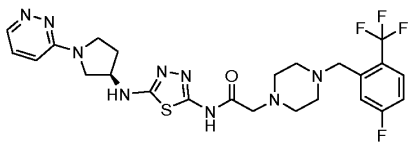
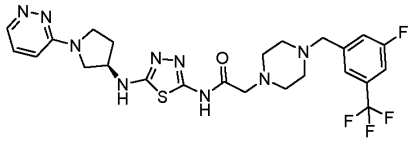
	N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(4-{spiro[4.5]decan-8-yl}thiomorpholin-2-yl)acetamide	5.7 Hz, 1H), 3.62 – 3.44 (m, 3H), 3.19 – 3.10 (m, 1H), 2.96 – 2.77 (m, 2H), 2.73 – 2.52 (m, 6H), 2.36 – 2.21 (m, 2H), 2.13 – 2.01 (m, 1H), 1.61 – 1.40 (m, 8H), 1.38 – 1.17 (m, 8H). LCMS (Method 7, ESI) 514.77 [MH]+, RT 1.43.
Example 291	 2-(4-{bicyclo[2.2.2]octan-1-yl}morpholin-2-yl)-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.49 – 8.46 (m, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.5 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.43 – 4.32 (m, 1H), 3.79 – 3.68 (m, 3H), 3.60 – 3.53 (m, 2H), 3.53 – 3.46 (m, 1H), 3.40 – 3.37 (m, 1H), 2.85 – 2.77 (m, 1H), 2.69 – 2.61 (m, 1H), 2.58 – 2.52 (m, 1H), 2.34 – 2.26 (m, 1H), 2.18 – 2.01 (m, 2H), 1.94 – 1.83 (m, 1H), 1.59 – 1.38 (m, 14H). LCMS (Method 7, ESI) 499.35 [MH]+, RT 3.12.
Example 292	 (*R*)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(3-(trifluoromethoxy)benzyl)piperazin-1-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.48 (dd, *J* = 4.4, 0.8 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.35-7.32 (m, 2H), 7.27-7.23 (m, 2H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.39 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.75 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.59-3.49 (m, 5H), 3.24 (s, 2H), 2.51 (s, 4H), 2.40 (s, 4H), 2.35-2.27 (m, 1H), 2.10-2.05 (m, 1H). LCMS (Method 26, ESI) 564.2 $[M+H]^+$, RT 1.688 min. Prep-HPLC (Method 1)
Example 293	 (*R*)-N-(5-((1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(4-(trifluoromethoxy)benzyl)piperazin-1-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.49 (d, *J* = 9.2 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 9.6 Hz, 1H), 4.40-4.37 (m, 1H), 3.74 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.58-3.49 (m, 5H), 3.23 (s, 2H), 2.50 (s, 4H), 2.39 (s, 4H), 2.33-2.25 (m, 1H), 2.11-2.05 (m, 1H). LCMS (Method 26, ESI) 598.2 $[M+H]^+$, RT 1.778 min. Prep-HPLC (Method 1)

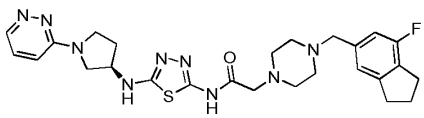
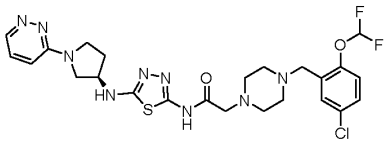
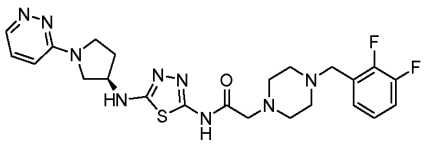
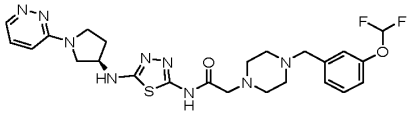
Example 294	 (*R*)-2-(4-(2-chloro-4-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.84 (s, 1H), 7.72 (s, 2H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.34 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.6, 1.2 Hz, 1H), 4.39 (q, *J* = 4.8 Hz, 1H), 3.75 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.63 (s, 2H), 3.59-3.49 (m, 5H), 3.25 (s, 2H), 2.54 (s, 4H), 2.50 (s, 4H), 2.33-2.27 (m, 1H), 2.10-2.06 (m, 1H). LCMS (Method 26, ESI) 582.15 [M+H]$^+$, RT 1.791 min. Prep-HPLC (Method 1)
Example 295	 (R)-2-(4-(3-chloro-5-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 8.48 (dd, *J* = 4.0, 0.8 Hz, 1H), 7.74 (s, 1H), 7.69-7.63 (m, 3H), 7.34 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.41-4.37 (m, 1H), 3.75 (dd, *J* = 10.8, 6.4 Hz, 1H), 3.58-3.49 (m, 5H), 3.24 (s, 2H), 2.51- 2.50 (m, 4H), 2.42-2.27 (m, 5H), 2.10-2.05 (m, 1H). LCMS (Method 26, ESI) 582.1 [MH]$^+$, RT 1.799 min. Prep-HPLC (Method 3)
Example 296	 (R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(2-(trifluoromethoxy)benzyl)piperazin-1-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.48 (dd, *J* = 4.4, 0.8 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1 H), 7.55 (dd, *J* = 6.4, 2.0 Hz, 1H), 7.42-7.32 (m, 4H), 6.87 (dd, *J* = 9.2, 0.8 Hz, 1H), 4.41-4.37 (m, 1H), 3.75 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.59-3.49 (m, 5H), 3.23 (s, 2H), 2.51-2.50 (m, 4H), 2.41-2.25 (m, 5H), 2.10-2.05 (m, 1H). LCMS (Method 26, ESI) 564.1 [MH]$^+$, RT 1.691 min. Prep-HPLC (Method 2)
Example 297	 (R)-2-(4-(3-fluoro-4-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 8.49 (d, *J* = 4.0 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.42 (d, *J* = 11.6 Hz, 1H), 7.37-7.32 (m, 2H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.39 (d, *J* = 4.4 Hz, 1H), 3.75 (dd, *J* = 11.6, 6.0 Hz, 1H), 3.61-3.50 (m, 5H), 3.25 (s, 2H), 2.51 (s, 4H), 2.42 (s, 4H), 2.34-2.25 (m, 1H), 2.11-2.04 (m, 1H). LCMS (Method 26,

		ESI) 566.1 $[M+H]^+$, RT 1.693 min. Prep-HPLC (Method 2)
Example 298	 (R)-2-(4-(3-bromo-5-fluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1 H), 7.44-7.32 (m, 3H), 7.17 (d, *J* = 9.6 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.40-4.37 (m, 1H), 3.75 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.59-3.49 (m, 5H), 3.24 (s, 2H), 2.51-2.50 (m, 4H), 2.40-2.25 (m, 5H), 2.11-2.05 (m, 1H). LCMS (Method 26, ESI) 576.0 $[MH]^+$, RT 1.693 min. Prep-HPLC (Method 3)
Example 299	 (R)-2-(4-(3-methoxy-4-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 8.48 (t, *J* = 4.0 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.34 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.17 (s, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.88-6.86 (m, 1H), 4.40-4.37 (m, 1H), 3.87 (s, 3H), 3.75 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.58-3.49 (m, 5H), 3.24 (s, 2H), 2.51 (s, 4H), 2.42 (s, 4H), 2.34-2.27 (m, 1H), 2.10-2.05 (m, 1H). LCMS (Method 26, ESI) 578.2 $[M+H]^+$, RT 1.658 min. Prep-HPLC (Method 1)
Example 300	 (R)-2-(4-(4-chloro-3-fluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.48 (dd, *J* = 4.4, 0.8 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1 H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.35-7.31 (m, 2H), 7.17 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.87 (dd, *J* = 9.2, 0.8 Hz, 1H), 4.40-4.37 (m, 1H), 3.75 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.59-3.47 (m, 5H), 3.23 (s, 2H), 2.51-2.50 (m, 4H), 2.40-2.25 (m, 5H), 2.11-2.05 (m, 1H). LCMS (Method 26, ESI) 532.2 $[MH]^+$, RT 1.643 min. Prep-HPLC (Method 3)
Example 301		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.48 (d, *J* = 3.6 Hz, 1H), 7.67 (d, *J* = 6.4 Hz, 1 H), 7.35-7.29 (m, 2H), 7.23 (s, 1 H), 7.14 (d, *J* = 9.6 Hz, 1H), 6.88 (d, *J* = 9.2 Hz, 1H), 4.42-4.36 (m, 1H), 3.75 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.61-3.49 (m,

	(R)-2-(4-(3-chloro-5-fluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	5H), 3.24 (s, 2H), 2.51-2.50 (m, 4H), 2.40-2.25 (m, 5H), 2.11-2.04 (m, 1H). LCMS (Method 26, ESI) 532.1 $[MH]^+$, RT 1.662 min. Prep-HPLC (Method 2)
Example 302	 (R)-2-(4-(3,4-difluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.48 (dd, J = 4.4, 1.2 Hz, 1H), 7.67 (d, J = 6.4 Hz, 1 H), 7.40-7.30 (m, 3H), 7.15-7.12 (m, 1H), 6.88 (dd, J = 9.2, 1.2 Hz, 1H), 4.40-4.37 (m, 1H), 3.75 (dd, J = 10.8, 5.6 Hz, 1H), 3.58-3.45 (m, 5H), 3.24 (s, 2H), 2.51-2.50 (m, 4H), 2.38-2.25 (m, 5H), 2.11-2.05 (m, 1H). LCMS (Method 26, ESI) 516.3 $[MH]^+$, RT 1.553 min. Prep-HPLC (Method 2)
Example 303	 (R)-2-(4-(3,5-difluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.48 (dd, J = 4.4, 1.2 Hz, 1H), 7.67 (d, J = 6.0 Hz, 1 H), 7.33 (dd, J = 9.2, 4.4 Hz, 1H), 7.13-7.01 (m, 3H), 6.87 (dd, J = 9.2, 1.2 Hz, 1H), 4.40-4.37 (m, 1H), 3.75 (dd, J = 11.2, 6.0 Hz, 1H), 3.59-3.49 (m, 5H), 3.24 (s, 2H), 2.51-2.50 (m, 4H), 2.40-2.25 (m, 5H), 2.10-2.05 (m, 1H). LCMS (Method 26, ESI) 516.3 $[MH]^+$, RT 1.582 min. Prep-HPLC (Method 2)
Example 304	 (R)-2-(4-(3,5-difluoro-4-methoxybenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.48 (dd, J = 4.4, 1.2 Hz, 1H), 7.67 (d, J = 6.0 Hz, 1H), 7.33 (dd, J = 9.2, 4.4 Hz, 1H), 7.09-7.02 (m, 2H), 6.87 (dd, J = 9.2, 1.2 Hz, 1H), 4.40-4.37 (m, 1H), 3.89 (s, 3H), 3.75 (dd, J = 10.8, 2.0 Hz, 1H), 3.58-3.48 (m, 3H), 3.42 (s, 2H), 3.23 (s, 2H), 2.51 (s, 4H), 2.39 (s, 4H), 2.32-2.25 (m, 1H), 2.10-2.05 (m, 1H). LCMS (Method 26, ESI) 546.2 $[M+H]^+$, RT 1.569 min. Prep-HPLC (Method 1)
Example 305	 N-(5-(((3S,4S)-4-fluoro-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.55 (dd, J = 4.4, 1.2 Hz, 1H), 7.75 (d, J = 5.6 Hz, 1H), 7.43-7.38 (m, 3H), 7.31 (d, J = 8.0 Hz, 2H), 6.97 (dd, J = 9.2, 1.2 Hz, 1H), 5.45-5.32 (m, 1H), 4.51-4.46 (m, 1H), 3.85-3.81 (m, 2H), 3.76-3.71 (m,

	2-yl)-2-(4-(4-(trifluoromethoxy)benzyl)piperazin-1-yl)acetamide	2H), 3.48 (s, 2H), 3.24 (s, 2H), 2.51 (s, 4H), 2.39 (s, 4H). LCMS (Method 26, ESI) 582.1 $[M+H]^+$, RT 1.700 min. Prep-HPLC (Method 3)
Example 306	 (R)-2-(4-(2-chloro-5-(trifluoromethoxy)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.35-7.31 (m, 2H), 6.87 (dd, *J* = 9.2, 0.8 Hz, 1H), 4.42-4.36 (m, 1H), 3.75 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.59-3.49 (m, 5H), 3.25 (s, 2H), 2.54-2.51 (m, 4H), 2.51-2.50 (m, 4H), 2.38-2.25 (m, 1H), 2.11-2.04 (m, 1H). LCMS (Method 26, ESI) 597.9 $[M+H]^+$, RT 2.086 min. Prep-HPLC (Method 2)
Example 307	 (*R*)-2-(4-(3-chloro-4-(trifluoromethoxy)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.52 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.40 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.40-4.37 (m, 1H), 3.75 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.59-3.50 (m, 5H), 3.24 (s, 2H), 2.51 (s, 4H), 2.40 (s, 4H), 2.34-2.25 (m, 1H), 2.11-2.04 (m, 1H). LCMS (Method 26, ESI) 598.2 $[M+H]^+$, RT 1.811 min. Prep-HPLC (Method 3)
Example 308	 (*R*)-2-(4-(3-(difluoromethoxy)-4-methylbenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.66 (d, *J* = 10.0 Hz, 1 H), 7.35-7.31 (m, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 74.4 Hz, 1H), 7.10-7.06 (m, 2H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.40-4.35 (m, 1H), 3.78-3.72 (m, 1H), 3.59-3.48 (m, 3H), 3.44 (s, 2H), 3.23 (s, 2H), 2.51-2.50 (m, 4H), 2.40-2.25 (m, 5H), 2.20 (s, 3H) 2.10-2.06 (m, 1H). LCMS (Method 26, ESI) 560.0 $[M+H]^+$, RT 1.845 min. Prep-HPLC (Method 3)

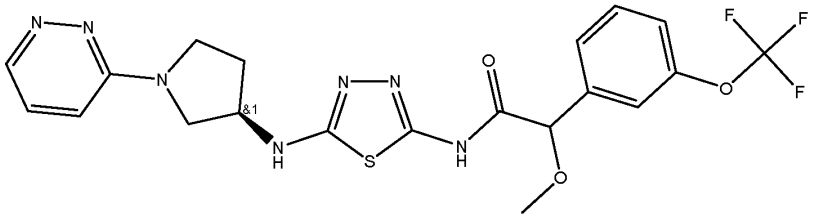
Example 309	 ((*R*)-2-(4-(3,5-dichloro-4-methylbenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1 H), 7.38-7.31 (m, 3H), 6.87 (dd, *J* = 8.8, 1.2 Hz, 1H), 4.40-4.36 (m, 1H), 3.78-3.73 (m, 1H), 3.59-3.48 (m, 3H), 3.44 (s, 2H), 3.23 (s, 2H), 2.51-2.50 (m, 4H), 2.40-2.25 (m, 8H), 2.10-2.07 (m, 1H). LCMS (Method 26, ESI) 562.0 [M+H]$^+$, RT 2.094 min. Prep-HPLC (Method 3)
Example 310	 (*R*)-2-(4-(2,4-dichloro-6-fluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H), 7.54 (t, *J* = 5.6 Hz, 1H), 7.50 (dd, *J* = 9.6, 6.0 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.39 (q, *J* = 4.4 Hz, 1H), 3.75 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.58-3.48 (m, 5H), 3.21 (s, 2H), 2.45 (br, 8H), 2.32-2.27 (m, 1H), 2.10-2.05 (m, 1H). LCMS (Method 26, ESI) 566.0 [M+H]$^+$, RT 1.767 min. Prep-HPLC (Method 3)
Example 311	 (*R*)-2-(4-(5-fluoro-2-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 8.48 (d, *J* = 3.6 Hz, 1H), 7.78 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.56 (dd, *J* = 9.6, 6.0 Hz, 1H), 7.35-7.29 (m, 2H), 6.87 (d, *J* = 9.2 Hz, 1H), 4.39 (q, *J* = 4.8 Hz, 1H), 3.75 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.62 (s, 2H), 3.59-3.49 (m, 3H), 3.26 (s, 2H), 2.55 (s, 4H), 2.45 (s, 4H), 2.24-2.25 (m, 1H), 2.11-2.05 (m, 1H). LCMS (Method 26, ESI) 566.2 [M+H]$^+$, RT 1.795 min. Prep-HPLC (Method 3)
Example 312	 (*R*)-2-(4-(3-fluoro-5-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.52 (s, 1H), 7.48 (d, *J* = 9.2 Hz, 1H), 7.33 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.87 (dd, *J* = 9.2, 5.2 Hz, 1H), 4.42-4.36 (m, 1H), 3.75 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.59-3.49 (m, 5H), 3.24 (s, 2H), 2.51 (s, 4H), 2.42

	yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	(s, 4H), 2.34-2.25 (m, 1H), 2.11-2.05 (m, 1H). LCMS (Method 26, ESI) 566.2 $[M+H]^+$, RT 1.743 min. Prep-HPLC (Method 2)
Example 313	 (*R*)-2-(4-((7-fluoro-2,3-dihydro-1H-inden-5-yl)methyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.66 (d, *J* = 6.4 Hz, 1 H), 7.35-7.31 (m, 1H), 6.99 (m, 1H), 6.86 (t, *J* = 10.0 Hz, 1H), 4.40-4.36 (m, 1H), 3.78-3.72 (m, 1H), 3.59-3.48 (m, 3H), 3.42 (s, 2H), 3.22 (s, 2H), 2.89-2.82 (m, 4H), 2.51-2.50 (m, 4H), 2.40-2.25 (m, 5H), 2.10-2.07 (m, 3H). LCMS (Method 26, ESI) 538.1 $[M+H]^+$, RT 1.918 min. Prep-HPLC (Method 3)
Example 314	 (*R*)-2-(4-(5-chloro-2-(difluoromethoxy)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.66 (d, *J* = 6.4 Hz, 1H), 7.48 (d, *J* = 2.8 Hz, 1H), 7.41 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.35-7.33 (m, 1H), 7.32-6.97 (m, 2H), 6.87 (dd, *J* = 8.8, 0.8 Hz, 1H), 4.41-4.37 (m, 1H), 3.75 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.59-3.49 (m, 5H), 3.23 (s, 2H), 2.51-2.50 (m, 5H), 2.43-2.27 (m, 4H), 2.10-2.06 (m, 1H). LCMS (Method 26, ESI) 580.2 $[M+H]^+$, RT 1.743 min. Prep-HPLC (Method 2)
Example 315	 (*R*)-2-(4-(2,3-difluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.48 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H), 7.37-7.30 (m, 2H), 7.23-7.15 (m, 2H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.42-4.35 (m, 1H), 3.75 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.61-3.48 (m, 5H), 3.22 (s, 2H), 2.51 (s, 4H), 2.42 (s, 4H), 2.34-2.25 (m, 1H), 2.11-2.04 (m, 1H). LCMS (Method 26, ESI) 516.2 $[M+H]^+$, RT 1.557 min. Prep-HPLC (Method 3)
Example 316		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 8.48 (dd, *J* = 4.4, 0.8 Hz, 1H), 7.66 (d, *J* = 6.0 Hz, 1H), 7.41-7.32 (m, 2.25H), 723 (s, 0.5H), 7.17 (d, *J* = 7.6 Hz , 1H

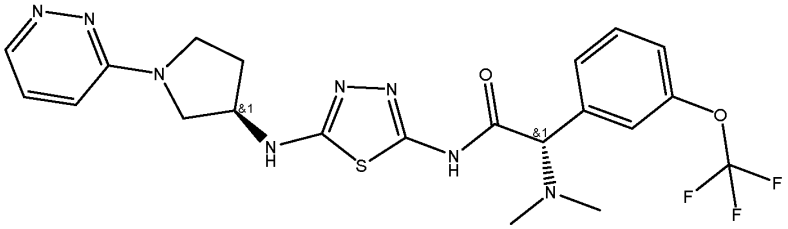
	(*R*)-2-(4-(3-difluoromethoxy)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide	), 7.32-6.97 (m, 2H), 7.09 (s, 1H), 7.05 (d, *J* = 7.6 Hz , 1.24H), 6.87 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.40 – 4.37 (m, 1H), 3.75 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.58-3.48 (m, 5H), 3.23 (s, 2H), 2.51-2.50 (m, 4H), 2.40-2.25 (m, 4H), 2.10-2.05 (m, 1H). LCMS (Method 26, ESI) 546.1 $[M+H]^+$, RT 1.599 min. Prep-HPLC (Method 3)

Reference Examples

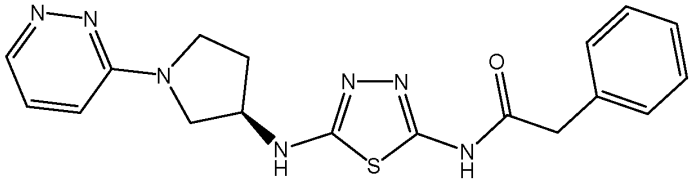
Reference Example 1 (RE1) corresponds to Compound 9a in WO2015/181539 (AstraZeneca AB and Cancer Research Technology Limited):



Reference Example 2 (RE2) corresponds to Compound 4a in WO2017/093301 (AstraZeneca AB and Cancer Research Technology Limited):



Reference Example 3 (RE3) corresponds to Compound 23 in Zhang et al., 2019:



Biological Example 1 – GLS1 inhibition in enzymatic and cellular assays

GLS1 Enzymatic assay

The inhibitory properties against GLS1 of the tested compounds were assessed by conducting a three-stage coupled endpoint enzymatic assay. Briefly, in the first stage, L-glutamine was converted to L-glutamate by the GLS1 enzyme. Then, L-glutamate was utilized by another enzyme used in the reaction, glutamate dehydrogenase (GDH), to form α-ketoglutarate, which is associated with the reduction of NAD to NADH. Finally, NADH was oxidized to NAD with concomitant reduction of resazurin to fluorescent resorufin. The resorufin level was measured with Ex554/Em596. A decrease in signal intensity indicates GLS1 activity inhibition.

All reaction mixtures required for conducting the assay were prepared with use of 2x Assay Buffer pH=8.5 (100 mM phosphate buffer pH=8.5, 300 mM NaCl, 0.5 mM EDTA, 100 mM HEPES pH=8.5, 0.1% BSA). All compounds were tested in duplicates at a concentration range of 0.325 nM –5 μM (11 concentrations). DMSO (compounds solvent) and 5 μM reference compound CB-839 were included on a plate as high control and low control, respectively. For running an assay run, reference compound CB-839 and test compounds were dispensed on a 384-well plate (with DMSO normalization to a final volume of 202 nL). Thereafter, 15 μL of 1.33x Enzyme Mix (2.67 mM NAD, 8 U/mL GDH, 2 nM GLS1 in 1x Assay Buffer) was dispensed on a plate for compounds preincubation with the enzyme for 1h at 25 °C. Then, in order to start the enzymatic reaction, 5 μL of 4x Substrate Mix (40 mM L-glutamine, 1 mM ADP, 400 μM resazurin, 4 U/mL diaphorase in 1x Assay Buffer) was dispensed on a plate with compounds and Enzyme Mix, followed by 1h incubation at 25 °C. The reaction was then stopped by adding 10 μL of 6% SDS solution and the fluorescence was measured with a microplate reader. Conducting the assay led to the determination of the potency of test compounds to inhibit GLS1 activity by generating concentration-response curves. Their specificity was additionally verified by running a counterscreen experiment, where test compounds were checked for the eventual inhibitory effect on the remaining enzymatic elements of the assay. For this purpose, 1.33x Enzyme Mix without GLS1 and 4x Substrate Mix containing 800 μM L-glutamate were used. For counterscreen experiments, the reference compound and test compounds were tested in a single concentration of 5 μM in duplicates.

GLS1 cell assay

The commercial *Glutamine/Glutamate-Glo™ Assay* kit provided by Promega was adjusted to measure changes in intracellular glutamate level in human lung carcinoma A549 cell line (ATCC No. CCL-185^{TM}) and in 384-well plate format after treatment with compounds of formula (I) and the reference examples.

A549 cells (ATCC No. CCL-185TM) were maintained in growth media consisting of DMEM high glucose (Gibco), 100 U/mL Penicillin-Streptomycin, 1 mM Sodium Pyruvate, 10 % FBS. The cells were cultured at 37°C/95% Air, 5% CO2 in a humidified incubator and passaged at 80-90% confluency.

A549 cells were seeded into poly-D-lysine coated 384-well plates (Corning) at 10,000 cells/well density and in total volume of 40 µL/well. After overnight incubation at 37°C/95% Air, 5% CO_2 in a humidified incubator, the growth medium was removed and the cells were washed 2 x with 50 µL of warm assay medium composed of: DMEM no glucose, no glutamine, no phenol red (Gibco), 5 mM Glucose, 1 mM Sodium Pyruvate, 10% dialyzed FBS. Immediately after washing, warm assay medium was added in volume of 40 µL/well.

Compounds were dispensed into plate using D300e Digital Dispenser (Tecan) with a consistent concentration of 0.1% DMSO applied to all wells. After treatment cells were incubated for 2 hours at 37°C, 5% CO2 and then 10 µL of freshly prepared assay medium containing 5 x 1.25 mM L-Gln were added to each well. Afterwards, plates were incubated at 37°C/95% Air, 5% CO2 in a humidified incubator for a further 24 hours.

The assay medium was removed completely and the cells were rinsed quickly 3 x with 60 µL of cold PBS. As instructed by the *Glutamine/Glutamate-Glo*™ Assay kit (Promega), 15 µL of cold PBS and 7.5 µL of Inactivation Solution I were added to each well and plates were mixed by shaking for 5 min. Afterwards, 7.5 µL of Tris Solution I were dispensed and plates were mixed again for 1 min. Lysates were frozen for about 24 hours at -20°C.

Lysates were thawed at RT and diluted 2 x by adding lysis buffer composed of: 15 µL PBS, 7.5 µL Inactivation Solution I and 7.5 µL Tris Solution I. Glutamate Detection Reagent was prepared according to *Glutamine/Glutamate-Glo*™ Assay kit (Promega) protocol. After mixing, 12.5 µL of lysates were transferred to a new 384-well assay plate (OptiPlate-384, Perkin Elmer). As a positive control 12.5 µL of 50 µM glutamate (provided by Promega kit and prepared from 10 mM stock in lysis buffer) was used. A negative control was 12.5 µL of lysis buffer. 12.5 µL of Glutaminase Buffer (provided by Promega kit) were dispensed to all samples and plate was mixed by shaking for 1 min. Then, 25 µL of Glutamate Detection Reagent were added to each sample and mixed again for 1 min. A ratio of a Sample:Glutaminase Buffer:Glutamate Detection Reagent volume was established as 1:1:2. Plates were incubated for 60 min. at RT and protected from light. The final luminescence signal was recorded by using a plate reader.

To confirm that samples were within the linear range of the assay, a standard curve for glutamate was generated according to *Glutamine/Glutamate-Glo*™ Assay kit (Promega).

Dose response curves for tested compounds (representing % of inhibition) and pIC_{50}/IC_{50} values were determined by using log(inhibitor) vs. response-variable slope (four parameters) model. Results were normalized to high control (VHL CTL - 0% of normalization) and to low control (POS CTL - 100% of normalization).

A number of example compounds were tested in this assay and the results are shown in Table 1 below. Reference Examples 1, 2 and 3 were used as controls.

Table 1 – Cell and enzyme IC_{50} values (nM)

Compound	Cell IC_{50}	Enzyme IC_{50}	Compound	Cell IC_{50}	Enzyme IC_{50}
Reference Example 1	1.08	97.14	Reference Example 1	1.08	97.14
Reference Example 2	0.74	52.19	Reference Example 2	0.74	52.19
Reference Example 3	24.30	21.68	Reference Example 3	24.30	21.68
Example 1	3.5	29.4	**Example 159**	5.4	65.9
Example 2	6.4	125.9	**Example 160**	4.1	49.4
Example 3	9.1	24.6	**Example 161**	11.8	28.8
Example 4	3.4	29.0	**Example 162**	31.5	19.9
Example 5	3.5	15.8	**Example 163**	1.9	78.4
Example 6	49.9	56.4	**Example 164**	11.8	30.4
Example 7	5.6	18.8	**Example 165**	27.9	18.1
Example 8	6.6	30.2	**Example 166**	3.8	56.7
Example 9	10.0	37.6	**Example 167**	4.2	61.3
Example 10	10.6	223.4	**Example 168**	19.9	55.8
Example 11	70.2	55.0	**Example 169**	6.2	49.6
Example 12	5.5	40.1	**Example 170**	2.3	17.7
Example 15	1.6	52.7	**Example 171**	14.1	34.6
Example 16	4.1	73.2	**Example 172**	35.2	25.8
Example 17	24.6	115.4	**Example 173**	48.5	33.7
Example 18	24.8	107.2	**Example 174**	23.2	31.8
Example 19	11.7	62.7	**Example 175**	7.2	22.9

Compound	Cell IC_{50}	Enzyme IC_{50}	Compound	Cell IC_{50}	Enzyme IC_{50}
Reference Example 1	1.08	97.14	Reference Example 1	1.08	97.14
Reference Example 2	0.74	52.19	Reference Example 2	0.74	52.19
Reference Example 3	24.30	21.68	Reference Example 3	24.30	21.68
Example 20	12.0	51.2	**Example 176**	33.2	40.0
Example 21	2.8	57.6	**Example 177**	111.6	45.9
Example 22	8.1	68.9	**Example 178**	83.0	32.5
Example 23	7.9	144.6	**Example 179**	143.1	25.1
Example 24	30.6	118.7	**Example 180**	8.5	42.9
Example 25	12.5	28.8	**Example 181**	11.8	47.8
Example 26	4.7	37.6	**Example 182**	7.4	12.0
Example 27	5.4	23.7	**Example 183**	9.4	36.8
Example 28	14.0	34.9	**Example 184**	14.2	43.7
Example 29	5.9	46.2	**Example 185**	14.3	19.6
Example 30	3.9	58.5	**Example 186**	5.0	16.7
Example 31	1.6	45.0	**Example 187**	5.9	133.7
Example 32	17.4	37.4	**Example 188**	4.8	62.9
Example 33	9.3	42.1	**Example 189**	4.1	161.1
Example 34	9.3	42.5	**Example 190**	14.4	30.7
Example 35	24.1	52.3	**Example 191**	22.7	20.0
Example 36	4.4	24.2	**Example 192**	29.6	18.5
Example 37	7.4	62.5	**Example 193**	25.4	20.6
Example 38	2.8	121.3	**Example 194**	3.4	35.1
Example 39	9594.9	77.4	**Example 195**	3.0	37.4
Example 40	10000.0	102.8	**Example 196**	3.4	31.9
Example 41	81.6	55.6	**Example 197**	57.9	28.1
Example 42	40.5	235.9	**Example 198**	13.4	116.4
Example 43	27.2	39.5	**Example 199**	16.7	89.6
Example 44	5.4	30.9	**Example 200**	7.5	275.2
Example 45	31.1	86.5	**Example 201**	5.6	15.9
Example 46	7.1	47.0	**Example 202**	7.4	16.2
Example 47	19.8	50.4	**Example 203**	23.8	17.5
Example 48	26.0	71.9	**Example 204**	16.3	54.4

Compound	Cell IC_{50}	Enzyme IC_{50}	Compound	Cell IC_{50}	Enzyme IC_{50}
Reference Example 1	1.08	97.14	Reference Example 1	1.08	97.14
Reference Example 2	0.74	52.19	Reference Example 2	0.74	52.19
Reference Example 3	24.30	21.68	Reference Example 3	24.30	21.68
Example 49	0.8	85.3	**Example 205**	44.0	76.8
Example 50	1.8	96.3	**Example 206**	10.1	42.8
Example 51	4.2	58.9	**Example 207**	129.6	69.6
Example 52	36.7	38.8	**Example 208**	83.5	58.6
Example 53	35.7	39.2	**Example 209**	115.7	80.0
Example 54	5.5	109.5	**Example 210**	34.6	28.1
Example 55	11.9	53.3	**Example 211**	1.7	40.3
Example 56	47.8	42.9	**Example 212**	6.4	53.4
Example 57	34.5	68.2	**Example 213**	7.9	66.9
Example 58	15.5	27.8	**Example 214**	9.3	52.8
Example 59	1.6	65.3	**Example 215**	3.2	17.7
Example 60	1.7	52.0	**Example 216**	4.2	21.4
Example 61	3.7	106.9	**Example 217**	35.9	119.3
Example 62	489.1	63.2	**Example 218**	150.4	254.0
Example 63	18.2	43.6	**Example 219**	24.3	72.3
Example 64	14.4	45.2	**Example 220**	40.1	118.3
Example 65	12.7	35.2	**Example 221**	154.9	296.5
Example 66	20.0	53.2	**Example 222**	29.7	82.5
Example 67	2.5	82.5	**Example 223**	32.1	78.2
Example 68	12.8	109.2	**Example 224**	90.1	120.1
Example 69	1.8	56.0	**Example 225**	20.1	66.3
Example 70	12.1	212.0	**Example 226**	28.0	40.1
Example 71	1.7	44.9	**Example 227**	33.4	67.9
Example 72	3.4	37.2	**Example 228**	27.7	37.1
Example 73	0.9	67.1	**Example 229**	31.1	33.7
Example 74	268.7	37.8	**Example 230**	33.5	257.8
Example 75	2014.8	3519.4	**Example 231**	8.5	74.0
Example 76	64.0	34.4	**Example 232**	2.0	27.4
Example 77	76.2	45.0	**Example 233**	1.7	30.9

Compound	Cell IC_{50}	Enzyme IC_{50}	Compound	Cell IC_{50}	Enzyme IC_{50}
Reference Example 1	1.08	97.14	Reference Example 1	1.08	97.14
Reference Example 2	0.74	52.19	Reference Example 2	0.74	52.19
Reference Example 3	24.30	21.68	Reference Example 3	24.30	21.68
Example 78	2.8	22.2	**Example 234**	4.0	30.1
Example 79	5.5	23.2	**Example 235**	5.3	36.7
Example 80	4.3	23.0	**Example 236**	1.8	92.2
Example 81	6.3	24.1	**Example 237**	6.2	50.0
Example 82	23.2	21.9	**Example 238**	25.9	90.0
Example 83	327.2	71.3	**Example 239**	2.1	32.1
Example 84	28.3	21.4	**Example 240**	9.8	32.1
Example 85	51.8	50.0	**Example 241**	5.6	49.6
Example 86	34.0	52.2	**Example 242**	3.6	27.4
Example 87	1.7	22.2	**Example 243**	2.4	21.0
Example 88	34.4	36.9	**Example 244**	1.6	29.8
Example 89	78.8	37.5	**Example 245**	2.7	21.8
Example 90	111.6	52.2	**Example 246**	2.1	24.2
Example 91	4.0	19.9	**Example 247**	6.6	27.3
Example 92	2.0	82.7	**Example 248**	15.0	24.1
Example 93	31.5	40.7	**Example 249**	32.1	54.1
Example 94	25.0	71.1	**Example 250**	74.8	93.9
Example 95	2.8	12.7	**Example 251**	10.0	23.0
Example 96	58.2	40.6	**Example 252**	6.4	15.4
Example 97	81.0	41.2	**Example 253**	21.3	25.9
Example 98	51.7	39.3	**Example 254**	1.7	20.0
Example 99	5.2	36.7	**Example 255**	5.7	26.6
Example 100	2.6	31.6	**Example 256**	1.0	21.7
Example 101	15.8	27.6	**Example 257**	1.2	15.5
Example 102	5.8	69.4	**Example 258**	5.3	18.9
Example 103	7.9	67.4	**Example 259**	9.2	22.4
Example 104	5.3	54.4	**Example 260**	12.2	34.1
Example 105	4.2	106.0	**Example 261**	6.3	18.8
Example 106	3.7	87.3	**Example 262**	6.6	22.6

Compound	Cell IC_{50}	Enzyme IC_{50}	Compound	Cell IC_{50}	Enzyme IC_{50}
Reference Example 1	1.08	97.14	Reference Example 1	1.08	97.14
Reference Example 2	0.74	52.19	Reference Example 2	0.74	52.19
Reference Example 3	24.30	21.68	Reference Example 3	24.30	21.68
Example 107	4.1	66.2	**Example 263**	11.1	29.7
Example 108	7.5	32.8	**Example 264**	5.1	22.6
Example 109	18.9	35.6	**Example 265**	3.1	13.3
Example 110	4.7	25.7	**Example 266**	7.2	20.4
Example 111	40.4	19.4	**Example 267**	1.7	16.4
Example 112	18.1	37.5	**Example 268**	3.1	16.5
Example 113	8.6	64.7	**Example 269**	3.0	17.0
Example 114	1.7	30.8	**Example 270**	1.7	14.5
Example 115	1.3	64.4	**Example 271**	5.6	22.4
Example 116	5.7	23.6	**Example 272**	2.3	16.4
Example 117	3.4	23.3	**Example 273**	7.8	23.2
Example 118	11.2	14.0	**Example 274**	9.0	36.6
Example 119	7.8	27.0	**Example 275**	2.8	18.8
Example 120	5.5	19.8	**Example 276**	14.6	31.2
Example 121	14.1	26.1	**Example 277**	152.3	112.1
Example 122	4.7	19.1	**Example 278**	16.8	49.4
Example 123	4.1	24.9	**Example 279**	14.6	31.2
Example 124	15.0	17.4	**Example 280**	9.4	25.9
Example 125	13.7	30.7	**Example 281**	17.8	65.8
Example 126	5635.7	2904.5	**Example 282**	36.3	100.0
Example 127	8591.5	5000.0	**Example 283**	11.7	47.2
Example 128	5.5	14.0	**Example 284**	2.3	11.9
Example 129	10.3	25.8	**Example 285**	3.4	19.7
Example 130	6.1	21.4	**Example 286**	84.2	74.0
Example 131	9.3	178.5	**Example 287**	48.0	53.5
Example 132	8.0	20.3	**Example 288**	206.5	144.9
Example 133	23.6	29.7	**Example 289**	3.4	23.0
Example 135	1.8	8.3	**Example 290**	2.9	25.0
Example 136	22.4	51.4	**Example 291**	28.8	30.4

Compound	Cell IC_{50}	Enzyme IC_{50}	Compound	Cell IC_{50}	Enzyme IC_{50}
Reference Example 1	1.08	97.14	Reference Example 1	1.08	97.14
Reference Example 2	0.74	52.19	Reference Example 2	0.74	52.19
Reference Example 3	24.30	21.68	Reference Example 3	24.30	21.68
Example 137	52.7	235.6	**Example 292**	1.1	NT
Example 138	22.5	69.1	**Example 293**	3.0	NT
Example 139	66.1	22.2	**Example 294**	2.0	NT
Example 140	47.2	18.7	**Example 295**	1.3	NT
Example 141	12.6	53.8	**Example 296**	3.0	NT
Example 142	12.4	32.6	**Example 297**	0.9	NT
Example 143	1.7	24.6	**Example 298**	1.7	NT
Example 144	5.9	15.5	**Example 299**	1.1	NT
Example 145	2.7	29.0	**Example 301**	2.7	NT
Example 146	3.0	26.0	**Example 302**	6.9	NT
Example 147	6.2	19.2	**Example 303**	6.3	NT
Example 148	1.6	10.9	**Example 304**	3.4	NT
Example 149	20.3	79.6	**Example 305**	1.7	NT
Example 150	12.1	65.4	**Example 306**	1.3	NT
Example 151	1.9	28.1	**Example 307**	1.0	NT
Example 152	3.8	17.1	**Example 308**	2.9	NT
Example 153	1.2	19.7	**Example 309**	0.9	NT
Example 154	2.4	13.1	**Example 310**	2.5	NT
Example 155	8.0	40.2	**Example 312**	1.4	NT
Example 156	7.2	28.2	**Example 313**	1.2	NT
Example 157	1.5	71.4	**Example 315**	8.3	NT
Example 158	10.8	65.1	**Example 316**	7.6	NT

[a]NT means not tested in the assay

All compounds of formula (I) which were tested in this assay were active in the cell and/or enzyme assay as shown by the values in Table 1. Certain compounds of formula (I) that were tested in this assay were more potent than Reference Example 1 in the cell or enzyme assay. Certain compounds of formula (I) that were tested in this assay were more potent than Reference Example 2 in the enzyme assay. Certain compounds of formula (I) that were tested in this assay were more potent than Reference Example 3 in the cell and/or enzyme assay.

Biological Example 2 – PK data

PK experiments were performed according to the protocols described in Tables 2 and 3 below.

Table 2: PK protocol for RE1 and RE2

Dose Route(s) & Level	IN @ 2mg/kg	
Dose Concentration & Volume	RE1 and RE2 – 1 mg/mL @ 2 mL/kg	
Dose Frequency	Single	
Dose Vehicle & Formulation Preparation	IN: 5% (v/v) DMSO in 12% (2-hydroxypropyl)-β-cyclodextrin 0.9% (w/v) aqueous NaCl	
Animal Information	Species/Strain/ Sex	Mouse/C57bl/6/male
	Weight	Approximately 20-30 g (all animals weighed prior to dosing).
	Housing & Husbandry	Group/singly housed as appropriate in the animal facility and maintained under a 12 h light/dark cycle with free access to food and water.
	Dose Groups & n =	Terminal sampling at following 8 time points (n=3 per time point) was performed: 0.02, 0.08, 0.17, 0.43, 1.00, 4.00, 8.00 & 24.00 h post dosing Total: 24 plasma samples per compound concentration (total 48 samples) 24 lung samples per compound concentration (Total 48 samples)
	Fed/Fasted	Fed
Sampling Information	Serial/Terminal	Terminal
	Occasions	Day 1 only
	Sample(s)	Terminal samples only

Per compound concentration	Time-points (h)	Terminal sampling at following 8 time points (n=3 per time point) was performed: 0.02, 0.08, 0.17, 0.43, 1.00, 4.00, 8.00 & 24.00 h Total: 24 plasma samples per compound concentration (Total 48 samples); 24 lung samples per compound concentration (Total 48 samples)
Method	Terminal blood samples of individual animals at each time point were delivered into labelled polypropylene tubes containing anticoagulant (heparin) and held on wet ice for a maximum of 30 minutes. The blood samples were then centrifuged for plasma (4°C, 21100 g for 5 min) and the resulting plasma transferred into labelled safe-lock Eppendorf 1.5 mL clear tubes. Terminal lung samples (rinsed with saline post excision) were collected into pre-weighed tubes. The tubes were then weighed prior to storage. Appropriate matrix samples were provided for bioanalytical purposes. All samples were stored immediately after collection at ≤-80°C until processed for bio-analysis.	

Table 3: PK protocol for Compounds of formula (I)

Dose Route(s) & Level	IN @ 2 mg/kg	
Dose Concentration & Volume	IN: 1 mg/mL @ 2 mL/kg	
Dose Frequency	Single	
Dose Vehicle & Formulation Preparation	IN/: pH 5.2 citrate buffer	
Animal Information	Species/Strain/ Sex	Mouse/Balbc/male
	Weight	Approximately 20-30 g (all animals weighed prior to dosing).
	Housing & Husbandry	Group/singly housed as appropriate in the animal facility and maintained under a 12 h light/dark cycle with free access to food and water.
	Dose Groups & n =	IN – 3 mice per timepoint per compound
	Fed/Fasted	Fed

Sampling Information Per Dose Route	Serial/Terminal	IN: Terminal
	Occasions	Day 1 only
	Sample(s)	Blood for plasma and tissues
	IN Dosing Time-points	Terminal sampling at following 6 timepoints (n=3 per time point) for plasma and tissues (brain, liver, and lung samples): 5 min, 15 min, 30 min, 2 h, 6 h & 24 h post dosing
Method	Blood samples of individual animals at each timepoint were delivered into EDTA- coated tubes and held on wet ice for a maximum of 30 minutes. The blood samples were then centrifuged for plasma (4°C, 1560 g for 10 min) and the resulting plasma transferred into polypropylene tubes. Terminal lung (both lungs combined), brain and liver samples (rinsed with saline post excision) were collected into pre-weighed tubes. The tubes were then weighed prior to storage. Appropriate matrix samples will also be provided for bioanalytical purposes. All samples will be stored immediately after collection at ≤-80°C until processed for bioanalysis.	

Table 4 – *In-vivo* pharmacokinetic assessment of compounds in lung, dosed intranasally in mouse

Compound	**Reference Example 1**	**Reference Example 2**	**Example 110**	**Example 36**
Dose (mg/kg)	2	2	2	2
C_{max} (ng/g)	1537	10850	119833	27200
AUC_{last} (h*ng/g)	521	2624	127878	49897

The results in Table 4 show that compounds of the invention are expected to have improved pharmacokinetic properties compared with compounds in the prior art, such as an improved duration in the lung. Example 36 and Example 110 were shown to have a higher lung concentrations and longer duration compared with both Reference Examples 1 and 2 as shown by the higher C_{max} and higher AUC_{last} values.

Biological Example 3 – Solubility Studies

Compounds tested in this assay were prepared as 10 mM stock solutions in DMSO. The assay was performed using Multiscreen Vacuum Manifold. PBS buffer, pH=7.4 was spiked with stock solution and incubated for 90 minutes at RT. After that time solution/suspension was filtrated. The concentration of each compound was determined on the base of prepared calibration curve using UV-VIS (Biotec Synergy 2 (250 – 500 nm, interval range 10 nm) spectrophotometry method. The assay was made in triplicate.

Example 36, Example 110, Example 176 and Example 181 were tested in this assay and the results are shown in Table 5 below. Reference Example 3 was used as a control.

Table 5 – Kinetic solubility data

Compound	**Reference Example 3**	**Example 176**	**Example 36**	**Example 110**	**Example 181**
Kinetic Solubility (μM)	101.72	530.07	252.47	463.19	508.85

The results in Table 5 show that compounds of the invention are expected to have improved solubility (for example, improved kinetic solubility) compared with compounds of the prior art. Example 36, Example 110, Example 176 and Example 181 were shown to have improved kinetic solubility compared with Reference Example 3, and thus have preferred drug properties compared with Reference Example 3.

References

The following publication cited in this specification are herein incorporated by reference in their entirety.

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Ge J, Cui H, Xie N, Banerjee S, Guo S, Dubey S, Barnes S, Liu G. Glutaminolysis Promotes Collagen Translation and Stability via α-Ketoglutarate-mediated mTOR Activation and Proline Hydroxylation. *Am. J. Respir. Cell. Mol. Biol.* 2018, **58**(3), 378-390.

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Miscellaneous

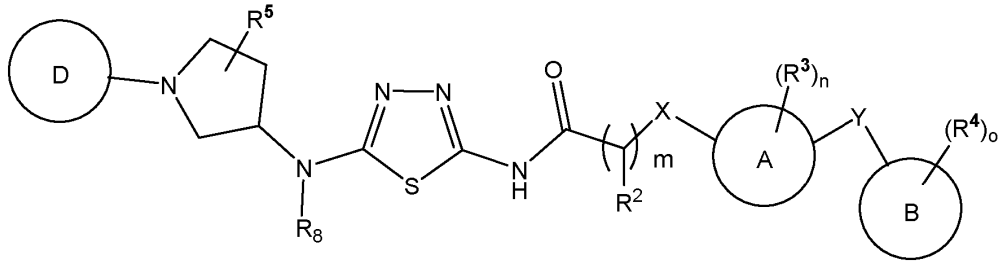
All references referred to in this application, including patent and patent applications, are incorporated herein by reference to the fullest extent possible.

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

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

CLAIMS

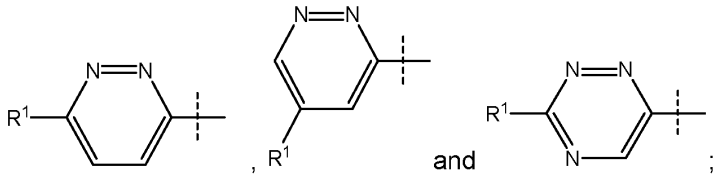
1. A compound of formula (I):



(I)

wherein:

D is selected from the group consisting of:



wherein R^1 is selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl and NH_2;

R^2 is selected from the group consisting of H, C_{1-4} alkyl, C_{1-4} alkoxy, $NR^{2a}R^{2b}$ and C_{0-3}alkyleneC_{3-6}cycloalkyl;

wherein: R^{2a} is independently H or C_{1-3}alkyl;

R^{2b} is independently H or C_{1-3}alkyl;

each R^3 is independently selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and C_{1-4} haloalkoxy;

each R^4 is independently selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CO_2R^{4a}, SC_{1-4}alkyl, OC_{0-3}alkyleneC_{3-6}cycloalkyl and C_{0-3}alkyleneC_{3-6}cycloalkyl wherein the C_{3-6}cycloalkyl is optionally substituted by one or two R^{4b}; or when ring B is phenyl two R^4 groups which are attached to adjacent carbon atoms join to form a C_{4-7}cycloalkyl ring;

wherein: R^{4a} is independently H or C_{1-3}alkyl;

R^{4b} is independently halo or C_{1-3}alkyl;

R^5 is H or halo;

A is selected from the group consisting of 4-10 membered heterocyclyl, 6-11 membered heterospirocycloalkyl and C_{3-6}cycloalkyl;

B is selected from the group consisting of phenyl, C_{5-10}cycloalkyl, 4-7 membered heterocyclyl, 4-10 membered heteroaryl and C_{6-11} spirocycloalkyl;

X is either absent or is selected from the group consisting of O, S and NR^6C_{1-4}alkylene;

wherein R^6 is independently H or C_{1-3}alkyl;

Y is either absent or is selected from the group consisting of O, S, C_{1-4}alkylene and NR^7C_{1-4}alkylene, wherein the C_{1-4}alkylene group is optionally substituted by one or more R^9;

wherein R^7 is independently H or C_{1-3}alkyl;

R^8 is independently H or C_{1-3}alkyl;

R^9 is independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} alkoxy and $NR^{2a}R^{2b}$;

m is 0, 1 or 2;

n is 0, 1 or 2; and

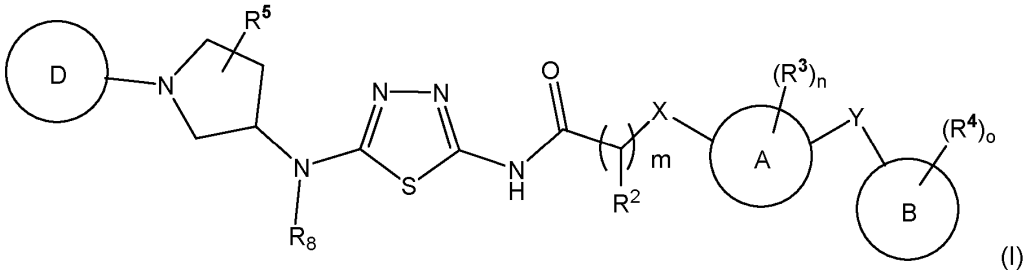
o is 0, 1, 2, 3 or 4;

wherein:

when B is phenyl, o is 1, 2, 3 or 4;

or a salt and/or solvate thereof.

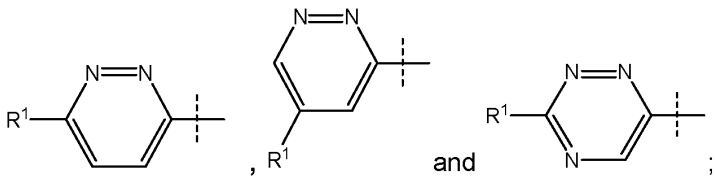
2. A compound or a salt and/or solvate thereof which is a compound of formula (IB):



(I)

wherein:

D is selected from the group consisting of:



;

wherein R^1 is selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl and NH_2;

R^2 is selected from the group consisting of H, C_{1-4} alkyl, C_{1-4} alkoxy, $NR^{2a}R^{2b}$ and C_{0-3}alkyleneC_{3-6}cycloalkyl;

wherein: R^{2a} is independently H or C_{1-3}alkyl;

R^{2b} is independently H or C_{1-3}alkyl;

R^3 is selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and C_{1-4} haloalkoxy;

R^4 is selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CO_2R^{4a}, SC_{1-4}alkyl, OC_{0-3}alkyleneC_{3-6}Cycloalkyl and C_{0-3}alkyleneC_{3-6}Cycloalkyl wherein the C_{3-6}Cycloalkyl is optionally substituted by one or two R^{4b};

wherein: R^{4a} is independently H or C_{1-3}alkyl;

R^{4b} is independently halo or C_{1-3}alkyl;

R^5 is H or halo;

A is selected from the group consisting of 4-10 membered heterocyclyl, 6-11 membered heterospirocycloalkyl and C_{3-6}cycloalkyl;

B is selected from the group consisting of phenyl, C_{5-10}cycloalkyl, 4-7 membered heterocyclyl, 4-10 membered heteroaryl and C_{6-11} spirocycloalkyl;

X is either absent or is selected from the group consisting of O, S and NR^6C_{1-4}alkylene;

wherein R^6 is independently H or C_{1-3}alkyl;

Y is either absent or is selected from the group consisting of O, S, C_{1-4}alkylene and NR^7C_{1-4}alkylene;

wherein R^7 is independently H or C_{1-3}alkyl;

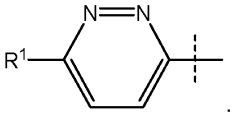
R^8 is independently H or C_{1-3}alkyl;

m is 0, 1 or 2;

n is 0, 1 or 2; and

o is 0, 1, 2, 3 or 4;

or a salt and/or solvate thereof.

3. The compound or a salt and/or solvate of a compound of formula (I) according to claim 1 or claim 2 wherein D is 

.

4. The compound or a salt and/or solvate thereof according to any one of claims 1 to 3 wherein R^1 is H.

5. The compound or a salt and/or solvate thereof according to any one of claims 1 to 3 wherein R^1 is Cl.

6. The compound or a salt and/or solvate thereof according to any one of claims 1 to 5 wherein R^2 is H.

7. The compound or a salt and/or solvate thereof according to any one of claims 1 to 5 wherein R^2 is C_{1-4} alkyl, e.g. methyl.

8. The compound or a salt and/or solvate thereof according to any one of claims 1 to 5 wherein R^2 is C_{1-4} alkoxy.

9. The compound or a salt and/or solvate thereof according to any one of claims 1 to 5 wherein R^2 is $NR^{2a}R^{2b}$.

10. The compound or a salt and/or solvate thereof according to claim 9 wherein R^{2a} and R^{2b} are both methyl.

11. The compound or a salt and/or solvate thereof according to any one of claims 1 to 5 wherein R^2 is C_{0-3}alkyleneC_{3-6}cycloalkyl.

12. The compound or a salt and/or solvate thereof according to claim 11 wherein R^2 is selected from the group consisting of cyclopropyl, CH_2-cyclopropyl and cyclobutyl.

13. The compound or a salt and/or solvate thereof according to any one of claims 1 to 12 wherein R^3 is halo.

14. The compound or a salt and/or solvate thereof according to any one of claims 1 to 12 wherein R^3 is hydroxy.

15. The compound or a salt and/or solvate thereof according to any one of claims 1 to 12 wherein R^3 is C_{1-4} alkyl e.g., methyl, ethyl or isopropyl.

16. The compound or a salt and/or solvate thereof according to any one of claims 1 to 12 wherein R^3 is C_{1-4} haloalkoxy.

17. The compound or a salt and/or solvate thereof according to any one of claims 1 to 16 wherein R^4 is halo.

18. The compound or a salt and/or solvate thereof according to any one of claims 1 to 16 wherein R^4 is hydroxy.

19. The compound or a salt and/or solvate thereof according to any one of claims 1 to 16 wherein R^4 is C_{1-4} alkyl.

20. The compound or a salt and/or solvate thereof according to any one of claims 1 to 16 wherein R^4 is C_{1-4} alkoxy.

21. The compound or a salt and/or solvate thereof according to any one of claims 1 to 16 wherein R^4 is C_{1-4} haloalkyl.

22. The compound or a salt and/or solvate thereof according to any one of claims 1 to 16 wherein R^4 is C_{1-4} haloalkoxy.

23. The compound or a salt and/or solvate thereof according to any one of claims 1 to 16 wherein R^4 is CO_2R^{4a}.

24. The compound or a salt and/or solvate thereof according to any one of claims 1 to 16 wherein R^4 is SC_{1-4}alkyl.

25. The compound or a salt and/or solvate thereof according to any one of claims 1 to 16 wherein R^4 is OC_{3-6}cycloalkyl.

26. The compound or a salt and/or solvate thereof according to any one of claims 1 to 16 wherein R^4 is selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and C_{1-4} haloalkoxy.

27. The compound or a salt and/or solvate thereof according to any one of claims 1 to 26 wherein R^5 is H.

28. The compound or a salt and/or solvate thereof according to any one of claims 1 to 27 wherein A is a 4-10 membered heterocyclyl.

29. The compound or a salt and/or solvate thereof according to any one of claims 1 to 28 wherein B is phenyl.

30. The compound or a salt and/or solvate thereof according to claim 29, wherein two R^4 groups which are attached to adjacent carbon atoms join to form a C_{4-7}cycloalkyl ring.

31. The compound or a salt and/or solvate thereof according to any one of claims 1 to 28 wherein B is 4-10 membered heteroaryl.

32. The compound or a salt and/or solvate thereof according to any one of claims 1 to 31 wherein X is absent.

33. The compound or a salt and/or solvate thereof according to any one of claims 1 to 32 wherein Y is C_{1-4}alkylene e.g. CH_2.

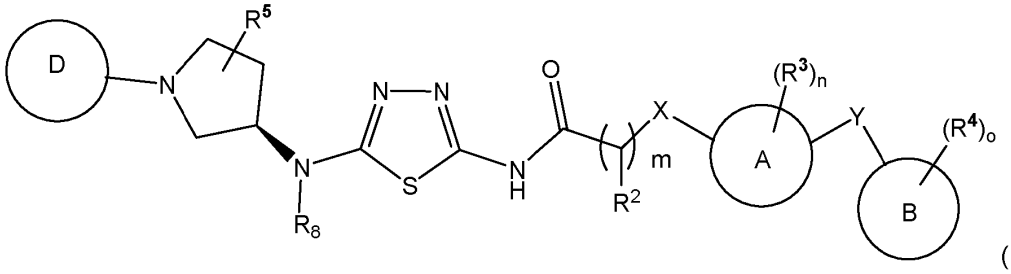
34. The compound or a salt and/or solvate thereof according to any one of claims 1 to 33 wherein R^8 is H.

35. The compound or a salt and/or solvate thereof according to any one of claims 1 to 34 wherein n is 0 and m is 1.

36. The compound or a salt and/or solvate thereof according to any one of claims 1 to 35 wherein o is 1.

37. The compound or a salt and/or solvate thereof according to any one of claims 1 to 35 wherein o is 2.

38. The compound or a salt and/or solvate of a compound of formula (I) according to any one of claims 1 to 37 which is a compound of formula (IA):



(IA)

wherein each of R^2, R^3, R^4, R^4, R^5, R^8, m, n, o, X, Y, A, B and D is as defined in any one of claims 1 to 37;
or a salt and/or solvate thereof.

39. A compound according to claim 1 which is selected from the list consisting of:
(*R*)-3-(4-((2-isopropoxyphenyl)thio)piperidin-1-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;
(*R*)-2-(1-(methyl(3-(trifluoromethoxy)benzyl)amino)cyclobutyl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(*R*)-3-(4-((3,5-difluorophenyl)thio)piperidin-1-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;

(*R*)-3-(4-(2-isopropoxyphenyl)piperidin-1-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;

(*R*)-2-(2-(2-(isopropylthio)benzyl)-2,6-diazaspiro[3.4]octan-6-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(4-(2-methylbenzyl)thiomorpholin-2-yl)-*N*-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(*R*)-2-(2-(3,5-dimethylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(*R*)-2-(2-(2-(isopropylthio)benzyl)-2,8-diazaspiro[4.5]decan-8-yl)-*N*-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl *N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamate;

2-{1-[(4-methoxy-3,5-dimethylphenyl)methyl]piperidin-4-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(4-{[4-(trifluoromethoxy)phenyl]methyl}piperazin-1-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetamide;

(3*R*)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-1-{[4-(trifluoromethoxy) phenyl]methyl}piperidine-3-carboxamide;

(3*S*)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-1-{[4-(trifluoromethoxy) phenyl]methyl}piperidine-3-carboxamide;

(3*S*)-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-1-{[3-(trifluoromethoxy) phenyl]methyl}piperidine-3-carboxamide;

(3*R*)-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-1-{[3-(trifluoromethoxy) phenyl]methyl}piperidine-3-carboxamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*S*)-1-{[3-(trifluoromethoxy)phenyl] methyl}piperidin-3-yl]acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)propanamide;

(*R*)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)propanamide;

(*S*)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)propanamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3R)-1-{[4-(trifluoromethoxy)phenyl] methyl}piperidin-3-yl]acetamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*R*)-1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-3-yl]acetamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3S)-1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-3-yl]acetamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[5-(trifluoromethyl)pyridin-3-yl]methyl}piperidin-4-yl)propanamide;
2-(4-methyl-1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(4-{[4-(trifluoromethoxy)phenyl]methyl}-1,4-diazepan-1-yl)acetamide
2-(4-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperazin-1-yl)-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{3-benzyl-3-azaspiro[5.5]undecan-9-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-(1-{[4-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-(1-{[6-methyl-4-(trifluoromethyl)pyridin-2-yl]methyl}piperidin-4-yl)-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{1-[(3,5-dimethylphenyl)methyl]piperidin-4-yl}-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-{[3-(difluoromethoxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*R*,5*S*)-3,5-dimethyl-4-{[4-(trifluoromethoxy)phenyl]methyl}piperazin-1-yl]-N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
3-[(4-{[(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamoyl]methyl}piperidin-1-yl)methyl]benzoic acid;
4-[(4-{[(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)carbamoyl]methyl}piperidin-1-yl)methyl]benzoic acid;
2-(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(dimethylamino)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)acetamide;

2-(1-{[4-(difluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*R*)-1-{[3-(trifluoromethoxy)phenyl]methyl}pyrrolidin-3-yl]acetamide;

2-[(3*S*)-1-[(4,4-dimethylcyclohexyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3*S*)-1-{[3-(trifluoromethoxy)phenyl]methyl} pyrrolidin-3-yl]acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(5-{[5-(trifluoromethyl)pyridin-3-yl]methyl}-5-azaspiro[2.5]octan-7-yl)acetamide;

2-(5-{[5-methoxy-6-(trifluoromethyl)pyridin-2-yl]methyl}-5-azaspiro[2.5]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)sulfanyl]acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)sulfanyl]acetamide;

2-[(3*S*)-1-[(3-chlorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(6-{[3-(difluoromethoxy)phenyl]methyl}-6-azaspiro[3.4]octan-2-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-{3-[(4,6-dimethylpyridin-2-yl)methyl]-3-azaspiro[5.5]undecan-9-yl}-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-{4-[(4,4-dimethylcyclohexyl)methyl]piperazin-1-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-{1-[(3,3,5,5-tetramethylcyclohexyl)methyl] piperidin-4-yl}acetamide;

2-(2-{[3-(difluoromethoxy)phenyl]methyl}-2-azaspiro[3.3]heptan-6-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-{1-[(4,4-dimethylcyclohexyl)methyl]piperidin-4-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

3-(1-{[3-(difluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)propanamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-8-{[3-(trifluoromethoxy)phenyl]methyl}-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-{4-[(3,3,5,5-tetramethylcyclohexyl)methyl]piperazin-1-yl}acetamide;
2-{1-[methyl({[3-(trifluoromethoxy)phenyl]methyl})amino]cyclopropyl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-(1-{[4-hydroxy-3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{1-[(2-chlorophenyl)methyl]piperidin-4-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-(4-methyl-1-{[3-(trifluoromethoxy)phenyl]methyl}piperazin-2-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-4-methyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*R*)-4-methyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-methoxy-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[4-(trifluoromethoxy)phenyl] methyl}piperidin-4-yl)acetamide;
(*R*)-2-methoxy-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)acetamide;
(*S*)-2-methoxy-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)acetamide;
4-[(4,4-dimethylcyclohexyl)methyl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)thiomorpholine-2-carboxamide;
2-{4-[(4,4-dimethylcyclohexyl)methyl]morpholin-2-yl}-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-((*R*)-4-((4,4-dimethylcyclohexyl)methyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-4-((4,4-dimethylcyclohexyl)methyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-(1-{[3-(propan-2-yloxy)pyridin-2-yl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(1-{[3-(trifluoromethoxy)phenyl]methyl}azetidin-3-yl)acetamide;
2-(1-{[2-(difluoromethoxy)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-(4-{[3-(propan-2-yloxy)pyridin-2-yl]methyl}-4-azaspiro[2.5]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-({1-[(3,5-dimethylphenyl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(2-{[3-(trifluoromethoxy)phenyl]methyl}-6-oxa-2-azaspiro[3.4]octan-7-yl)acetamide;

N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-2-(3-(trifluoromethoxy)benzyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)acetamide;

N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-2-(3-(trifluoromethoxy)benzyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)acetamide;

2-(2-{[3-(difluoromethoxy)phenyl]methyl}-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(2,2-dimethyl-1-{[3-(propan-2-yloxy)pyridin-2-yl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(2-{[2-(cyclopentyloxy)phenyl]methyl}-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-[(2-cyclobutoxyphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-{[2-(cyclopentyloxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-({1-[(2-cyclobutoxyphenyl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(4-cyclohexylmorpholin-2-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-{[2-(3,3-difluorocyclobutoxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(4-cyclopentylmorpholin-2-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(2-{[2-(propan-2-ylsulfanyl)phenyl]methyl}-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide

2-(1-{[(4,4-dimethylcyclohexyl)methyl](methyl)amino}cyclopropyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(4-hydroxy-1-{[2-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-4-yl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-{4-[(4,4-dimethylcyclohexyl)methyl]-1,4-diazepan-1-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-({1-[(3-tert-butyl-1,2-oxazol-5-yl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-{2-[(4,4-dimethylcyclohexyl)methyl]-6-oxa-2-azaspiro[3.4]octan-7-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-((*R*)-2-((4,4-dimethylcyclohexyl)methyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-2-((4,4-dimethylcyclohexyl)methyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[(1-{[2-(propan-2-yloxy)phenyl] methyl}piperidin-3-yl)sulfanyl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(((*R*)-1-(2-isopropoxybenzyl)piperidin-3-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(((*S*)-1-(2-isopropoxybenzyl)piperidin-3-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[(1-{[2-(methylsulfanyl)phenyl]methyl}piperidin-3-yl)oxy]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(((*R*)-1-(2-(methylthio)benzyl)piperidin-3-yl)oxy)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(((*S*)-1-(2-(methylthio)benzyl)piperidin-3-yl)oxy)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[(1-{[2-(propan-2-ylsulfanyl)phenyl]methyl}piperidin-3-yl)oxy]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(((*R*)-1-(2-(isopropylthio)benzyl)piperidin-3-yl)oxy)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(((*S*)-1-(2-(isopropylthio)benzyl)piperidin-3-yl)oxy)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[4-(4,4-dimethylcyclohexyl)morpholin-2-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-4-(4,4-dimethylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*R*)-4-(4,4-dimethylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[(2-{[2-(propan-2-yloxy)phenyl]methyl}-2-azaspiro[3.3]heptan-6-yl)sulfanyl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-[(3,5-dimethylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(1-{[2-(propan-2-yloxy)phenyl]methyl}piperidin-4-yl)sulfanyl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)butanamide;

N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-{4-[(1s,4s)-4-tert-butylcyclohexyl]morpholin-2-yl}acetamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-{4-[(1r,4r)-4-tert-butylcyclohexyl]morpholin-2-yl}acetamide;
2-[(3*S*)-1-[(4-ethyl-2-fluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[4-(3,3,4,4-tetramethylcyclopentyl)morpholin-2-yl]acetamide;
2-[(3*R*)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(4-fluoro-3,5-dimethylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(3-fluoro-5-methylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(4-fluoro-3-methoxy-5-methylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(4-ethoxy-3,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-{[3-fluoro-5-(propan-2-yloxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{3-[(5-ethyl-3-methyl-1,2-oxazol-4-yl)methyl]-3-azaspiro[5.5]undecan-9-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-{[3-methyl-5-(propan-2-yloxy)phenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{4-[(1*S*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]morpholin-2-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{(*R*)-4-[(1*S*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]morpholin-2-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-{(*S*)-4-[(1*S*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]morpholin-2-yl}-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(3-ethoxy-4,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(3-fluoro-5-methoxy-4-methylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-{[3-(difluoromethoxy)-5-methylphenyl]methyl}piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(3*S*)-1-[(2-ethyl-1-benzofuran-3-yl)methyl]piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(3-fluoro-4,5-dimethylphenyl)methyl]piperidin-3-yl]-*N*-(5-{[(*3R)*-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(2,5-dimethylthiophen-3-yl)methyl]piperidin-3-yl]-*N*-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-({1-[(2,5-dimethylthiophen-3-yl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[(3*S*)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]-*N*-(5-{methyl[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[4-(4,4-dimethylcyclohexyl)morpholin-2-yl]-*N*-(5-{methyl[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[4-(4,4-dimethylcyclohexyl)piperazin-1-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-({1-[(1-tert-butyl-1H-pyrrol-3-yl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-({1-[(1-tert-butyl-1H-pyrazol-4-yl)methyl]piperidin-4-yl}sulfanyl)-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[4-(3,3,5,5-tetramethylcyclohexyl)piperazin-1-yl]acetamide;
N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(4-{spiro[4.5]decan-8-yl}piperazin-1-yl)acetamide;
2-(4,4-difluoro-1-{spiro[2.5]octan-6-yl}piperidin-3-yl)-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-(1-cyclohexyl-4,4-difluoropiperidin-3-yl)-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[1-(4,4-dimethylcyclohexyl)-4,4-difluoropiperidin-3-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-[4-(4,4-diethylcyclohexyl)morpholin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;
2-((R)-4-(4,4-diethylcyclohexyl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((S)-4-(4,4-diethylcyclohexyl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-(((R)-1-(1,2,4-triazin-6-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(4,4-dimethylcyclohexyl)morpholin-2-yl)acetamide;

N-(5-{[(3R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-[(3S)-1-[(3,5-difluorophenyl)methyl]piperidin-3-yl]acetamide;

2-[4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(*R*)-4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(*S*)-4-(2-cyclohexylpropan-2-yl)morpholin-2-yl]-*N*-(5-{[(3*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-(1-cycloheptyl-4,4-difluoropiperidin-3-yl)-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

isopropyl (R)-4-((4-(2-oxo-2-((5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)piperidin-1-yl)methyl)benzoate;

isopropyl (R)-3-((4-(2-oxo-2-((5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)piperidin-1-yl)methyl)benzoate;

(R)-2-(1-(3-methyl-5-(trifluoromethoxy)benzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(2,4,6-trimethylbenzyl)piperidin-4-yl)acetamide;

(R)-2-(1-(2-methyl-4-(trifluoromethoxy)benzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(1-(3-methyl-4-(trifluoromethyl)benzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-((5-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-yl)acetamide;

(R)-2-(1-((5-methoxy-6-(trifluoromethyl)pyridin-2-yl)methyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((S)-1-(3-methyl-5-(trifluoromethoxy)benzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(1-(3-(difluoromethoxy)-5-methylbenzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

isobutyl (R)-4-((4-(2-oxo-2-((5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)ethyl)piperidin-1-yl)methyl)picolinate;

(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(1-(2-(trifluoromethoxy)benzyl)piperidin-4-yl)acetamide;

(R)-2-(1-(4-fluoro-2-(trifluoromethoxy)benzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(1-(2-(difluoromethoxy)-5-methylbenzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(1-(2-(isopropylthio)benzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-((1-(2-isopropoxybenzyl)piperidin-4-yl)thio)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(1-(3-isopropoxybenzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(1-(2-cyclobutoxybenzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(1-(2-isopropoxy-4-methylbenzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(2-(3-(difluoromethoxy)benzyl)-2-azaspiro[3.5]nonan-7-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(2-(3-(trifluoromethoxy)benzyl)-2-azaspiro[3.3]heptan-6-yl)acetamide;
2-((S)-1-(2-isopropoxybenzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((R)-1-(2-isopropoxybenzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((S)-1-(2-isopropoxyphenethyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((R)-1-(2-isopropoxyphenethyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
8-(3,5-dimethylbenzyl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
8-(2-isopropoxybenzyl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
(R)-2-(3-((6-(difluoromethyl)pyridin-3-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(3-((5-(trifluoromethyl)pyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)acetamide;
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(3-((2,4,6-trimethylpyridin-3-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)acetamide;
(R)-2-(3-((5-chloropyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(3-((5-bromopyridin-3-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(6-(3-(trifluoromethoxy)benzyl)-6-azaspiro[3.4]octan-2-yl)acetamide;
N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((2r,4R)-6-(3-(trifluoromethoxy)benzyl)-6-azaspiro[3.4]octan-2-yl)acetamide;
N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((2s,4S)-6-(3-(trifluoromethoxy)benzyl)-6-azaspiro[3.4]octan-2-yl)acetamide;
(R)-2-(6-(3-(difluoromethoxy)-5-methylbenzyl)-6-azaspiro[3.4]octan-2-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(6-(2-isopropoxy-4-methylbenzyl)-6-azaspiro[3.4]octan-2-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((2r,4R)-6-(2-isopropoxy-4-methylbenzyl)-6-azaspiro[3.4]octan-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((2s,4S)-6-(2-isopropoxy-4-methylbenzyl)-6-azaspiro[3.4]octan-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
8-(3-(difluoromethoxy)benzyl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
(*R*)-8-(3-(difluoromethoxy)benzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
(*S*)-8-(3-(difluoromethoxy)benzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
(R)-2-(3-((3-cyclobutoxypyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-(1-(3,5-dimethylbenzyl)piperidin-4-yl)-2-methoxy-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-(1-(2-cyclobutoxybenzyl)piperidin-4-yl)-2-methoxy-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-(1-(2-(isopropylthio)benzyl)piperidin-4-yl)-2-methoxy-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(3-((5-chloropyridin-3-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(3-((4-bromopyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(3-((5-bromopyridin-2-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(4-ethyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*R*)-4-ethyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-4-ethyl-1-(3-(trifluoromethoxy)benzyl)piperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-(1-(2-isopropoxybenzyl)piperidin-4-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide;
(*R*)-2-(1-(2-isopropoxybenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide;
(*S*)-2-(1-(2-isopropoxybenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide;
(R)-3-(1-(2-isopropoxybenzyl)piperidin-4-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;
(R)-2-((1-(2-(isopropylthio)benzyl)piperidin-4-yl)oxy)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
8-(2-cyclobutoxybenzyl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
(*R*)-8-(2-cyclobutoxybenzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
(*S*)-8-(2-cyclobutoxybenzyl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-oxa-8-azaspiro[4.5]decane-3-carboxamide;
2-((*R*)-2-(2-(isopropylthio)benzyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-2-(2-(isopropylthio)benzyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-cyclobutyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(*R*)-2-cyclobutyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(*S*)-2-cyclobutyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
3-cyclopropyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;
(*R*)-3-cyclopropyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;

(*S*)-3-cyclopropyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)propanamide;

3-methyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide;

(*R*)-3-methyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide;

(*S*)-3-methyl-2-(1-(2-methylbenzyl)piperidin-4-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)butanamide;

2-(4-cyclohexylmorpholin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*R*)-4-cyclohexylmorpholin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-4-cyclohexylmorpholin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[4-(4,4-dimethylcyclohexyl)-1,4-oxazepan-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(1-(4-(difluoromethoxy)benzyl)piperidin-4-yl)-2-ethoxy-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(S)-2-(1-(4-(difluoromethoxy)benzyl)piperidin-4-yl)-2-ethoxy-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((1-(1-(2-isopropoxyphenyl)ethyl)piperidin-4-yl)thio)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((1-((*R*)-1-(2-isopropoxyphenyl)ethyl)piperidin-4-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((1-((*S*)-1-(2-isopropoxyphenyl)ethyl)piperidin-4-yl)thio)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((S)-1-(3,5-difluoro-4-methylbenzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((S)-1-(3,5-difluoro-2-methylbenzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(1-(3,5-difluorobenzyl)azepan-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(methyl(2-(1-(3-(trifluoromethoxy)benzyl)piperidin-4-yl)propan-2-yl)amino)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-(4-((4,4-dimethylcyclohexyl)methyl)thiomorpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((3S)-1-(1-(3,5-difluorophenyl)ethyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-1-((*S*)-1-(3,5-difluorophenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-1-((*R*)-1-(3,5-difluorophenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-(4-(4-isopropylcyclohexyl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-4-((1*r*,4*S*)-4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*R*)-4-((1*r*,4*R*)-4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-4-((1*s*,4*R*)-4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*R*)-4-((1*s*,4*S*)-4-isopropylcyclohexyl)morpholin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(2-(3-fluoro-5-methylbenzyl)-2,6-diazaspiro[3.4]octan-6-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*R*)-1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-1-(3-(difluoromethoxy)benzyl)-4-isopropylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[2.5]octan-6-yl)morpholin-2-yl)acetamide;
N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((S)-4-(spiro[2.5]octan-6-yl)morpholin-2-yl)acetamide;
N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((R)-4-(spiro[2.5]octan-6-yl)morpholin-2-yl)acetamide;
N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[3.5]nonan-2-yl)morpholin-2-yl)acetamide;
N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-4-(spiro[3.5]nonan-2-yl)morpholin-2-yl)acetamide;
N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-4-(spiro[3.5]nonan-2-yl)morpholin-2-yl)acetamide;
(R)-2-(8-(2-(isopropylthio)benzyl)-2,8-diazaspiro[4.5]decan-2-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((S)-1-(4-ethyl-3-fluorobenzyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((3S)-1-(1-(3-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-1-((*S*)-1-(3-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-1-((*R*)-1-(3-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((3S)-1-(1-(2-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-1-((*S*)-1-(2-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
2-((*S*)-1-((*R*)-1-(2-fluoro-4-methylphenyl)ethyl)piperidin-3-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[3.4]octan-2-yl)morpholin-2-yl)acetamide;
N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-4-(spiro[3.4]octan-2-yl)morpholin-2-yl)acetamide;
N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-4-(spiro[3.4]octan-2-yl)morpholin-2-yl)acetamide;
(R)-2-(2-(3-fluoro-5-methylbenzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(2-(2-(methylthio)benzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(2-(2-(isopropylthio)benzyl)-2,6-diazaspiro[3.5]nonan-6-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[4.5]decan-8-yl)morpholin-2-yl)acetamide;
N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*R*)-4-(spiro[4.5]decan-8-yl)morpholin-2-yl)acetamide;
N-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((*S*)-4-(spiro[4.5]decan-8-yl)morpholin-2-yl)acetamide;
N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(spiro[3.5]nonan-7-yl)morpholin-2-yl)acetamide;
N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((R)-4-(spiro[3.5]nonan-7-yl)morpholin-2-yl)acetamide;

N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((S)-4-(spiro[3.5]nonan-7-yl)morpholin-2-yl)acetamide;

tert-butyl 4-(((S)-3-(2-((5-(((R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)amino)-2-oxoethyl)piperidin-1-yl)methyl)piperidine-1-carboxylate;

2-(4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*R*)-4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((*S*)-4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)-*N*-(5-(((*R*)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((R)-4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((S)-4-((4,4-dimethylcyclohexyl)methyl)-1-methylpiperazin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-(((R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(4,4-dimethylcyclohexyl)morpholin-2-yl)acetamide;

N-(5-(((R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((S)-4-(4,4-dimethylcyclohexyl)morpholin-2-yl)acetamide;

N-(5-(((R)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-((R)-4-(4,4-dimethylcyclohexyl)morpholin-2-yl)acetamide;

2-(4-(2,4-dimethylpentan-3-yl)morpholin-2-yl)-N-(5-(((R)-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-((S)-1-(3,5-difluorobenzyl)piperidin-3-yl)-N-(5-(((3S,4S)-4-fluoro-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

2-[4-(4,4-dimethylcyclohexyl)-1-methylpiperazin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(R)-4-(4,4-dimethylcyclohexyl)-1-methylpiperazin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[(S)-4-(4,4-dimethylcyclohexyl)-1-methylpiperazin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

2-[4-(4,4-dimethylcyclohexyl)thiomorpholin-2-yl]-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)-2-(4-{spiro[4.5]decan-8-yl}thiomorpholin-2-yl)acetamide;

2-(4-{bicyclo[2.2.2]octan-1-yl}morpholin-2-yl)-N-(5-{[(3R)-1-(pyridazin-3-yl)pyrrolidin-3-yl]amino}-1,3,4-thiadiazol-2-yl)acetamide;

(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(3-(trifluoromethoxy)benzyl)piperazin-1-yl)acetamide;
(R)-N-(5-((1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(4-(trifluoromethoxy)benzyl)piperazin-1-yl)acetamide;
(R)-2-(4-(2-chloro-4-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-chloro-5-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(2-(trifluoromethoxy)benzyl)piperazin-1-yl)acetamide;
(R)-2-(4-(3-fluoro-4-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-bromo-5-fluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-methoxy-4-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(4-chloro-3-fluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-chloro-5-fluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3,4-difluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3,5-difluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3,5-difluoro-4-methoxybenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
N-(5-(((3S,4S)-4-fluoro-1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)-2-(4-(4-(trifluoromethoxy)benzyl)piperazin-1-yl)acetamide;
(R)-2-(4-(2-chloro-5-(trifluoromethoxy)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-chloro-4-(trifluoromethoxy)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-(difluoromethoxy)-4-methylbenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
((R)-2-(4-(3,5-dichloro-4-methylbenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;

(R)-2-(4-(2,4-dichloro-6-fluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(5-fluoro-2-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(3-fluoro-5-(trifluoromethyl)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-((7-fluoro-2,3-dihydro-1H-inden-5-yl)methyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(5-chloro-2-(difluoromethoxy)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
(R)-2-(4-(2,3-difluorobenzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide; and
(R)-2-(4-(3-difluoromethoxy)benzyl)piperazin-1-yl)-N-(5-((1-(pyridazin-3-yl)pyrrolidin-3-yl)amino)-1,3,4-thiadiazol-2-yl)acetamide;
or a salt and/or solvate of any one thereof such as a pharmaceutically acceptable salt and/or solvate thereof.

40. The compound or a salt and/or solvate thereof according to any one of claims 1 to 39 which is a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof.

41. The pharmaceutically acceptable salt and solvate according to claim 40.

42. The pharmaceutically acceptable salt according to claim 40.

43. The pharmaceutically acceptable solvate according to claim 40.

44. The compound according to any one of claims 1 to 39.

45. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 40 to 44 and one or more pharmaceutically acceptable diluents or carriers.

46. A compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 40 to 44 or a pharmaceutical composition according to claim 45 for use as a medicament.

47. A compound or a pharmaceutically acceptable salt and/or solvate thereof according to any

one of claims 40 to 44 or a pharmaceutical composition according to claim 45 for use in treating or preventing fibrotic and/or inflammatory diseases.

48. Use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 40 to 44 or a pharmaceutical composition according to claim 45 in the manufacture of a medicament for treating or preventing fibrotic and/or inflammatory diseases.

49. A method of treating or preventing fibrotic and/or inflammatory diseases which comprises administering of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 40 to 44, or a pharmaceutical composition according to claim 45.

50. The compound or pharmaceutically acceptable salt and/or solvate thereof for use according to claim 47, the pharmaceutical composition for use according to claim 47, use according to claim 48 or the method according to claim 49, wherein the fibrotic and/or inflammatory disease is a fibrotic and/or inflammatory disease of the lung.

51. The compound or pharmaceutically acceptable salt and/or solvate thereof for use according to claim 47, the pharmaceutical composition for use according to claim 47, use according to claim 48 or the method according to claim 49, wherein the fibrotic and/or inflammatory disease is an interstitial lung disease.

52. The compound or pharmaceutically acceptable salt and/or solvate thereof for use, pharmaceutical composition for use, use or method according to claim 51, wherein the interstitial lung disease is selected from the group consisting of idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, lung cancer, radiation induced fibrosis, pulmonary hypertension, asthma, respiratory viral infection and long covid.

53. The compound or pharmaceutically acceptable salt and/or solvate thereof for use according to claim 47, the pharmaceutical composition for use according to claim 47, use according to claim 48 or the method according to claim 49, wherein the fibrotic and inflammatory disease is selected from the group consisting of diabetes, non-alcoholic fatty liver disease/cirrhosis, chronic kidney disease, osteoporosis, osteoarthritis and obesity.

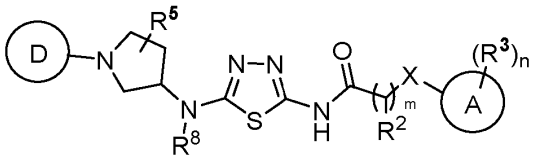
54. The compound or pharmaceutically acceptable salt and/or solvate thereof for use according to claim 47, the pharmaceutical composition for use according to claim 47, use

according to claim 48 or the method according to claim 49, wherein the fibrotic disease is fibrosis or non-alcoholic steatohepatitis.

55. The compound or pharmaceutically acceptable salt and/or solvate thereof for use according to claim 47, the pharmaceutical composition for use according to claim 47, use according to claim 48 or the method according to claim 49, wherein the inflammatory disease is selected from the group consisting of inflammation psoriasis, psoriatic arthritis, hidradenitis suppurativa, rheumatoid arthritis, ankylosing spondylitis and inflammatory bowel disease.

56. A compound selected from the group consisting of:

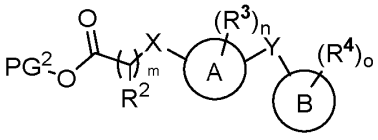
- a compound of formula (XII):



(XII);

wherein R^2, R^3, R^5, R^8, m, n, X, A and D are as in any one of claims 1 to 39 and;

- a compound of formula (XVI):



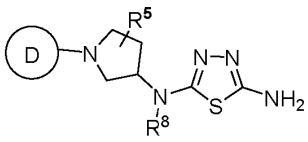
(XVI);

wherein R^2, R^3, R^4, m, n, o, X, Y, A and B are as in any one of claims 1 to 39, and PG^2 is a carboxylic acid protecting group such as methyl or benzyl;

or a salt, such as a pharmaceutically acceptable salt thereof of any one thereof.

57. A process for the preparation of a compound of formula (I), or a salt such as a pharmaceutically acceptable salt thereof, which comprises:

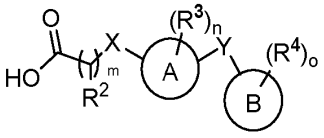
(a) reacting a compound of formula (III):



(III)

or a salt such as a pharmaceutically acceptable salt thereof;

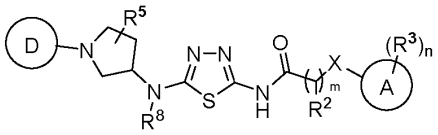
with a compound of formula (II):


(II);

or a salt such as a pharmaceutically acceptable salt thereof;

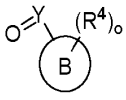
wherein R^2, R^3, R^4, R^5, R^8, m, n, o, X, Y, A and B are as defined in any one of claims 1 to 39;

(b) reacting a compound of formula (XII):


(XII);

or a salt such as a pharmaceutically acceptable salt thereof;

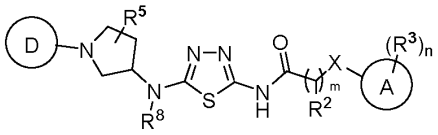
with a compound of formula (XI):


(XI)

or a salt such as a pharmaceutically acceptable salt thereof;

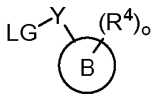
wherein R^2, R^3, R^4, R^5, R^8, m, n, o, X, Y, A and B are as defined in any one of claims 1 to 39; or

(c) reacting a compound of formula (XII):


(XII);

or a salt such as a pharmaceutically acceptable salt thereof;

with a compound of formula (XI):


(XV)

or a salt such as a pharmaceutically acceptable salt thereof;

wherein R^2, R^3, R^4, R^5, R^8, m, n, o, X, Y, A and B are as defined in any one of claims 1 to 39

and LG is a leaving group such as halo e.g. chloro.