TETRAHYDROISOQUINOLINE COMPOUNDS AS NRF2 ACTIVATORS

INTRODUCTION

[0001] The present invention relates to tetrahydroisoquinoline compounds. More specifically, the present invention relates to tetrahydroisoquinoline compounds that are Nrf2 activators. The present invention also relates to processes for the preparation of these compounds, to pharmaceutical compositions comprising them, and to their use in the treatment of diseases or disorders associated with Nrf2 activation and/or inhibition of Keap1-Nrf2 protein-protein interactions.

BACKGROUND OF THE INVENTION

[0002] Nuclear factor erythroid 2-related factor 2 (Nrf2) is a basic leucine zipper (bZIP) transcription factor and a member of the Cap 'n' Collar (CNC) family of transcription factors. It is a key master of the inducible cell defence system, mediating the expression of more than 100 oxidative stress-related genes that include phase I and II detoxification enzymes and antioxidant proteins. These genes all contain the antioxidant response element (ARE) in their promoter regulatory regions, which is the binding target of Nrf2. Under basal conditions the levels of Nrf2 are tightly regulated by the adaptor protein Keap1, a cytosolic actin-bound repressor protein, which binds to Nrf2 and leads to proteasomal degradation *via* the Cul3-based E3 ubiquitin ligase complex. Under conditions of oxidative stress, Keap1 is inactivated leading to an increase in the level of *de novo* synthesised Nrf2 which translocates to the nucleus, binds to AREs with a resulting up-regulation in cytoprotective gene expression.

[0003] It has been shown that Nrf2 mRNA expression in COPD subjects was significantly lower than that in control subjects and Nrf2 mRNA were negatively correlated with pack year. Nrf2 protein in COPD subjects was significantly lower than that in control subjects. CSE-induced A549 cell apoptosis was increased in a time-dependent and concentration-dependent manner, and was significantly increased by Nrf2 knockdown (Yamada, *BMC Pulmonary Medicine*, doi:10.1186/s12890-016-0189-1). Therefore, elevation of Nrf2 levels in the lungs of COPD patients should lead to a reduction in the inflammatory processes that lead to deleterious structural modifications of the lung and slow disease progression. Nrf2 may also be expected to show positive benefits in other respiratory diseases that exhibit oxidative stress components (Cho, *Toxicol Appl Pharmacol*, doi: 10.1016/j.taap.2009.07.024) such as acute, chronic and severe asthma (Sussan, *Am J Physiol Lung Cell Mol Physiol*, doi:10.1152/ajplung.00398.2014), acute lung injury/acute

respiratory distress syndrome, with or without accompanying multi organ dysfunction syndrome (Yan, *Free Radical Biol Med*, doi:10.1016/j.freeradbiomed.2018.04.557; de la Vega *Curr Pharmacol Rep*, doi:10.1007/s40495-016-0053-2), pulmonary fibrosis, including idiopathic pulmonary fibrosis (Kikuchi, *Respir Res*, doi:10.1186/1465-9921-11-31) and cystic fibrosis (Chen, *PLoS One,* doi:10.1371/journal.pone.0003367). Indeed, the combination of cytoprotection by restoring redox and protein homeostasis, promoting resolution of inflammation, and facilitating repair in the lungs by Nrf2 activators has highlighted their potential for the treatment of COVID-19 (Cuadrado et al, Trends Pharmacol Sci, doi:10.1016/j.tips.2020.07.003).

[0004] The cardiac protective nature of Nrf2 in models of atherosclerosis, ischaemia, reperfusion, cardiac hypertrophy and heart failure has been demonstrated (Chen, *Physiol Genomics,* doi:10.1152/physiolgenomics.00041.2017). The Nrf2 activator Bardoxolone methyl has recently completed a Phase II study in patients with pulmonary arterial hypertension (PAH), with a Phase III study underway based on a significant improvement in 6 minute walking distance. Bardoxolone reacts covalently with Keap1 but compounds activating Nrf2 *via* alternative mechanisms of Keap1 binding should also be expected to be therapeutically useful in PAH, particularly in patients that also have an underlying connective tissue disorder (CTD), such as scleroderma or lupus erythematosus. Oxidative stress is elevated in the diseased myocardium, leading to raised levels of reactive oxygen species which impact negatively on cardiac function (Bolli, *Circ*, doi: 10.1161/circ.76.2.3111744). Nrf2 activation has been shown to suppress myocardial oxidative stress, cardiac apoptosis, hypertrophy, fibrosis and dysfunction in mouse models of pressure overload (Wang, *J Card Failure*, doi:10.1016/j.cardfail.2012.06.003) and to protect against cardiac ischemic/reperfusion injury in rodent models (Zhang, *J Mol Cell Cardiol,* doi:10.1016/j.yjmcc.2010.05.01). Furthermore, excessive production of oxidizing agents in detriment of antioxidant defences in the cardiovascular system has also been described in metabolic diseases such as obesity, metabolic syndrome and diabetes mellitus where activation of Nrf2 has also been suggested as a promising therapeutic strategy (da Costa, *Front Pharmacol.*, doi:10.3389/fphar.2019.00382). In addition, the Nrf2 activator sulforaphane reduces hepatic glucose production and improves glucose control in patients with type 2 diabetes (Axelsson, *Sci Transl Med.,* doi: 10.1126/scitranslmed.aah4477) and bardoxolone methyl has been shown to induce weight loss in generally obese patients in proportion to baseline BMI alongside improving glycaemic control (Chertow et al, J Diabetes Complications, doi: 10.1016/j.jdiacomp.2018.09.005). Age-associated mitochondrial dysfunction and oxidative damage are primary causes for multiple health problems including sarcopenia

and cardiovascular disease and treatment of aging mice with the Nrf2 activator Sulforaphane restored Nrf2 activity, mitochondrial function, cardiac function, exercise capacity, glucose tolerance, and activation/differentiation of skeletal muscle satellite cells (Bose et al, Aging cell, doi:10.1111/acel.13261). Thus, it is expected that drugs leading to activation of Nrf2 should be useful in a number of cardiovascular and metabolic diseases including, but not limited to, atherosclerosis, hypertension, heart failure, myocardial infarction and repair, cardiac remodelling, cardiac arrhythmias, heart failure with reduced ejection fraction, diabetic cardiomyopathy, diabetic nephropathy, metabolic syndrome, obesity, diabetes mellitus (type 1 or type 2) and insulin resistance.

[0005] Subarachnoid haemorrhage (SAH) is a devastating condition with high morbidity and mortality rates due to the lack of effective therapy. Early brain injury (EBI) and cerebral vasospasm (CVS) are the two most important pathophysiological mechanisms for brain injury and poor outcomes for patients with SAH (clinicaltrials.gov/ct2/show/NCT0261474, *SFX01 After Subarachnoid Haemorrhage (SAS)*). Evidence from experimental SAH research indicates a protective role of the Nrf2/ARE pathway in EBI and CVS after SAH. Administration of sulforaphane (SFN) to rats following SAH enhances the activity of the Nrf2-ARE pathway, attenuates vasospasm in basilar arteries and suppresses the release of proinflammatory cytokines (Zhao, *Brain Res.*, doi: 10.1016/j.brainres.2016.09.035). Intracerebral haemorrhage (ICH) is the primary event in 10-15% of the 15 million strokes occurring annually worldwide. *In vitro* studies demonstrated that Nrf2 activators rapidly increased HO-1 expression in astrocytes and reduced their vulnerability to haemoglobin or hemin. Systemic treatment with small molecule Nrf2 activators increased HO-1 expression in perivascular cells, particularly astrocytes. When tested in mouse or rat ICH models, Nrf2 activators were consistently protective, improving barrier function and attenuating edema, inflammation, neuronal loss and neurological deficits (Chen-Roetling, *Curr Pharm Des*, doi:10.2174/1381612822666161027150616). Ischemic stroke induces reactive oxygen species, causing oxidative and inflammatory responses in ischemic brain. To date, recombinant tissue plasminogen activator is the only available therapy for the treatment of ischemic stroke. However, the treatment does not prevent oxidative stress and inflammation in the ischemic brain. D3T, a sulfur-containing dithiolethione compound, is found in cruciferous vegetables and has been reported to induce anti-oxidant genes through activation of Nrf2. D3T has been shown (Yen, *J Immunol* 2017, 198 (1 supplement) 206.20) to attenuate brain infarct and ameliorate neurological deficits in stroke animals. In addition, D3T reduced CNS infiltrating inflammatory immune cells including neutrophils and monocytes in the ischemic brain. Moreover, D3T-induced suppression of inflammatory cytokine production was observed in wild-type but not in Nrf2-

deficient microglia. Furthermore, the protective effect of D3T on the attenuation of ischemic brain infarct was abolished in Nrf2-deficient stroke animals and in the stroke animals administered with HO-1 inhibitor. These results suggest that D3T-mediated suppression of inflammation in the ischemic brain is mediated through Nrf2/HO-1 pathway, and thus that targeting the Nrf2/HO-1 pathway may be a promising therapeutic strategy for the amelioration of neuroinflammation in ischemic stroke.

[0006] Nrf2 is believed to play a key role in some hemoglobinopathies, such as beta-thalassemia and sickle cell disease (SCD). SCD is a recessive inherited disorder caused by a single missense mutation which leads to the mutated beta-globin protein haemoglobin S (HbS). At low oxygen concentrations HbS polymerises, leading to misshapen red blood cells which are prone to rupture, releasing free heme into plasma. The resulting oxidative stress and inflammation leads to damage in multiple organs of the body. Ablation of Keap1 and the resulting constitutive activation of Nrf2 has been shown to lead to improved outcomes in SCD model mice (Zhu, *Blood,* doi:10.1182/blood-2017-10-810531; Keleku-Lukwete *PNAS*, doi:10.1073/pnas.1509158112). Nrf2 activation has been shown to slow down the progression of haemolytic anemia and organ disfunction (Ghosh, *JCI Insight*, doi: 10.1172/jci.insight.81090) and loss of Nrf2 function worsens the pathophysiology of SCD in transgenic SCD mice (Zhu, *Blood*, doi.org/10.1182/blood-2017-10-810531). Global activation of Nrf2 with the known compound D3T reduces lethality in a haem-induced acute chest syndrome model in transgenic SCD mice (Ghosh, *Brit. J. Haematology* doi: 10.1111/bjh.15401). In addition, Nrf2 activators have also been shown to modulate foetal haemoglobin (HbF) expression through direct binding in the gamma-globin promoter and modification of chromatin structure in the beta-globin locus. In sickle erythroid cells, Nrf2 provides unique benefits through HbF induction to inhibit haemoglobin S polymerization and protection against oxidative stress due to chronic haemolysis (Zhu, *Exp Biol Med* doi: 10.1177/1535370219825859). Thus, the development of small molecule activators of Nrf2 has the potential to ameliorate the clinical severity of sickle cell disease and other diseases where increasing HbF is beneficial such as beta-thalassemia.

[0007] The function of Nrf2 is altered in many neurodegenerative disorders, such as Huntington's disease, Parkinson's Disease, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal dementia, multiple sclerosis and Friedreich's ataxia (Dinkova-Kostova, *FEBS*, doi:10.1111/febs.14379). Nrf2 activation mitigates multiple pathogenic processes involved in these neurodegenerative disorders through upregulation of antioxidant defences, inhibition of inflammation, improvement of mitochondrial function, and maintenance of protein homeostasis. Small molecule pharmacological activators of Nrf2 have shown protective effects in numerous animal models of neurodegenerative

diseases (Joshi, *Neurobiol Aging*, doi:10.1016/j.neurobiolaging.2014.09.004; Alarcon-Aguilar, *Neurobiol Aging*, doi:10.1016/j.neurobiolaging.2014.01.143 and in cultures of human cells expressing mutant proteins. Tecfidera (dimethyl fumarate) activates Nrf2 (in addition to other mechanisms) and is approved in the US to treat relapsing-remitting multiple sclerosis. The Nrf2 activator Omaveloxolone (RTA-408) currently in Phase II trials for the treatment of the inherited neurodegenerative disorder Friedrich's ataxia, has met its primary endpoint of change in the modified Friedrich's Ataxia Rating Scale (mFARS) relative to placebo after 48 weeks of treatment. Targeting Nrf2 signalling may therefore provide a therapeutic option to delay onset, slow progression, and ameliorate symptoms of neurodegenerative disorders. Due to the role of oxidative stress and mitochondrial dysfunction in disorders of the CNS, treatment of chronic pain and schizophrenia with Nrf2 activators has also been suggested.

[0008] Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints and is characterized by periods of disease flares and remissions. Multiple joints can be affected sometimes resulting in permanent joint destruction and deformity. Nrf2 has been found to be activated in the joints of arthritic mice and of RA patients. Nrf2-knockout mice have more severe cartilage injuries and more oxidative damage, with the expression of Nrf2 target genes being enhanced in Nrf2-wild-type but not in knockout mice during antibody-induced arthritis (Wruck, *BMJ Annals of Rheumatic Diseases*, doi:10.1136/ard.2010.132720). Additionally, in an animal model of rheumatoid arthritis, using the transfer of serum from K/BxN transgenic mice to Nrf2(-/-) mice, Nrf2 deficiency accelerated the incidence of arthritis, and animals showed a widespread disease affecting both front and hind paws (Maicas, *Antioxidants & Redox Signaling*, doi:10.1089/ars.2010.3835).

[0009] Ulcerative colitis (UC) and Crohn's disease (CD) are chronic relapsing-remitting forms of inflammatory bowel disease (IBD) that are caused by dysfunction of the intestinal epithelium. Damage to the intestinal epithelial cells can disrupt the barrier function of the intestinal epithelium, facilitating an aberrant immune response and inflammatory conditions. Thus, the intact intestinal epithelium is critical for the healthy gut, and cyto-protective agents that could target the intestinal epithelial cells would be beneficial for the treatment of UC and CD. Antioxidant levels and oxidative stress biomarkers are typically correlated with disease severity in IBD and a number of genome-wide association studies have linked IBD-associated single nucleotide polymorphismsm (SNPs) to multiple genes involved in the response to oxidative stress, with many regulated by Nrf2 (Khor et al, Nature, doi:10.1038/nature10209). CPUY192018, a small-molecule inhibitor of the Keap1-Nrf2 protein-protein interaction (and hence Nrf2 activator) has demonstrated a

cytoprotective effect in an experimental model of UC induced by dextran sodium sulphate in both NCM460 cells and mouse colon (Lu, *Scientific Reports*, doi:10.1038/srep26585). It has also been shown that Nrf2 knockout mice show an increased susceptibility to colitis-associated colorectal cancer (Khor, *Cancer Prev Res* (Phila), doi:10.1158/1940-6207).

[0010] Fumaderm, a mixture of dimethyl fumarate (DMF) and three salts of monoethyl fumarate, was licensed in Germany in 1994 for the treatment of psoriasis. The likely bioactive form of DMF, monomethyl fumarate (MMF) has been shown to increase total and nuclear Nrf2 levels in primary mouse keratinocytes and lead to enhanced mRNA expression of several Nrf2-downstream effectors such as heme oxygenase-1 and peroxiredoxin-6. (Helwa, *J Pharmacol. Exp. Ther.*, doi:10.1124/jpet.116.239715). Other skin disorders may benefit from treatment with Nrf2 activators such as radiation-induced dermatitis/skin damage, atopic dermatitis and wound healing (Wu et al, Mol Med Rep. 2019 Aug;20(2):1761-1771).

[0011] Activation of Nrf2 has been shown to have beneficial effects in diseases of both the liver and kidney. NAFLD (Non-alcoholic fatty liver disease) is recognized as the leading cause of chronic liver disease worldwide. NAFLD represents a spectrum of diseases, some of which can progress to cirrhosis and hepatocellular carcinoma (HCC). Although all subtypes of NAFLD increase the risk for cardiovascular events and mortality, NASH (non-alcoholic steatohepatitis) is the main diagnostic subtype of NAFLD which predisposes patients to cirrhosis and liver-related complications. There are currently approved drug treatments for NAFLD and NASH. However, knockout of Nrf2 in mice profoundly predisposes to NASH stimulated by either a methionine- and choline-deficient (MCD) diet (Chowdry, *Free Radic Biol Med*, doi:10.1016/j.freeradbiomed.2009.11.007) or a high fat (HF) diet (Okada, *J Gastroenterol*, doi:10.1007/s00535-012-0659-z), and pharmacologic activation of Nrf2 has been shown to reverse NASH in mouse models (Sharma, *Cell Mol Gastroenterol Hepatol*, doi:10.1016/j.jcmgh.2017.11.016). Other liver diseases may benefit from treatment with Nrf2 activators such as toxin-induced liver disease, viral hepatitis and cirrhosis. Oxidative-stress molecules, such as reactive oxygen species, accumulate in the kidneys of animal models for acute kidney injury (AKI), in which Nrf2 is transiently and slightly activated. Genetic or pharmacological enhancement of Nrf2 activity in the renal tubules significantly ameliorates damage related to AKI and prevents AKI progression to chronic kidney disease (CKD) by reducing oxidative stress. However, a Phase III clinical trial of a KEAP1 inhibitor, CDDO-Me or bardoxolone-methyl, for patients with stage 4 CKD and type-2 diabetes mellitus (T2DM) was terminated due to the occurrence of cardiovascular events. Because recent basic studies have accumulated positive effects of KEAP1 inhibitors in moderate stages of CKD, Phase II trials have been

restarted. The data from the ongoing projects demonstrate that a Nrf2 activator/KEAP1 inhibitor improves the glomerular filtration rate in patients with stage 3 CKD and T2DM without safety concerns (Nezu, *Am J Nephrol,* doi:10.1159/000475890). Inflammatory reactions and oxidative stress are implicated in the pathogenesis of focal segmental glomerulosclerosis (FSGS), a common chronic kidney disease with relatively poor prognosis and unsatisfactory treatment regimens. CXA-10 which upregulates Nrf2 pathways is currently in clinical trials for Focal Segmental Glomerulosclerosis (FIRSTx - A Study of Oral CXA-10 in Primary Focal Segmental Glomerulosclerosis (FSGS); clinicaltrials.gov/ct2/show/NCT03422510). Bardoxolone methyl has been shown in a PhII trial to lead to significant improvement in kidney function in patients with either autosomal dominant polycystic kidney disease (ADPKD), CKD associated with type 1 diabetes (T1D), IgA nephropathy (IgAN) or FSGS after 12 weeks of treatment (https://www.reatapharma.com/press-releases/reata-announces-positive-phase-2-data-for-bardoxolone-methyl-in-patients-with-focal-segmental-glomerulosclerosis-and-in-patients-from-all-four-cohorts-of-phoenix/). Alport Syndrome is the second most common inherited cause of kidney failure caused by a genetic defect in type IV collagen, a component in building the glomerular basement membrane. As bardoxolone methyl is thought to affect the underlying pathologic processes associated with mitochondrial dysfunction, inflammation and oxidative stress, it is currently being studied in these patients suggesting Nrf2 activators will be potentially useful in this disease.

[0012] Oxidative stress plays a critical role in the initiation and progression of cancer (Gorrini, *Nat Rev Drug Discov.*, doi:10.1038/nrd4002). Due to its importance in the maintenance of redox cellular homeostasis, Nrf2 is considered a cytoprotective transcription factor and tumour suppressor. At lower homeostatic levels Nrf2 is able to eliminate ROS, carcinogens and other DNA-damaging agents, leading to the inhibition of tumour initiation and metastasis (Milkovic et al. Redox Biol. doi:10.1016/j.redox.2017.04.013). Evgen is currently evaluating SFX-01 (sulforaphane-cyclodextrin complex) in the Treatment and Evaluation of Metastatic Breast Cancer (STEM) (clinicaltrials.gov/ct2/show/NCT02970682) which includes ER+/HER- metastatic breast cancer. Bardoxolone derivatives have been shown to prevent lung cancer induced by vinyl carbamate in A/J mice (Liby, *Cancer Res.* doi:10.1158/0008-5472). Thus, activators of Nrf2 may have a role in the prevention of cancer.

[0013] Age related macular degeneration (AMD) is the principal cause of blindness in western countries and oxidative stress plays a major role in AMD pathogenesis and progression. It has been shown that Nrf2 activators are able to protect cells cultured to mimic the external layer of the retina from oxidative stress suggesting the potential for

vision preservation in early AMD patients (Bellezza, Front Pharmacol. 2018; 9: 1280). In addition, Nrf2 activators may also be useful in other eye conditions such as Fuchs Endothelial Corneal Dystrophy and uveitis.

[0014] Recently, Nrf-2 activators have also been suggested to have benefit for the treatment of preeclampsia via suppression of oxidative stress and endothelial cell apoptosis (Jiang et al, Oxid Med Cell Longev doi:10.1155/2021/8839394).

[0015] Therefore, there is an ongoing need for agents capable of Nrf2 activation, given the role of Nrf2 in multiple indications.

SUMMARY OF THE INVENTION

[0016] In one aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof as defined herein.

[0017] In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0018] In another aspect, the present invention relates to a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in therapy.

[0019] In another aspect, the present invention relates to a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of diseases or disorders mediated by Nrf2 activation.

[0020] In another aspect, the present invention relates to the use of a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of diseases or disorders mediated by Nrf2 activation.

[0021] In another aspect, the present invention relates to a method of treating a disease or disorder mediated by Nrf2 activation, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[0022] Examples of diseases or disorders mediated by Nrf2 activation include chronic obstructive pulmonary disease, asthma, pulmonary arterial hypertension, diabetes

mellitus, chronic kidney disease, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Friedreich's ataxia, sickle cell disease and non-alcoholic steatohepatitis.

[0023] In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of chronic obstructive pulmonary disease, asthma, pulmonary arterial hypertension, diabetes mellitus, chronic kidney disease, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Friedreich's ataxia, sickle cell disease or non-alcoholic steatohepatitis.

[0024] In another aspect, the present invention provides the use of a compound, or a pharmaceutically acceptable salt, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease, asthma, pulmonary arterial hypertension, diabetes mellitus, chronic kidney disease, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Friedreich's ataxia, sickle cell disease or non-alcoholic steatohepatitis.

[0025] In another aspect, the present invention provides a method of treating chronic obstructive pulmonary disease, asthma, pulmonary arterial hypertension, diabetes mellitus, chronic kidney disease, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Friedreich's ataxia, sickle cell disease or non-alcoholic steatohepatitis, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[0026] The present invention further provides a method of synthesising a compound, or a pharmaceutically acceptable salt thereof, as defined herein.

[0027] In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, obtainable by, or obtained by, or directly obtained by a method of synthesis as defined herein.

[0028] In another aspect, the present invention provides novel intermediates as defined herein which are suitable for use in any one of the synthetic methods set out herein.

[0029] Preferred, suitable, and optional features of any one particular aspect of the present invention are also preferred, suitable, and optional features of any other aspect.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0030] Unless otherwise stated, the following terms used in the specification and claims

have the following meanings set out below.

[0031] It is to be appreciated that references to "treating" or "treatment" include prophylaxis as well as the alleviation of established symptoms of a condition. "Treating" or "treatment" of a state, disorder or condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, *i.e.*, arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, *i.e.*, causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

[0032] A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0033] In this specification the term "alkyl" includes both straight and branched chain alkyl groups. References to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only. For example, "(1-6C)alkyl" includes (1-4C)alkyl, (1-3C)alkyl, propyl, isopropyl and *t*-butyl. A similar convention applies to other radicals, for example "phenyl(1-6C)alkyl" includes phenyl(1-4C)alkyl, benzyl, 1-phenylethyl and 2-phenylethyl.

[0034] In this specification the term "alkylene" includes both straight and branched chain divalent alkyl groups. For example, "C_{1-4}alkylene" includes methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene and butylene.

[0035] In this specification the term "alkoxy" includes both straight and branched chain alkyl groups singularly bonded to oxygen. For example, "C_{1-4}alkoxy" includes methoxy, ethoxy, *iso*-propoxy and *t*-butoxy.

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

[0037] "Cycloalkyl" means a hydrocarbon monocyclic or bicyclic ring containing carbon atoms. Examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl. Bicyclic rings may be fused or spiro attached;

examples of bicyclic cycloalkyl groups include bicyclo[2.2.2]octane, bicyclo[2.1.1]hexane, bicyclo[1.1.1]pentane, spiro[2.4]heptane, bicyclo[4.1.0]heptane and bicyclo[2.2.1]heptane.

[0038] The term "halo" refers to fluoro, chloro, bromo and iodo.

[0039] The term "haloalkyl" is used herein to refer to an alkyl group respectively in which one or more hydrogen atoms have been replaced by halogen (e.g. fluorine) atoms. Examples of haloalkyl groups include fluoroalkyl groups such as $-CHF_2$, $-CH_2CF_3$, or perfluoroalkyl/alkoxy groups such as $-CF_3$, or $-CF_2CF_3$.

[0040] The term "heterocyclyl", "heterocyclic" or "heterocycle" means a non-aromatic saturated or partially saturated monocyclic, fused, bridged, or spiro bicyclic heterocyclic ring system(s). Monocyclic heterocyclic rings contain from about 3 to 12 (suitably from 3 to 7) ring atoms, with from 1 to 5 (suitably 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur in the ring. Bicyclic heterocycles contain from 7 to 17 member atoms, suitably 7 to 12 member atoms, in the ring. Bicyclic heterocyclic(s) rings may be fused, spiro, or bridged ring systems. Examples of heterocyclic groups include cyclic ethers such as oxiranyl, oxetanyl, tetrahydrofuranyl, dioxanyl, and substituted cyclic ethers. Heterocycles containing nitrogen include, for example, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrotriazinyl, tetrahydropyrazolyl, and the like. Typical sulfur containing heterocycles include tetrahydrothienyl, dihydro-1,3-dithiol, tetrahydro-2*H*-thiopyran, and hexahydrothiepine. Other heterocycles include dihydro-oxathiolyl, dihydroisoxazolyl (such as 4,5-dihydroisoxazolyl), dihydropyridinyl (such as 1,2-dihydropyridinyl or 1,6-dihydropyridinyl), tetrahydro-oxazolyl, tetrahydro-oxadiazolyl, tetrahydro-dioxazolyl, tetrahydro-oxathiazolyl, hexahydrotriazinyl, tetrahydro-oxazinyl, morpholinyl, thiomorpholinyl, tetrahydropyrimidinyl, dioxolinyl, octahydrobenzofuranyl, octahydrobenzimidazolyl, and octahydrobenzothiazolyl. For heterocycles containing sulfur, the oxidized sulfur heterocycles containing SO or SO_2 groups are also included. Examples include the sulfoxide and sulfone forms of tetrahydrothienyl and thiomorpholinyl such as tetrahydrothiene 1,1-dioxide and thiomorpholinyl 1,1-dioxide. A suitable value for a heterocyclyl group which bears 1 or 2 oxo (=O) or thioxo (=S) substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl. Particular heterocyclyl groups are saturated monocyclic 3 to 7 membered heterocyclyls containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur, for example azetidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, thiomorpholinyl, thiomorpholinyl 1,1-dioxide, piperidinyl, homopiperidinyl, piperazinyl or homopiperazinyl. As the skilled person would appreciate, any heterocycle may be linked to another group

via any suitable atom, such as *via* a carbon or nitrogen atom. Suitably, the term "heterocyclyl", "heterocyclic" or "heterocycle" will refer to 4, 5, 6 or 7 membered monocyclic rings as defined above.

[0041] The term "heteroaryl" or "heteroaromatic" means an aromatic mono-, bi-, or polycyclic ring incorporating one or more (for example 1-4, particularly 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur. Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring, for example a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulfur and oxygen. Typically, the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general, the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five. Suitably, the term "heteroaryl" or "heteroaromatic" will refer to 5 or 6 membered monocyclic heteroaryl rings as defined above.

[0042] Non-limiting examples of heteroaryl include furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, isoindolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, purinyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl, pteridinyl, naphthyridinyl, carbazolyl, phenazinyl, benzisoquinolinyl, pyridopyrazinyl, thieno[2,3-*b*]furanyl, 2*H*-furo[3,2-*b*]-pyranyl, 5*H*-pyrido[2,3-*d*]-o-oxazinyl, 1*H*-pyrazolo[4,3-*d*]-oxazolyl, 4*H*-imidazo[4,5-*d*]thiazolyl, pyrazino[2,3-*d*]pyridazinyl, imidazo[2,1-*b*]thiazolyl, imidazo[1,2-*b*][1,2,4]triazinyl. "Heteroaryl" also covers partially aromatic bi- or polycyclic ring systems wherein at least one ring is an aromatic ring and one or more of the other ring(s) is a non-aromatic, saturated or partially saturated ring, provided at least one ring contains one or more heteroatoms selected from nitrogen, oxygen or sulfur. Examples of partially aromatic heteroaryl groups include for example, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 2-oxo-1,2,3,4-tetrahydroquinolinyl, dihydrobenzthienyl, dihydrobenzfuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,3]dioxolyl, 2,2-dioxo-1,3-dihydro-2-benzothienyl, 4,5,6,7-tetrahydrobenzofuranyl, indolinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazinyl,

3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, 4,5,6,7-tetrahydrobenzo[*d*]isoxazolyl, 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyridinyl, 5,6-dihydro-8*H*-[1,2,4]triazolo[3,4-*c*][1,4]oxazinyl, 5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazolyl, 6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazolyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyridinyl, 6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazinyl and 1,4,5,6-tetrahydrocyclopenta[*d*][1,2,3]triazol-5-yl.

[0043] Non-limiting examples of five membered heteroaryl groups include but are not limited to pyrrolyl, furanyl, thienyl, imidazolyl, furazanyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl and tetrazolyl groups.

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

[0045] Particular non-limiting examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuranyl, benzothiophenyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, isobenzofuranyl, indolyl, isoindolyl, indolizinyl, indolinyl, isoindolinyl, purinyl (e.g., adeninyl, guaninyl), indazolyl, benzodioxolyl, pyrrolopyridine, and pyrazolopyridinyl groups.

[0046] Particular non-limiting examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinolinyl, isoquinolinyl, chromanyl, thiochromanyl, chromenyl, isochromenyl, chromanyl, isochromanyl, benzodioxanyl, quinolizinyl, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl groups.

[0047] Particular non-limiting examples of bicyclic heteroaryl groups containing a five membered ring fused to a five membered ring include but are not limited to 6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazolyl, 5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazolyl and 1,4,5,6-tetrahydrocyclopenta[*d*][1,2,3]triazol-5-yl.

[0048] The term “aryl" means a cyclic or polycyclic aromatic ring having from 5 to 12 carbon atoms. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. In this particular embodiment, an aryl is phenyl or naphthyl, especially phenyl.

[0049] The term "optionally substituted" refers to either groups, structures, or molecules that are substituted and those that are not substituted.

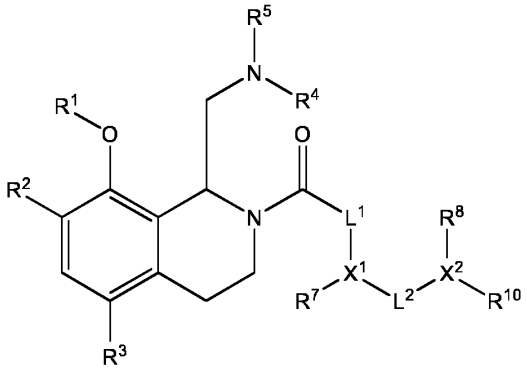
[0050] Where optional substituents are chosen from “one or more” groups it is to be understood that this definition includes all substituents being chosen from one of the

specified groups or the substituents being chosen from two or more of the specified groups.

[0051] The phrase "compound of the invention" means those compounds which are disclosed herein, both generically and specifically.

Compounds of the Invention

[0052] In a first aspect, the present invention provides a compound of Formula I



(I)

wherein:

X^1 is nitrogen or a group $-CR^6$;

X^2 is nitrogen or a group $-C^*R^9$;

R^1 is selected from C_{1-4}alkylene-R^{11}, heterocyclyl and 8-10 membered bicyclic heteroaryl, wherein said heterocyclyl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, $-C(O)-R^{12}$, SO_2-R^{13}, C_{1-3}alkylene-OR^{14} and heteroaryl which is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy and cyano; and wherein said 8-10 membered bicyclic heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH and C_{1-3}alkoxy;

R^2 is selected from hydrogen, fluoro, chloro and C_{1-3}alkyl;

R^3 is selected from hydrogen, fluoro, chloro, bromo, C_{1-3}alkoxy, C_{1-3}alkyl, C_{1-3}haloalkyl and cyano;

R^4 is hydrogen or C_{1-4}alkyl;

R^5 is $-C(O)-C_{1-4}$alkyl, $-C(O)-C_{3-7}$cycloalkyl, -C(O)-heteroaryl or -C(O)-aryl, wherein said heteroaryl and aryl are optionally substituted with one or more substituents selected from C_{1-4}alkyl, halo, hydroxy, C_{1-3}alkoxy, CO_2R^{15} and cyano; or

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 4-, 5-, or 6-membered heterocyclyl ring, wherein said heterocyclyl ring:

comprises one or more -C(O)- moieties attached to the nitrogen atom;

optionally contains one or more additional heteroatoms selected from oxygen, nitrogen and sulfur;

optionally is fused to an aryl or heteroaryl ring;

optionally is spiro-attached to a C_{3-7}cycloalkyl group or a 3- to 6-membered heterocyclyl ring; and

optionally is substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20};

L^1 and L^2 are independently selected from a bond and $-CR^{21}R^{22}-$, provided that if L^2 is a bond both X^1 and X^2 cannot be nitrogen;

R^6 and R^7 are independently selected from hydrogen, C_{1-4}alkyl, and C_{3-7}cycloalkyl; or

R^6 and R^7, taken together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring;

R^8 is $C(=O)NR^{8a}R^{8b}$ or $-C(=O)R^{8c}$;

R^{8a} is hydrogen or C_{1-6}alkyl;

R^{8b} is hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl, wherein the C_{1-6}alkyl or C_{3-7}cycloalkyl groups are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20}; or

R^{8a} and R^{8b}, taken together with the nitrogen atom to which they are attached, form a 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring, wherein the heterocyclyl ring optionally contains one or more additional heteroatoms selected from oxygen, nitrogen and sulfur, and is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20};

R^{8c} is C_{1-3}alkyl or C_{1-3}haloalkyl;

R^9 is selected from hydrogen, C_{1-4}alkyl, hydroxy, C_{1-3}alkoxy and halo;

R^{10} is selected from hydrogen and C_{1-4}alkyl; or

R^9 and R^{10}, taken together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring; or

L^2 is a bond and R^7 and R^{10}, taken together with the atoms to which they are attached, form a 4-, 5-, 6- or 7-membered cycloalkyl or heterocyclyl ring, wherein:

said heterocyclyl ring contains 1 or 2 heteroatoms independently selected from nitrogen, oxygen and sulfur;

said cycloalkyl ring optionally comprises 1 or 2 carbon-carbon double bonds and is optionally bridged by a C_{1-3}alkylene group connecting two carbon atoms

of the ring, or R^9 is optionally a C_{1-3}alkylene group connecting C* to a carbon atom of the ring;

said cycloalkyl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl and deuterium; and

said cycloalkyl and heterocyclyl rings are optionally spiro-attached to a C_{3-7}cycloalkyl group;

R^{11} is selected from -C(O)-R^{24}, -SO_2-R^{25}, -NR^{26}C(O)-R^{27}, -$NR^{28}SO_2$-R^{29}, heterocyclyl, aryl and heteroaryl, wherein said aryl and heteroaryl groups are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocyclyl and cyano; and said heterocyclyl group is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, oxo and cyano;

R^{12} is selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, OR^{31}, $NR^{32}R^{33}$, aryl and heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy and cyano;

R^{13} is selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl and $NR^{34}R^{35}$, wherein said heteroaryl and heterocyclyl are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy and cyano;

R^{17} is selected from hydrogen, C_{1-4}alkyl, C(O)C_{1-3}alkyl and C(O)$NR^{36}R^{37}$;

R^{18}, R^{19} and R^{20} are independently selected from C_{1-4}alkyl, OH, C_{1-3}alkoxy and $NR^{38}R^{39}$;

R^{24} is selected from C_{1-4}alkyl, $NR^{40}R^{41}$ and OR^{42};

R^{25} is selected from C_{1-4}alkyl and $NR^{43}R^{44}$;

R^{27} is selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-3}haloalkyl, heterocyclyl, aryl and heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{45}, halo, OH, C_{1-3}alkoxy and cyano;

R^{29} is selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-3}haloalkyl, aryl and heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{46} halo, OH, C_{1-3}alkoxy and cyano;

R^{30} is selected from hydroxy, C_{1-3}alkoxy, C_{3-7}cycloalkyl, cyano and $NR^{47}R^{48}$;

R^{40} is selected from hydrogen and C_{1-4}alkyl;

R^{41} is selected from hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-3}alkoxy, aryl and heteroaryl; or

R^{40} and R^{41}, taken together with the nitrogen atom to which they are attached, form a 4-, 5-, or 6-membered heteroaryl or heterocyclyl ring, wherein said heteroaryl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{3-7}cycloalkyl and cyano;

R^{45} and R^{46} are independently selected from hydroxy, C_{1-3}alkoxy and C_{3-7}cycloalkyl; and

R^{14}, R^{15}, R^{16}, R^{21}, R^{22}, R^{23}, R^{26}, R^{28}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{42}, R^{43}, R^{44}, R^{47} and R^{48} are independently selected from hydrogen, C_{1-4}alkyl and C_{3-7}cycloalkyl;

or a pharmaceutically acceptable salt thereof.

[0053] Particular compounds of the invention include, for example, compounds of the formula I, or pharmaceutically acceptable salts thereof, wherein, unless otherwise stated, each of R^1, R^2, R^3, R^4, R^5, L^1, L^2, X^1, X^2, R^6, R^7, R^8, R^{8a}, R^{8b}, R^{8c}, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{17}, R^{18}, R^{19}, R^{20}, R^{24}, R^{25}, R^{27}, R^{29}, R^{30}, R^{40} and R^{41} has any of the meanings defined hereinbefore or in any of paragraphs (1) to (111) hereinafter. For the avoidance of doubt, the scope of the present invention encompasses compounds of formula I, or pharmaceutically acceptable salts thereof, wherein any of the substituent definitions defined herein may be combined with any of the other substituent definitions also defined herein:-

(1) R^1 is C_{1-4}alkylene-R^{11};

(2) R^1 is CH_2-R^{11};

(3) R^1 is CH_2CH_2-R^{11};

(4) R^1 is $CH_2CH_2CH_2$-R^{11};

(5) R^1 is CH(Me)-R^{11};

(6) R^1 is heterocyclyl, optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, -C(O)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy and cyano;

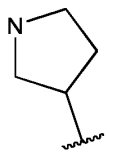
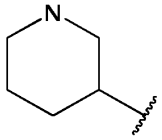
(7) R^1 is heterocyclyl, optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, -C(O)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl and C_{3-7}cycloalkyl;

(8) R^1 is piperidinyl or pyrrolidinyl, each optionally substituted with one or more substituents independently selected from -C(O)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl is optionally substituted with one or more

substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy and cyano;

(9) R^1 is pyrrolidinyl, optionally substituted with one or more substituents independently selected from -C(O)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl is optionally substituted with C_{1-4}alkyl or C_{3-7}cycloalkyl;

(10) R^1 is selected from one of the following groups:

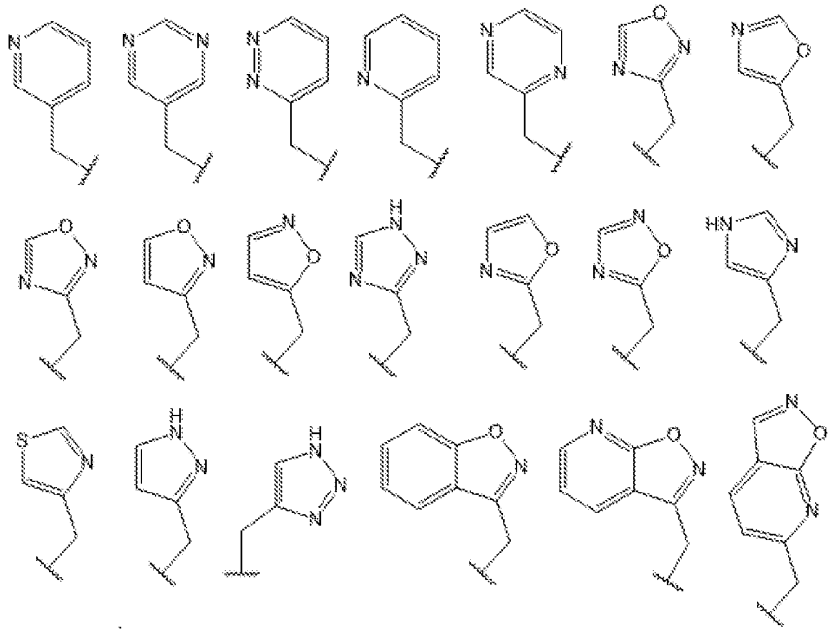

and

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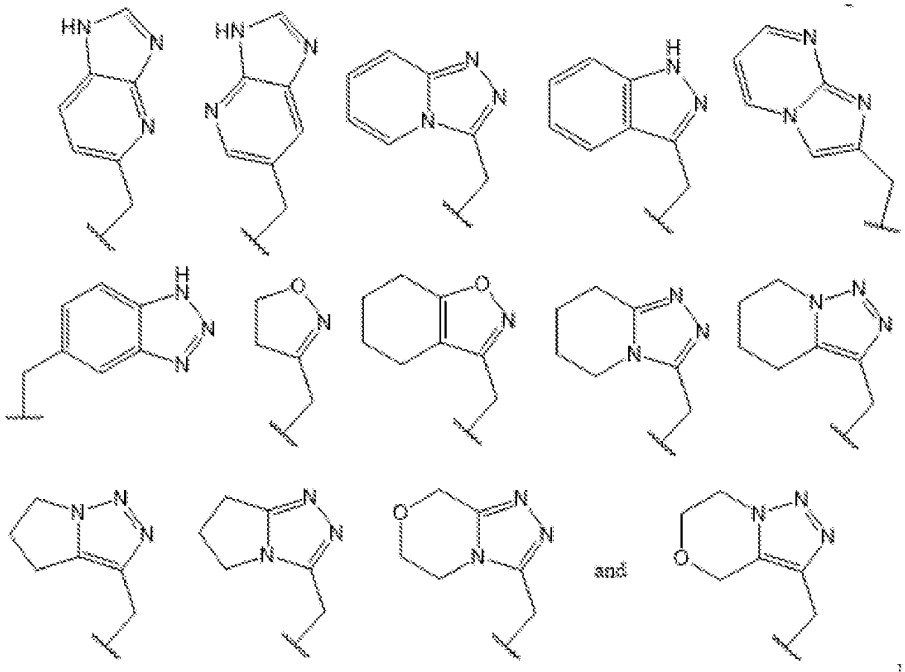
wherein ~~~ represents the point of attachment of the group to the oxygen atom of the rest of the compound and wherein each group is optionally substituted with one or more substituents independently selected from -C(O)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl is optionally substituted with C_{1-4}alkyl or C_{3-7}cycloalkyl;

(11) R^1 is an 8-10 membered bicyclic heteroaryl optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH and C_{1-3}alkoxy;

(12) R^1 is an 8-membered bicyclic heteroaryl optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, OH and C_{1-3}alkoxy;

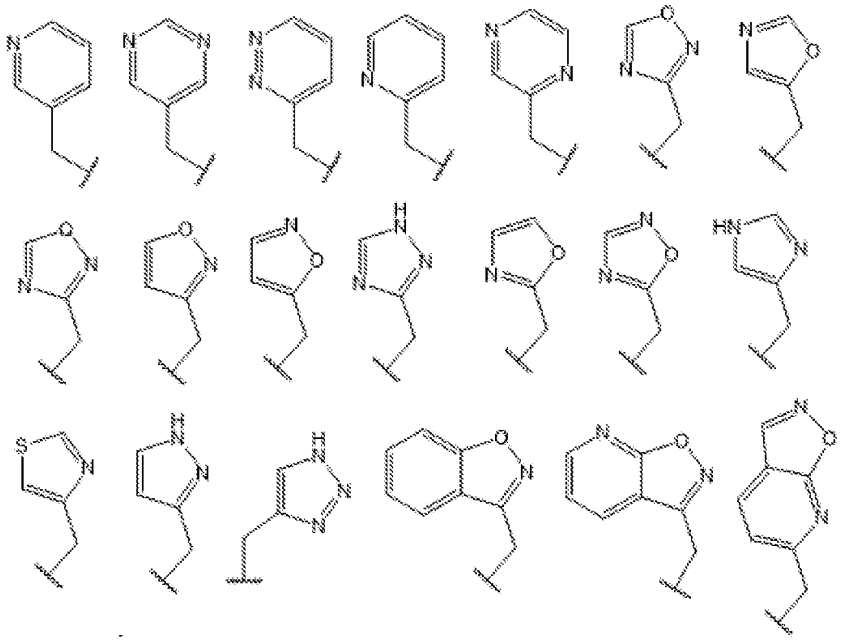
(13) R^1 is selected from one of the following groups:

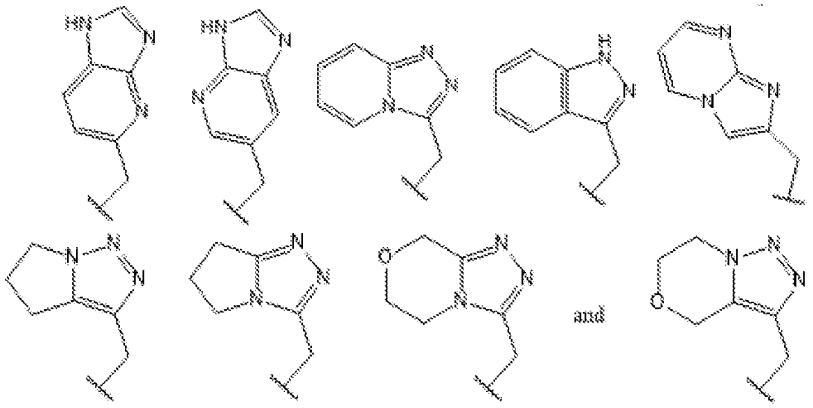




wherein ~~~ represents the point of attachment of the group to the oxygen atom of the rest of the compound and wherein each group is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocycloalkyl and cyano;

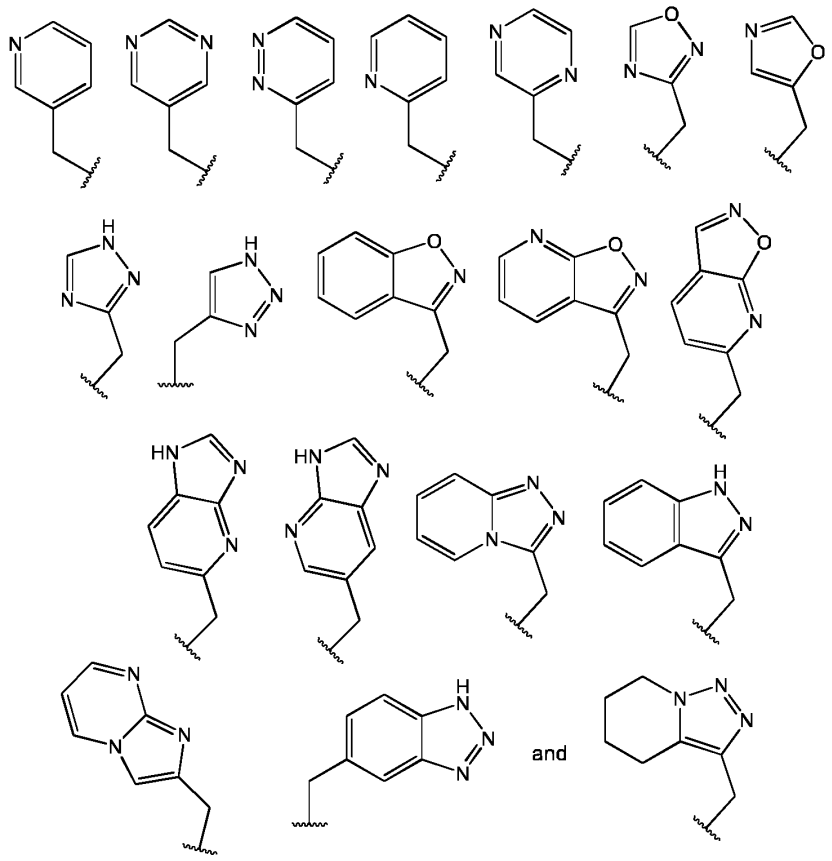
(14) R^1 is selected from one of the following groups:





wherein ~~~ represents the point of attachment of the group to the oxygen atom of the rest of the compound and wherein each group is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, C_{1-3}alkoxy and cyano;

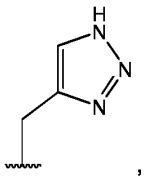
(15) R^1 is selected from one of the following groups:



wherein ~~~ represents the point of attachment of the group to the oxygen atom of the rest of the compound and wherein each group is optionally substituted with one

or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH and C_{1-3}alkoxy;

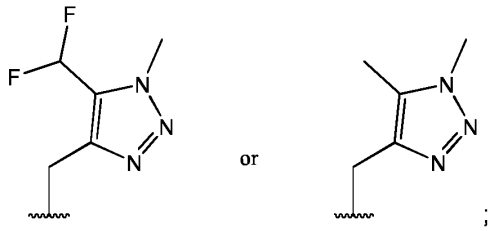
(16) R^1 is:



,

wherein ~~~ represents the point of attachment of the group to the oxygen atom of the rest of the compound and wherein the group is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl and C_{1-4}alkylene-R^{30};

(17) R^1 is:



or

;

(18) R^2 is selected from hydrogen, fluoro and chloro;

(19) R^2 is hydrogen or fluoro;

(20) R^3 is selected from hydrogen, chloro, bromo, C_{1-3}alkoxy, C_{1-3}alkyl, C_{1-3}haloalkyl and cyano;

(21) R^3 is selected from hydrogen, chloro, bromo, methoxy, methyl, trifluoromethyl and cyano;

(22) R^3 is selected from hydrogen and chloro;

(23) R^3 is chloro;

(24) R^4 is hydrogen;

(25) R^5 is -C(O)-C_{1-4}alkyl, -C(O)-C_{3-7}cycloalkyl, or -C(O)-aryl, wherein said aryl group is optionally substituted with one or more substituents selected from C_{1-4}alkyl, halo, hydroxy, C_{1-3}alkoxy, CO_2R^{15} and cyano;

(26) R^4 is hydrogen and R^5 is -C(O)-C_{1-4}alkyl or -C(O)-aryl, wherein said aryl group is optionally substituted with one or more substituents selected from C_{1-4}alkyl, halo, hydroxy, C_{1-3}alkoxy, CO_2R^{15} and cyano;

(27) R^4 is hydrogen and R^5 is -C(O)-C_{1-4}alkyl;

(28) R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 5-, or 6-membered heterocyclyl ring, wherein said heterocyclyl ring:
comprises one or more -C(O)- moieties attached to the nitrogen atom;
optionally contains one or more additional heteroatoms selected from oxygen, nitrogen and sulfur;
optionally is fused to an aryl ring;
optionally is spiro-attached to a C_{3-7}cycloalkyl group or a 3- to 5-membered heterocyclyl ring; and
optionally is substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20};

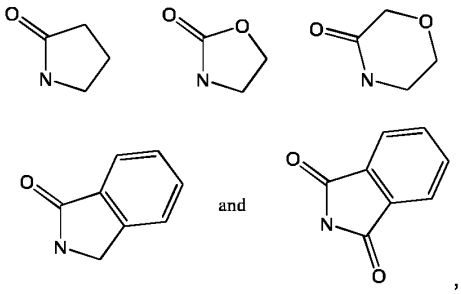
(29) R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 5-, or 6-membered heterocyclyl ring, wherein said heterocyclyl ring:
optionally contains one or more additional heteroatoms selected from oxygen, and nitrogen;
optionally is fused to an aryl ring;
optionally is spiro-attached to a C_{3-7}cycloalkyl group; and
optionally is substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20};

(30) R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 5-membered heterocyclyl ring, wherein said heterocyclyl ring:
comprises one or more -C(O)- moieties attached to the nitrogen atom;
optionally contains one or more additional heteroatoms selected from oxygen, and nitrogen;
optionally is fused to an aryl ring;
optionally is spiro-attached to a C_{3-7}cycloalkyl group; and
optionally is substituted with one or more substituents independently selected from C_{1-4}alkyl, halo and OH;

(31) R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 5-membered heterocyclyl ring, wherein said heterocyclyl ring comprises a -C(O)- moiety attached to the nitrogen atom and is optionally fused to a phenyl ring, or optionally spiro-attached to a cyclopropyl group; and said heterocyclyl ring is

optionally substituted with one or more substituents independently selected from methyl, fluoro and OH;

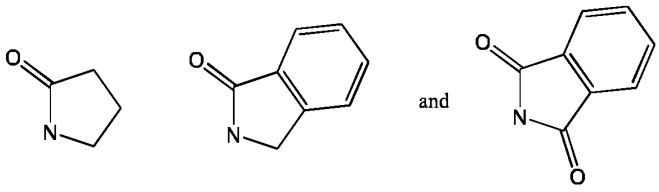
(32) R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a heterocyclic moiety selected from one of the following:



,

wherein the saturated ring of the heterocyclic moiety is optionally spiro-attached to a C_{3-7}cycloalkyl group, and wherein said heterocyclic moiety is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo and OH;

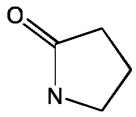
(33) R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a heterocyclic moiety selected from one of the following:



,

wherein the saturated ring of the heterocyclic moiety is optionally spiro-attached to a cyclopropyl group, and wherein said heterocyclic moiety is optionally substituted with one or more substituents independently selected from methyl, fluoro and OH;

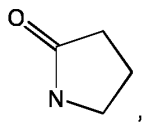
(34) R^4 and R^5, taken together with the nitrogen atom to which they are attached, form the following heterocyclic moiety:



,

wherein the heterocyclic moiety is optionally spiro-attached to a cyclopropyl group and is optionally substituted with one or more substituents independently selected from methyl and fluoro;

(35) R^4 and R^5, taken together with the nitrogen atom to which they are attached, form the following heterocyclic moiety:



wherein the heterocyclic moiety is optionally spiro-attached to a cyclopropyl group, and is optionally substituted with C_{1-3}alkyl, wherein said cyclopropyl and/or C_{1-3}alkyl group is attached to the heterocyclic ring at a position either alpha or beta to the carbonyl group;

(36) X^1 is a group $-CR^6$ and X^2 is a group $-C^*R^9$;

(37) X^1 is a group $-CR^6$ and X^2 is nitrogen;

(38) X^1 is nitrogen and X^2 is a group $-C^*R^9$;

(39) L^1 and L^2 are independently selected from a bond and $-CH_2-$;

(40) L^1 is a bond and L^2 is $-CH_2-$;

(41) L^1 is CH_2- and L^2 is a bond;

(42) L^1 and L^2 are both bonds;

(43) R^6 and R^7 are independently selected from hydrogen and C_{1-4}alkyl;

(44) R^6 and R^7 are independently selected from hydrogen and methyl;

(45) R^6 is hydrogen;

(46) R^7 is hydrogen;

(47) R^6 and R^7 are both hydrogen;

(48) R^6 and R^7, taken together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring;

(49) X^1 is a group $-CR^6$, X^2 is nitrogen or a group $-C^*R^9$ and R^8 is $-C(=O)NR^{8a}R^{8b}$;

(50) X^1 is a group $-CR^6$, X^2 is a group $-C^*R^9$ and R^8 is $-C(=O)NR^{8a}R^{8b}$;

(51) X^1 is nitrogen, X^2 is a group $-C^*R^9$ and R^8 is $-C(=O)NR^{8a}R^{8b}$;

(52) X^1 is a group $-CR^6$, X^2 is nitrogen and R^8 is $-C(=O)NR^{8a}R^{8b}$;

(53) X^1 is a group $-CR^6$, X^2 is nitrogen and R^8 is $-C(=O)R^{8c}$;

(54) R^8 is $C(=O)NR^{8a}R^{8b}$;

(55) R^8 is $-C(=O)R^{8c}$;

(56) R^{8a} is hydrogen or methyl;

(57) R^{8a} is hydrogen;

(58) R^{8b} is hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl, wherein the C_{1-6}alkyl group is optionally substituted with one or more substituents independently selected from halo, OH, C_{1-3}alkoxy, C_{3-7}cycloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20};

(59) R^{8b} is hydrogen, C_{1-4}alkyl or C_{3-5}cycloalkyl, wherein the C_{1-4}alkyl group is optionally substituted with one or more substituents independently selected from halo, OH, C_{1-3}alkoxy C_{3-7}cycloalkyl and cyano;

(60) R^{8b} is C_{1-4}alkyl or C_{3-5}cycloalkyl, wherein the C_{1-4}alkyl group is optionally substituted with one or more substituents independently selected from fluoro, OH, C_{1-3}alkoxy C_{3-7}cycloalkyl and cyano;

(61) R^{8b} is hydrogen, methyl, ethyl, n-propyl, cyclopropyl, cyclobutyl or cyclopropylmethyl wherein the methyl, ethyl or n-propyl groups are optionally substituted with one or more substituents independently selected from fluoro, OH, methoxy and cyano;

(62) R^{8b} is methyl, ethyl, n-propyl, cyclopropyl, cyclobutyl or cyclopropylmethyl;

(63) R^{8b} is methyl;

(64) R^{8a} is hydrogen and R^{8b} is hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl, wherein the C_{1-6}alkyl group is optionally substituted with one or more substituents independently selected from halo, OH, C_{1-3}alkoxy, C_{3-7}cycloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20};

(65) R^{8a} is hydrogen and R^{8b} is C_{1-6}alkyl or C_{3-7}cycloalkyl, wherein the C_{1-6}alkyl group is optionally substituted with one or more substituents independently selected from fluoro, OH, C_{1-3}alkoxy, C_{3-7}cycloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20};

(66) R^{8a} is hydrogen and R^{8b} is methyl, ethyl, n-propyl, cyclopropyl, cyclobutyl or cyclopropylmethyl;

(67) R^{8a} is hydrogen and R^{8b} is methyl;

(68) R^{8a} and R^{8b}, taken together with the nitrogen atom to which they are attached, form a 3-, 4-, or 5-membered heterocyclyl ring, wherein the heterocyclyl ring optionally contains one or more additional heteroatoms selected from oxygen, nitrogen and sulfur, and is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20};

(69) R^{8a} and R^{8b}, taken together with the nitrogen atom to which they are attached, form a 4-, or 5-membered heterocyclyl ring, wherein the heterocyclyl ring is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl,

halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20};

(70) R^{8a} and R^{8b}, taken together with the nitrogen atom to which they are attached, form an azetidinyl ring optionally substituted with one or more substituents independently selected from methyl, fluoro, OH, methoxy and C_{1-3}fluoroalkyl;

(71) R^{8c} is C_{1-3}alkyl or C_{1-3}fluoroalkyl;

(72) R^{8c} is C_{1-3}fluoroalkyl;

(73) R^{8c} is fluoromethyl, difluoromethyl or trifluoromethyl;

(74) R^9 is selected from hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy and halo;

(75) R^9 is selected from hydrogen, methyl, methoxy and fluoro;

(76) R^9 is selected from C_{1-4}alkyl, C_{1-3}alkoxy and halo;

(77) R^9 is selected from methyl, methoxy and fluoro;

(78) R^9 is hydrogen or C_{1-4}alkyl;

(79) R^9 is hydrogen or methyl;

(80) R^9 is methyl;

(81) R^{10} is selected from hydrogen and methyl;

(82) R^9 and R^{10}, taken together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring;

(83) L^2 is a bond and R^7 and R^{10}, taken together with the atoms to which they are attached, form a 4-, 5- or 6-membered cycloalkyl or heterocyclyl ring, wherein:
said heterocyclyl ring contains 1 or 2 heteroatoms independently selected from nitrogen, oxygen and sulfur;
said cycloalkyl ring optionally comprises 1 or 2 carbon-carbon double bonds and is optionally bridged by a C_{1-3}alkylene group connecting two carbon atoms of the ring, or R^9 is optionally a C_{1-3}alkylene group connecting C* to a carbon atom of the ring;
said cycloalkyl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy and deuterium; and
said cycloalkyl and heterocyclyl rings are optionally spiro-attached to a C_{3-7}cycloalkyl group;

(84) L^1 and L^2 are both bonds and R^7 and R^{10}, taken together with the atoms to which they are attached, form a 5- or 6-membered cycloalkyl or heterocyclyl ring, wherein:

said heterocyclyl ring contains 1 or 2 heteroatoms independently selected from nitrogen, oxygen and sulfur;

said cycloalkyl ring optionally comprises a carbon-carbon double bond and is optionally bridged by a C_{1-3}alkylene group connecting two carbon atoms of the ring, or R^9 is optionally a C_{1-3}alkylene group connecting C* to a carbon atom of the ring;

said cycloalkyl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy and deuterium; and

said cycloalkyl and heterocyclyl rings are optionally spiro-attached to a C_{3-7}cycloalkyl group;

(85) L^2 is a bond, X^1 is a group $-CR^6$, X^2 is a group $-C^*R^9$ and R^7 and R^{10}, taken together with the atoms to which they are attached, form a 5- or 6-membered cycloalkyl ring, wherein said cycloalkyl ring is optionally bridged by a C_{1-3}alkylene group connecting two carbon atoms of the ring, or R^9 is optionally a C_{1-3}alkylene group connecting C* to a carbon atom of the ring, and said cycloalkyl ring is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy and deuterium;

(86) L^2 is a bond, X^1 is a group $-CR^6$, X^2 is a group $-CR^9$ and R^7 and R^{10}, taken together with the atoms to which they are attached, form a cyclohexyl ring, wherein said cyclohexyl ring optionally comprises a carbon-carbon double bond and is optionally bridged by a C_{1-3}alkylene group connecting two carbon atoms of the ring, and said cyclohexyl ring is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH and deuterium;

(87) L^1 and L^2 are both bonds, X^1 is a group $-CR^6$, X^2 is nitrogen and R^7 and R^{10}, taken together with the atoms to which they are attached, form a 5- or 6-membered heterocyclyl ring, wherein said heterocyclyl ring is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy and deuterium; and said heterocyclyl ring is optionally spiro-attached to a C_{3-7}cycloalkyl group;

(88) L^1 and L^2 are both bonds, X^1 is a group $-CR^6$, X^2 is nitrogen and R^7 and R^{10}, taken together with the atoms to which they are attached, form a pyrrolidinyl or piperidinyl ring, wherein said ring is optionally substituted with one or more substituents independently selected from methyl, halo, OH, methoxy and deuterium; and said ring is optionally spiro-attached to a cyclopropyl group;

(89) L^1 and L^2 are both bonds, X^1 is nitrogen, X^2 is a group $-CR^9$ and R^7 and R^{10}, taken together with the atoms to which they are attached, form a 5- or 6-membered heterocyclyl ring, wherein said heterocyclyl ring is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy and deuterium; and said heterocyclyl ring is optionally spiro-attached to a C_{3-7}cycloalkyl group;

(90) L^1 and L^2 are both bonds, X^1 is nitrogen, X^2 is a group $-CR^9$ and R^7 and R^{10}, taken together with the atoms to which they are attached, form a pyrrolidinyl or piperidinyl ring, wherein said ring is optionally substituted with one or more substituents independently selected from methyl, halo, OH, methoxy and deuterium; and said ring is optionally spiro-attached to a cyclopropyl group;

(91) R^{11} is selected from $-C(O)-R^{24}$, $-SO_2-R^{25}$, $-NR^{26}C(O)-R^{27}$, $-NR^{28}SO_2-R^{29}$, and heteroaryl wherein said heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocyclyl and cyano;

(92) R^{11} is $-C(O)-R^{24}$ and R^{24} is selected from $NR^{40}R^{41}$ and OR^{42};

(93) R^{11} is $-NR^{26}C(O)-R^{27}$ and R^{27} is selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl and C_{3-7}cycloalkyl;

(94) R^{11} is $-NR^{28}SO_2-R^{29}$ and R^{29} is selected from C_{1-4}alkyl, C_{3-7}cycloalkyl and heteroaryl, wherein said heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl and C_{3-7}cycloalkyl;

(95) R^{11} is heteroaryl optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocyclyl and cyano;

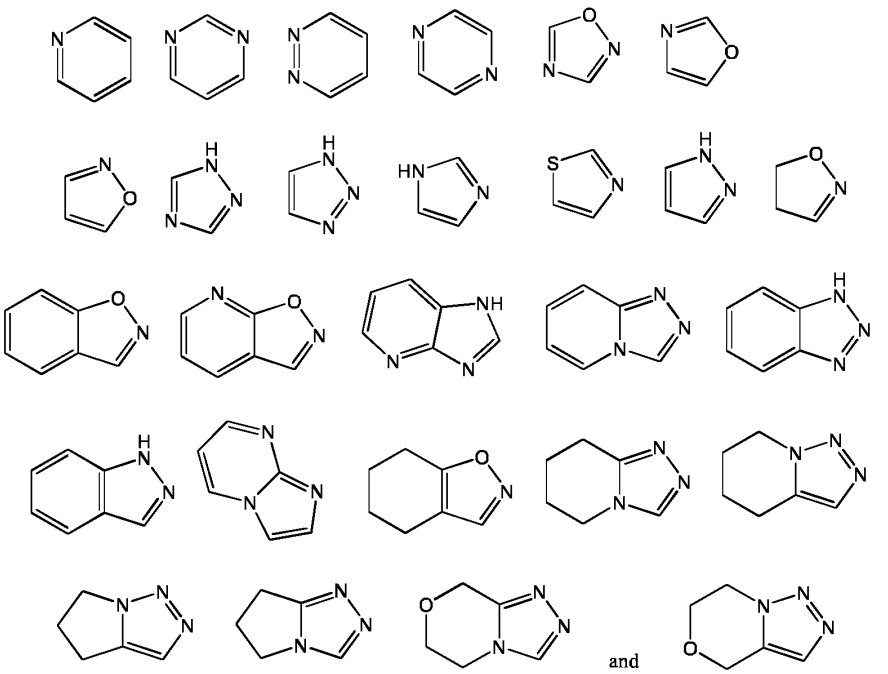
(96) R^{11} is heteroaryl optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, C_{1-3}alkoxy, and cyano;

(97) R^{11} is heteroaryl optionally substituted with one or more substituents independently selected from methyl, ethyl, isopropyl, difluoromethyl, trifluoromethyl, chloro, fluoro, cyclopropyl, methoxy, CH_2-R^{30} and $CH_2CH_2-R^{30}$;

(98) R^{11} is pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, oxazolyl, isoxazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, indazolyl, benzotriazolyl, benzisoxazolyl, isoxazolopyridinyl, imidazopyridinyl or triazolopyridinyl, each

optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocyclyl and cyano;

(99) R^{11} is heteroaryl selected from:



each heteroaryl being optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocycloalkyl and cyano;

(100) R^{11} is oxazolyl, isoxazolyl or 1,2,3-triazolyl, each optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocycloalkyl and cyano;

(101) R^{11} is 1,2,3-triazolyl optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocycloalkyl and cyano;

(102) R^{11} is heterocyclyl optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, oxo and cyano;

(103) R^{29} is selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-3}haloalkyl and heteroaryl, wherein said heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl and C_{1-3}haloalkyl;

(104) R^{29} is methyl, ethyl or cyclopropyl;

(105) R^{30} is selected from hydroxy, C_{1-3}alkoxy, C_{3-7}cycloalkyl and cyano;

(106) R^{30} is selected from hydroxy, methoxy, cyclopropyl and cyano;

(107) R^{40} is selected from hydrogen and methyl;

(108) R^{41} is selected from hydrogen, methyl, cyclopropyl, methoxy and phenyl;

(109) R^{40} and R^{41}, taken together with the nitrogen atom to which they are attached, form 5-membered heteroaryl or heterocyclyl ring, wherein said heteroaryl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{3-7}cycloalkyl and cyano;

(110) R^{40} and R^{41}, taken together with the nitrogen atom to which they are attached, form 5-membered heterocyclyl ring, wherein said heterocyclyl ring is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo and OH;

(111) R^{40} and R^{41}, taken together with the nitrogen atom to which they are attached, form 5-membered heterocyclyl ring, wherein said heterocyclyl ring is optionally substituted with one or more substituents independently selected from methyl, fluoro and OH.

[0054] Suitably, R^1 is as defined in any one of paragraphs (1) to (17) above. In an embodiment, R^1 is as defined in paragraph (2) or (3) above. In another embodiment, R^1 is as defined in paragraph (10) above. In a further embodiment, R^1 is as defined in paragraphs (16) to (17) above.

[0055] Suitably, R^2 is as defined in any one of paragraphs (18) to (19) above. In an embodiment, R^2 is as defined in paragraph (19) above.

[0056] Suitably, R^3 is as defined in any one of paragraphs (20) to (23) above. In another embodiment, R^3 is as defined in paragraphs (22) to (23) above.

[0057] Suitably, R^4 is as defined in paragraph (24) above.

[0058] Suitably, R^5 is as defined in paragraph (25) above.

[0059] Suitably, R^4 and R^5 are as defined in any one of paragraphs (26) to (35) above. In another embodiment, R^4 and R^5 are as defined in paragraph (27) above. In an embodiment, R^4 and R^5 are as defined in paragraphs (32) to (35) above. In a further embodiment, R^4 and R^5 are as defined in paragraph (35) above.

[0060] Suitably, X^1 and X^2 are as defined in any one of paragraphs (36) to (38) above. Preferably, X^1 and X^2 are as defined in paragraph (36) above. In another embodiment, X^1

and X^2 are as defined in any one of paragraphs (49) to (53) above. More preferably, X^1 and X^2 are as defined in paragraph (50) above.

[0061] Suitably, L^1 and L^2 are as defined in any one of paragraphs (39) to (42) above. In another embodiment, L^1 and L^2 are as defined in paragraph (42) above.

[0062] Suitably, R^6 and R^7 are as defined in any one of paragraphs (43) to (48) above. In another embodiment, R^6 and R^7 are as defined in paragraph (47) above.

[0063] Suitably, R^8 is as defined in any one of paragraphs (54) to (55) above. In an embodiment, R^8 is as defined in paragraph (54) above.

[0064] Suitably, R^{8a} is as defined in any one of paragraphs (56) to (57) above. In an embodiment, R^{8a} is as defined in paragraph (57) above.

[0065] Suitably, R^{8b} is as defined in any one of paragraphs (58) to (63) above. In an embodiment, R^{8b} is as defined in paragraph (62) or (63) above.

[0066] Suitably, R^{8a} and R^{8b} are as defined in any one of paragraphs (64) to (70) above. In an embodiment, R^{8a} and R^{8b} are as defined in paragraph (67) or (70) above.

[0067] In a particular embodiment, in any of the above paragraphs, it is provided that R^{8a} and R^{8b} cannot both be equal to hydrogen.

[0068] Suitably, R^{8c} is as defined in any one of paragraphs (71) to (73) above. In an embodiment, R^{8c} is as defined in paragraph (73) above.

[0069] Suitably, R^9 is as defined in any one of paragraphs (74) to (80) above. In an embodiment, R^9 is as defined in paragraph (79) or (80) above. In an embodiment, R^9 is as defined in paragraph (80) above.

[0070] Suitably, R^{10} is as defined in paragraph (81) above.

[0071] Suitably, R^9 and R^{10} are as defined in paragraph (82) above.

[0072] Suitably, L^1, L^2, R^7 and R^{10} are as defined in any one of paragraphs (83) to (90) above. In another embodiment, L^1, L^2, R^7 and R^{10} are as defined in paragraphs (84) to (86) above. In an embodiment, L^2, R^7 and R^{10} are as defined in paragraph (86) above.

[0073] Suitably, R^{11} is as defined in any one of paragraphs (91) to (102) above. In another embodiment, R^{11} is as defined in paragraphs (92) to (93) above. In another embodiment, R^{11} is as defined in paragraphs (99) to (101) above. In a further embodiment, R^1 is as defined in paragraph (2) above and R^{11} is as defined in paragraphs (99) to (101) above.

[0074] Suitably, R^{29} is as defined in paragraphs (103) to (104) above. In an embodiment, R^{29} is as defined in paragraph (104) above.

[0075] Suitably, R^{30} is as defined in paragraphs (105) to (106) above. In an embodiment, R^{30} is as defined in paragraph (106) above.

[0076] Suitably, R^{40} is as defined in paragraph (107) above.

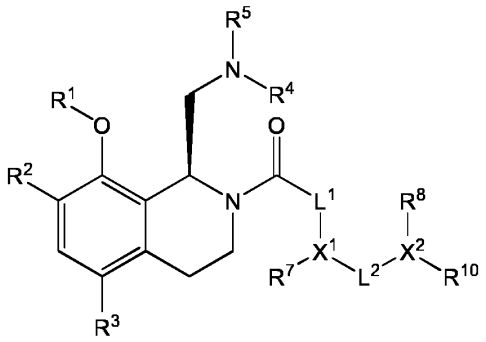
[0077] Suitably, R^{41} is as defined in paragraph (108) above.

[0078] Suitably, R^{40} and R^{41} are as defined in any one of paragraphs (109) to (111) above. In another embodiment, R^{40} and R^{41} are as defined in paragraph (111) above.

[0079] In an embodiment, the compound of formula (I) does not include (1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide, or (1*S*,2*R*)-2-((*S*)-8-(benzo[*d*]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide.

[0080] Conveniently, the compound of Formula (I) has one of the sub-structural formulae (IA) to (IQ) described hereinafter.

[0081] In a further group of compounds, the compounds have the structural formula IA shown below:



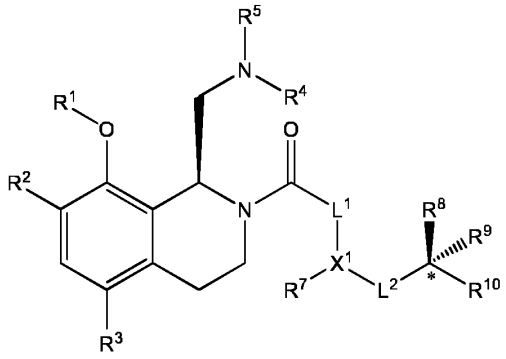
(IA)

wherein L^1, L^2, X^1, X^2 and R^1 to R^{10} are as defined hereinbefore.

[0082] In a further group of compounds, the compounds have the structural formula IA shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; X^1 and X^2 are as defined in any one of paragraphs (36) to (38) above; L^1 and L^2 are as defined in any one of paragraphs (39) to (42) above; R^6 and R^7 are as

defined in any one of paragraphs (43) to (48) above; R^8 is as defined in any one of paragraphs (54) to (55) above; R^9 is as defined in any one of paragraphs (74) to (80) above; and R^{10} is as defined in paragraph (81) above.

[0083] In a further group of compounds, the compounds have the structural formula IB shown below:

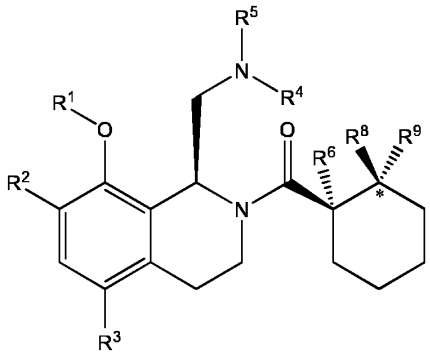


(IB)

wherein L^1, L^2, X^1 and R^1 to R^{10} are as defined hereinbefore.

[0084] In a further group of compounds, the compounds have the structural formula IB shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; X^1 is as defined in any one of paragraphs (36) to (38) above; L^1 and L^2 are as defined in any one of paragraphs (39) to (42) above; R^6 and R^7 are as defined in any one of paragraphs (43) to (48) above; R^8 is as defined in any one of paragraphs (54) to (55) above; R^9 is as defined in any one of paragraphs (74) to (80) above; and R^{10} is as defined in paragraph (81) above.

[0085] In a further group of compounds, the compounds have the structural formula IC shown below:

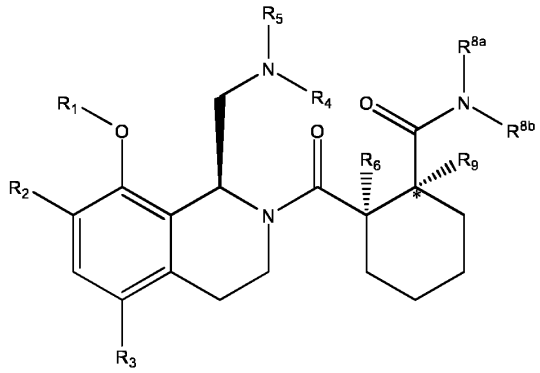


(IC)

wherein R^1 to R^6, R^8 and R^9 are as defined hereinbefore.

[0086] In a further group of compounds, the compounds have the structural formula IC shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; R^6 is as defined in paragraph (45) above; R^8 is as defined in any one of paragraphs (54) to (55) above; and R^9 is as defined in any one of paragraphs (74) to (80) above.

[0087] In a further group of compounds, the compounds have the structural formula ID shown below:

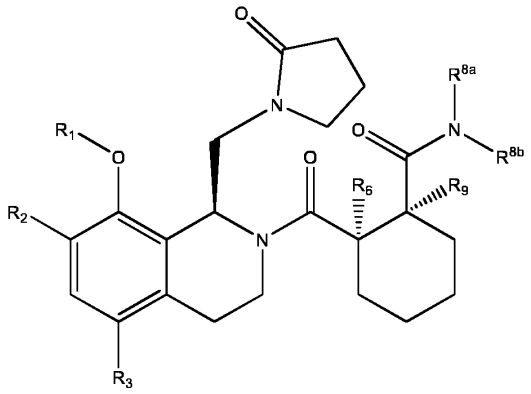


(ID)

wherein R^1 to R^6, R^{8a}, R^{8b} and R^9 are as defined hereinbefore.

[0088] In a further group of compounds, the compounds have the structural formula ID shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (18) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; R^6 is as defined in paragraph (44) above; R^{8a} is as defined in any one of paragraphs (56) to (57) above; R^{8b} is as defined in any one of paragraphs (58) to (63) above; or R^{8a} and R^{8b} combined are as defined in any one of paragraphs (68) to (70) above; and R^9 is as defined in any one of paragraphs (74) to (80) above.

[0089] In a further group of compounds, the compounds have the structural formula IE shown below:



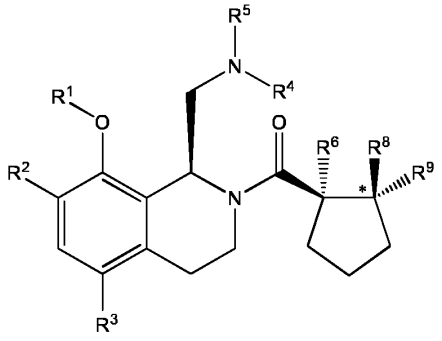
(IE)

wherein R^1 to R^3, R^6, R^{8a}, R^{8b} and R^9 are as defined hereinbefore.

[0090] In a further group of compounds, the compounds have the structural formula IE shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^6 is as defined in paragraph (44) above; R^{8a} is as defined in any one of paragraphs (56) to (57) above; R^{8b} is as defined in any one of paragraphs (58) to (63) above; or R^{8a} and R^{8b} combined are as defined in any one of paragraphs (68) to (70) above; and R^9 is as defined in any one of paragraphs (74) to (80) above.

[0091] In a further group of compounds, the compounds have the structural formula IE shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^6 is as defined in paragraph (45) above; R^{8a} is as defined in paragraph (57) above; R^{8b} is as defined in paragraph (63) above; or R^{8a} and R^{8b} combined are as defined in paragraph (70) above; and R^9 is as defined in paragraph (79) above.

[0092] In a further group of compounds, the compounds have the structural formula IF shown below:



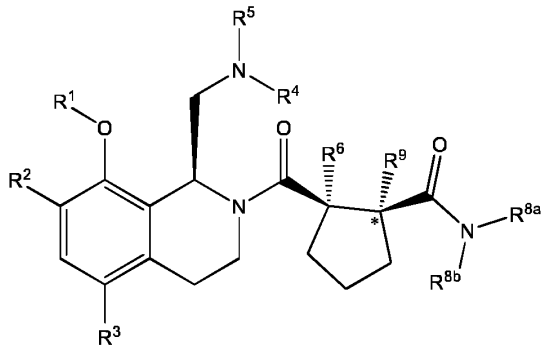
(IF)

wherein R^1 to R^6, R^8 and R^9 are as defined hereinbefore.

[0093] In a further group of compounds, the compounds have the structural formula IF shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; R^6 is as defined in paragraph (45) above; R^8 is as defined in any one of paragraphs (54) to (55) above; and R^9 is as defined in any one of paragraphs (74) to (80) above.

[0094] In a further group of compounds, the compounds have the structural formula IF shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; R^6 is as defined in paragraph (45) above; R^8 is as defined in paragraph (54) above; and R^9 is as defined in paragraph (79) above.

[0095] In a further group of compounds, the compounds have the structural formula IG shown below:

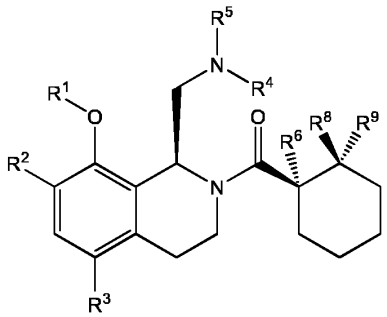


(IG)

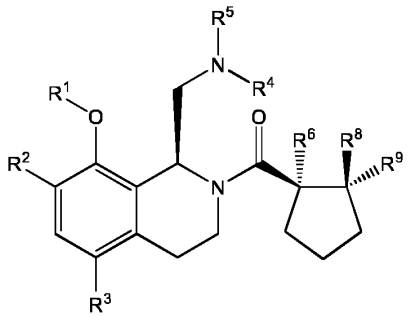
wherein R^1 to R^6, R^{8a}, R^{8b} and R^9 are as defined hereinbefore.

[0096] In a further group of compounds, the compounds have the structural formula IG shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; R^6 is as defined in paragraph (45) above; R^{8a} is as defined in any one of paragraphs (56) to (57) above; R^{8b} is as defined in any one of paragraphs (58) to (63) above; or R^{8a} and R^{8b} combined are as defined in any one of paragraphs (67) to (70) above; and R^9 is as defined in any one of paragraphs (74) to (80) above.

[0097] In a further group of compounds, the compounds have the Formula IC or Formula IF, or a pharmaceutically acceptable salt thereof:



(IC)



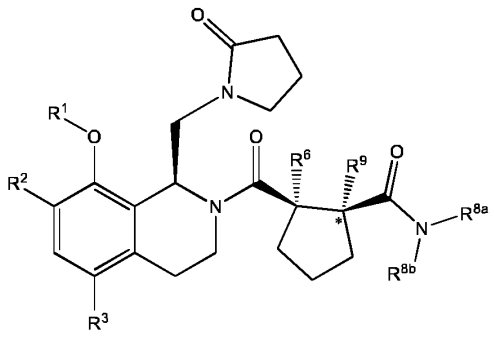
(IF)

wherein R^1 to R^6 and R^8 are as defined hereinbefore and R^9 is methyl; provided that the compound is not (1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide.

[0098] In a further group of compounds, the compounds have the structural formula IC or IF shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; R^6 is as defined in paragraph (45) above; R^8 is as defined in any one of paragraphs (54) to (55) above; and R^9 is methyl.

[0099] In a further group of compounds, the compounds have the structural formula IC or IF shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; R^6 is as defined in paragraph (45) above; R^8 is as defined in paragraph (54) above; and R^9 is methyl.

[00100] In a further group of compounds, the compounds have the structural formula IH shown below:

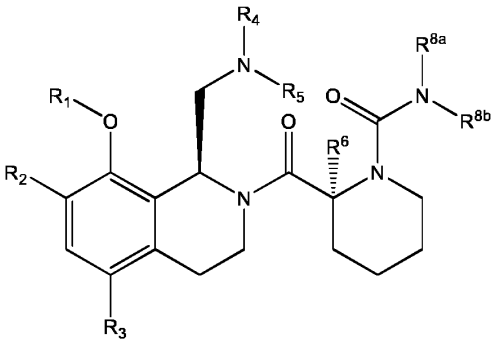


(IH)

wherein R^1 to R^3, R^6, R^{8a}, R^{8b} and R^9 are as defined hereinbefore.

[00101] In a further group of compounds, the compounds have the structural formula IH shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^6 is as defined in paragraph (45) above; R^{8a} is as defined in any one of paragraphs (56) to (57) above; R^{8b} is as defined in any one of paragraphs (58) to (63) above; or R^{8a} and R^{8b} combined are as defined in any one of paragraphs (67) to (70) above; and R^9 is as defined in any one of paragraphs (74) to (80) above.

[00102] In a further group of compounds, the compounds have the structural formula IJ shown below:

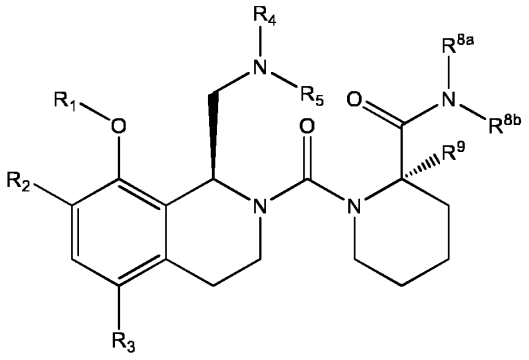


(IJ)

wherein R^1 to R^6, R^{8a} and R^{8b} are as defined hereinbefore.

[00103] In a further group of compounds, the compounds have the structural formula IJ shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; R^6 is as defined in paragraph (45) above; R^{8a} is as defined in any one of paragraphs (56) to (57) above; R^{8b} is as defined in any one of paragraphs (58) to (63) above; or R^{8a} and R^{8b} combined are as defined in any one of paragraphs (67) to (70) above.

[00104] In a further group of compounds, the compounds have the structural formula IK shown below:

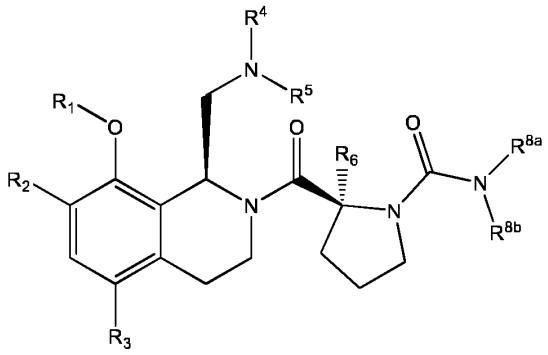


(IK)

wherein R^1 to R^5, R^{8a}, R^{8b} and R^9 are as defined hereinbefore.

[00105] In a further group of compounds, the compounds have the structural formula IK shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; R^{8a} is as defined in any one of paragraphs (56) to (57) above; R^{8b} is as defined in any one of paragraphs (58) to (63) above; or R^{8a} and R^{8b} combined are as defined in any one of paragraphs (67) to (70) above; and R^9 is as defined in any one of paragraphs (74) to (80) above.

[00106] In a further group of compounds, the compounds have the structural formula IL shown below:



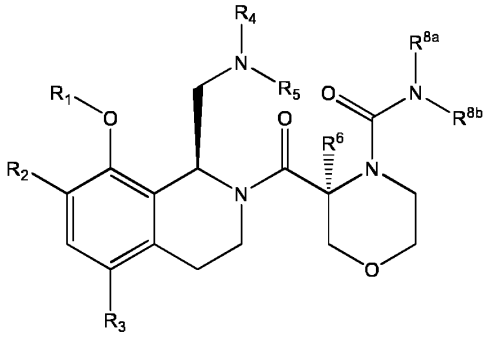
(IL)

wherein R^1 to R^6, R^{8a} and R^{8b} are as defined hereinbefore.

[00107] In a further group of compounds, the compounds have the structural formula IL shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and

(32) to (35) above; R^6 is as defined in paragraph (45) above; R^{8a} is as defined in any one of paragraphs (56) to (57) above; R^{8b} is as defined in any one of paragraphs (58) to (63) above; or R^{8a} and R^{8b} combined are as defined in any one of paragraphs (67) to (70) above.

[00108] In a further group of compounds, the compounds have the structural formula IM shown below:

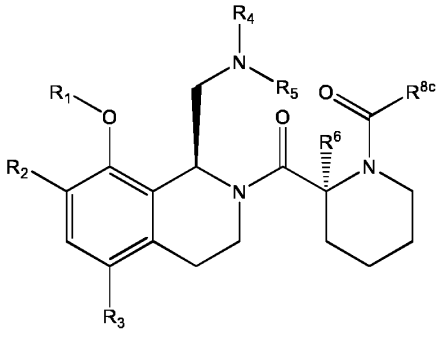


(IM)

wherein R^1 to R^6, R^{8a} and R^{8b} are as defined hereinbefore.

[00109] In a further group of compounds, the compounds have the structural formula IM shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; R^6 is as defined in paragraph (45) above; R^{8a} is as defined in any one of paragraphs (56) to (57) above; R^{8b} is as defined in any one of paragraphs (58) to (63) above; or R^{8a} and R^{8b} combined are as defined in any one of paragraphs (67) to (70) above.

[00110] In a further group of compounds, the compounds have the structural formula IN shown below:



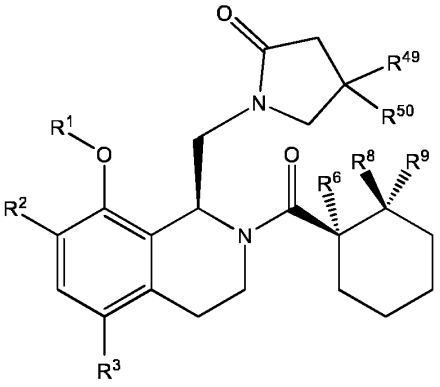
(IN)

wherein R^1 to R^6 and R^{8c} are as defined hereinbefore.

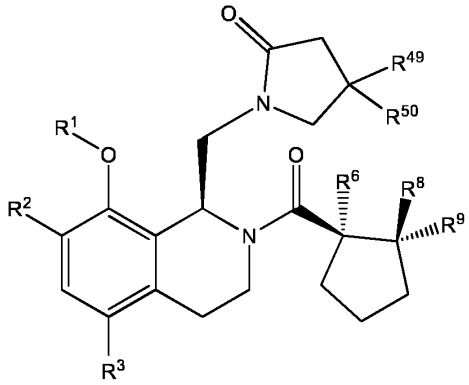
[00111] In a further group of compounds, the compounds have the structural formula IN shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to

(17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^4 and R^5 are as defined in any one of paragraphs (27) and (32) to (35) above; R^6 is as defined in paragraph (45) above; and R^{8c} is as defined in any one of paragraphs (71) to (73) above.

[00112] In a further group of compounds, the compounds have the Formula IP or IQ, or a pharmaceutically acceptable salt thereof:



(IP)



(IQ)

wherein R^1 to R^3, $R^6$and R^8 are as defined hereinbefore, R^9 is methyl and R^{49} and R^{50} are independently selected from hydrogen, C_{1-4}alkyl and halo; or R^{49} and R^{50}, together with the carbon atom to which they are attached, form a cyclopropyl or cyclobutyl ring.

[00113] In a further group of compounds, the compounds have the structural formula IP or IQ shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is as defined in any one of paragraphs (22) to (23) above; R^6 is as defined in paragraph (45) above; R^8 is as defined in any one of paragraphs (54) to (55) above; R^9 is methyl; and R^{49} and R^{50} are independently selected from hydrogen and C_{1-3}alkyl; or R^{49} and R^{50}, together with the carbon atom to which they are attached, form a cyclopropyl or cyclobutyl ring.

[00114] In a further group of compounds, the compounds have the structural formula IP or IQ shown above, wherein R^1 is as defined in any one of paragraphs (2) to (3), (10) or (16) to (17) above; R^2 is as defined in paragraph (19) above; R^3 is chloro; R^6 is as defined in paragraph (45) above; R^8 is as defined in paragraph (54) above; R^9 is methyl; and R^{49} and R^{50} are independently selected from hydrogen and methyl; or R^{49} and R^{50}, together with the carbon atom to which they are attached, form a cyclopropyl ring.

[00115] Particular compounds of the present invention include any one of the following:

(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(4-(methylamino)-4-oxobutoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;

N-(2-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(ethylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-5-methylisoxazole-3-carboxamide;

(1*S*,2*R*)-2-((*S*)-1-(cyclopropanecarboxamidomethyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;

(1*S*,2*R*)-2-((*S*)-8-((1*H*-pyrazol-5-yl)methoxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;

(1*S*,2*R*)-2-((*S*)-1-(acetamidomethyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;

(1*S*,2*R*)-*N*-methyl-2-((*S*)-1-((2-oxooxazolidin-3-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;

4-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)butanoic acid;

(*R*)-1-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylpiperidine-2-carboxamide;

(*S*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylpyrrolidine-1-carboxamide;

1-(((*S*)-5-chloro-2-((*S*)-1-(2,2-difluoroacetyl)piperidine-2-carbonyl)-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)pyrrolidin-2-one;

(*S*)-6-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methyl-5-azaspiro[2.4]heptane-5-carboxamide;

(1*R*,2*S*)-2-((*R*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(4-oxo-4-(pyrrolidin-1-yl)butoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;

5-cyclopropyl-N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)isoxazole-3-carboxamide;

N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-4,5-dimethylisoxazole-3-carboxamide;

(1S,2R)-2-((S)-8-(((S)-1-acetylpyrrolidin-3-yl)oxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

N-(2-(((S)-2-((1R,2S)-2-(cyclopropylcarbamoyl)cyclohexane-1-carbonyl)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-5-methylisoxazole-3-carboxamide;

N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(3-hydroxyazetidine-1-carbonyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-5-methylisoxazole-3-carboxamide;

N-(2-(((S)-2-((1R,2S)-2-(cyclobutylcarbamoyl)cyclohexane-1-carbonyl)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-5-methylisoxazole-3-carboxamide;

5-cyclopropyl-N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)isoxazole-3-carboxamide;

N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)benzo[d]oxazole-2-carboxamide;

N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)benzo[d]isoxazole-3-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(2-((5-methylisoxazole)-4-sulfonamido)ethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(pyrimidine-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-nicotinoylpyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-((5-methylisoxazol-4-yl)sulfonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)thiazole-2-carboxamide;

(1S,2R)-2-((S)-8-(((S)-1-(cyclopropanecarbonyl)pyrrolidin-3-yl)oxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(5-methylisoxazole-3-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(oxazol-5-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(2-methylthiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-8-(((S)-1-(2,4-dimethylthiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(2-methylthiazole-4-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(R)-4-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinolin-2(1H)-yl)-N,3-dimethyl-4-oxobutanamide;

(1S,2R)-N-methyl-2-((S)-1-((2-oxopyrrolidin-1-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(pyrazin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(S)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylpiperidine-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-propylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(2-methoxyethyl)cyclohexane-1-carboxamide;

(1S,2R)-N-(2,2-difluoroethyl)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(2,2,2-trifluoroethyl)cyclohexane-1-carboxamide;

(1S,2R)-N-(cyanomethyl)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;

(1S,2R)-N-(2,2-difluoro-3-hydroxypropyl)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(2-hydroxyethyl)cyclohexane-1-carboxamide;

1-((S)-1-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinolin-2(1H)-yl)-1-oxopropan-2-yl)-3-methylurea;

(1S,2R)-2-((S)-8-(((S)-1-acetylpyrrolidin-3-yl)oxy)-5-chloro-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

5-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinolin-2(1H)-yl)-N-methyl-5-oxopentanamide;

4-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinolin-2(1H)-yl)-N-methyl-4-oxobutanamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-ethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(3-hydroxypropyl)cyclohexane-1-carboxamide;

(1S,2R)-N-methyl-2-((S)-1-(propionamidomethyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-((1-methyl-1H-pyrazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-8-(((S)-1-acetylpyrrolidin-3-yl)oxy)-5-bromo-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

methyl (S)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)pyrrolidine-1-carboxylate;

(1S,2R)-2-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-ethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-bromo-8-((5-isopropyl-1,2,4-oxadiazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-bromo-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-isopropyl-1,2,4-oxadiazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(2R,3R)-4-((S)-5-chloro-8-((5-isopropyl-1,2,4-oxadiazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)-N,2,3-trimethyl-4-oxobutanamide;

(1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyridin-3-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyridazin-3-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyrazin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyrimidin-5-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclopentane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-(2-(1-methyl-1H-1,2,3-triazol-4-yl)ethoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((3-methyl-3H-imidazo[4,5-b]pyridin-6-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-(isoxazolo[5,4-b]pyridin-3-ylmethoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((3-methylisoxazolo[5,4-b]pyridin-6-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-8-([1,2,4]triazolo[4,3-a]pyridin-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-(imidazo[1,2-a]pyrimidin-2-ylmethoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-8-([1,2,4]triazolo[4,3-a]pyridin-3-ylmethoxy)-5-chloro-1-((1-oxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(2,2-difluoro-3-hydroxypropyl)cyclohexane-1-carboxamide;

(S)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylpiperidine-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((3-methyl-3H-imidazo[4,5-b]pyridin-5-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-indazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

3-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methyltetrahydrofuran-2-carboxamide;

(1S,2R)-2-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclopentane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((4,5-dimethyl-4H-1,2,4-triazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(S)-3-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylmorpholine-4-carboxamide;

(S)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylpyrrolidine-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1,5-dimethyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(S)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylpiperidine-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclopentane-1-carboxamide;

(1S,2R)-2-((1S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclopentane-1-carboxamide;

(1S,2R)-2-((1S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1,5-dimethyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(methoxymethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((3-oxomorpholino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-7-fluoro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-8-((4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridin-3-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1,5-dimethyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide; or

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

[00116] In an embodiment, the compound of formula (I) is selected from one of the following compounds:

(1*S*,2*R*)-2-((*S*)-5-bromo-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;

(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;

2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclopentane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((3-methyl-3H-imidazo[4,5-b]pyridin-6-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1*S*,2*R*)-2-((*S*)-5-chloro-8-((3-methylisoxazolo[5,4-*b*]pyridin-6-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-8-([1,2,4]triazolo[4,3-a]pyridin-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;

(1*S*,2*R*)-2-((*S*)-8-([1,2,4]triazolo[4,3-*a*]pyridin-3-ylmethoxy)-5-chloro-1-((1-oxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;

(*S*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylpiperidine-1-carboxamide;

(1S,2R)-2-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclopentane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((4,5-dimethyl-4H-1,2,4-triazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(S)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylpyrrolidine-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1,5-dimethyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(S)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylpiperidine-1-carboxamide;

(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclopentane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1,5-dimethyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(methoxymethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((3-oxomorpholino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-7-fluoro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-8-((4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridin-3-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1,5-dimethyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide; or

(1*R*,2*S*)-2-((*R*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

[00117] In an embodiment, the compound is a compound of formula (IC) or formula (IF) and is selected from one of the following compounds:

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclopentane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1,5-dimethyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclopentane-1-carboxamide;

(1S,2R)-2-((1S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclopentane-1-carboxamide;

(1S,2R)-2-((1S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1,5-dimethyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(methoxymethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((3-oxomorpholino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-7-fluoro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-8-((4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridin-3-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1,5-dimethyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide; or

(1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

[00118] The various functional groups and substituents making up the compounds of the present invention are typically chosen such that the molecular weight of the compound does not exceed 1000. More usually, the molecular weight of the compound will be less than 750, for example less than 700, or less than 650.

[00119] Suitable or preferred features of any compounds of the present invention may also be suitable features of any other aspect.

[00120] A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulfuric, phosphoric, trifluoroacetic, formic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

[00121] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed

"stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric centre, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric centre and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[00122] The compounds of this invention typically possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers, diastereoisomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 2001), for example by synthesis from optically active starting materials or by resolution of a racemic form. Some of the compounds of the invention may have geometric isomeric centres (E- and Z- isomers). It is to be understood that the present invention encompasses all optical, diastereoisomers and geometric isomers and mixtures thereof that possess Nrf2 activation activity.

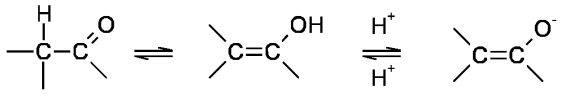
[00123] The present invention also encompasses compounds of the invention as defined herein which comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D) and ^{3}H (T); C may be in any isotopic form including ^{12}C, ^{13}C, and ^{14}C; and O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

[00124]It is also to be understood that certain compounds of the invention may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms that possess Nrf2 activation activity.

[00125] It is also to be understood that certain compounds of the invention may exhibit polymorphism, and that the invention encompasses all such forms that possess Nrf2 activation activity.

[00126] Compounds of the invention may exist in a number of different tautomeric forms and references to compounds of the invention include all such forms. For the avoidance

of doubt, where a compound can exist in one of several tautomeric forms, and only one is specifically described or shown, all others are nevertheless embraced by compounds of the invention. Examples of tautomeric forms include keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



[00127] Compounds of the invention containing an amine function may also form *N*-oxides. A reference herein to a compound of the formula I that contains an amine function also includes the *N*-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an *N*-oxide. Particular examples of *N*-oxides are the *N*-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. *N*-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, *N*-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* 1977, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

[00128] The compounds of the invention may be administered in the form of a pro-drug which is broken down in the human or animal body to release a compound of the invention. A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed when the compound of the invention contains a suitable group or substituent to which a property-modifying group can be attached.

[00129] Accordingly, the present invention includes those compounds of the formula I as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of the formula I that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the formula I may be a synthetically-produced compound or a metabolically-produced compound.

[00130] A suitable pharmaceutically acceptable pro-drug of a compound of the formula I is one that is based on reasonable medical judgement as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

[00131] Various forms of pro-drug have been described, for example in the following documents:

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

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

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

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

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

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

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

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

[00132] The *in vivo* effects of a compound of the formula I may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the formula I. As stated hereinbefore, the *in vivo* effects of a compound of the formula I may also be exerted by way of metabolism of a precursor compound (a pro-drug).

[00133] It shall also be appreciated that compounds of the formula I may also be covalently linked (at any suitable position) to other groups such as, for example, solubilising moieties (for example, PEG polymers), moieties that enable them to be bound to a solid support (such as, for example, biotin-containing moieties), and targeting ligands (such as antibodies or antibody fragments).

Synthesis

[00134] In the description of the synthetic methods described below and in the referenced synthetic methods that are used to prepare the starting materials, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be selected

by a person skilled in the art.

[00135] It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reaction conditions utilised.

[00136] Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively, necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

[00137] It will be appreciated that during the synthesis of the compounds of the invention in the processes defined below, or during the synthesis of certain starting materials, it may be desirable to protect certain substituent groups to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed.

[00138] For examples of protecting groups see one of the many general texts on the subject, for example, "Protecting groups in Organic Synthesis (3rd Ed), John Wiley & Sons, NY (1999)", T. Greene & P. Wuts. Protecting groups may be removed by any convenient method described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with the minimum disturbance of groups elsewhere in the molecule.

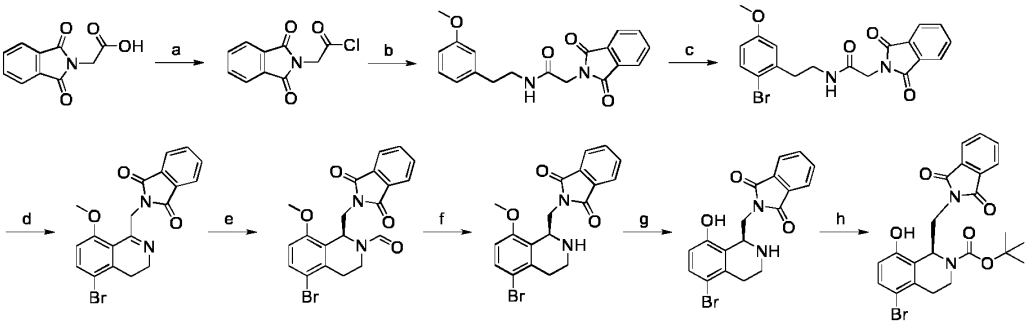
[00139] Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

[00140] By way of example, a suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed by, for example, hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively, an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for

example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example $BF_3.OEt_2$. A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

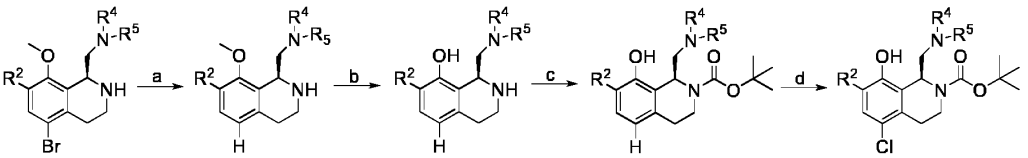
[00141] The person skilled in the art will recognise that the compounds of the invention may be prepared, in known manner, in a variety of ways. Compounds of formula I can be prepared by the methods given below, by the methods given in the experimental or by analogous methods. The routes described are merely illustrative of some of the methods that can be employed for the synthesis of compounds of formula I and the person skilled in the art will appreciate that the order of the reaction steps is not limited to those described. It will also be appreciated that the assignment of nucleophile and electrophile is not limited to that described herein and in some cases it may be appropriate for the assignment to be reversed. Different approaches to synthetic chemistry strategy are described in "Organic Synthesis: The Disconnection Approach", 2nd edition, S. Warren and P. Wyatt (2008).

[00142] The tetrahydroisoquinoline (THIQ) scaffold, wherein R^3 is bromo, may be constructed according to the route outlined in Scheme 1.



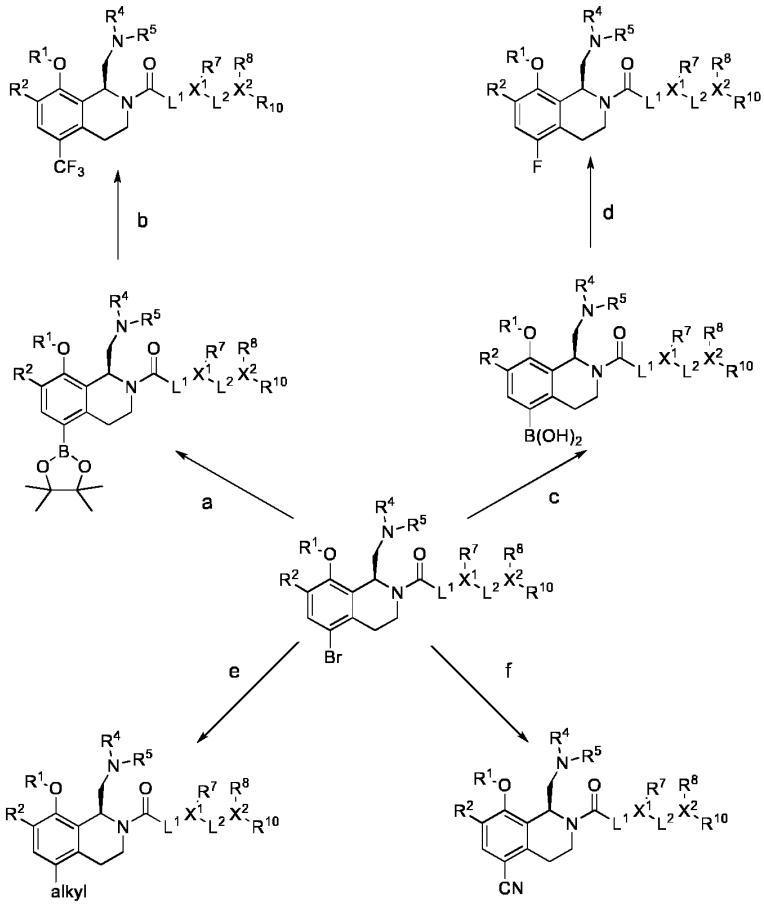
Scheme 1: a) $SOCl_2$, EtOAc; b) 2-(3-methoxyphenyl)ethan-1-amine, Et_3N, DCM; c) NBS, DMF; d) P_2O_5, MeCN; e) benzeneruthenium(II) chloride dimer, (1*S*,2*S*)-(+)-*N*-*p*-tosyl-1,2-diphenylethylene-diamine, Et_3N, HCO_2H, MeCN; f) HCl, THF; g) BBr_3, DCM; h) Boc_2O, DCM.

[00143] Variations at the R^3 position can be conveniently prepared from compounds of the invention or intermediates thereof wherein R^3 is bromo from chemistry well known in the art, as illustrated in Schemes 2 and 3. Compounds of the invention wherein R^3 is H, or Cl may be prepared from intermediates where R^3 is Br according to the method outlined in Scheme 2.



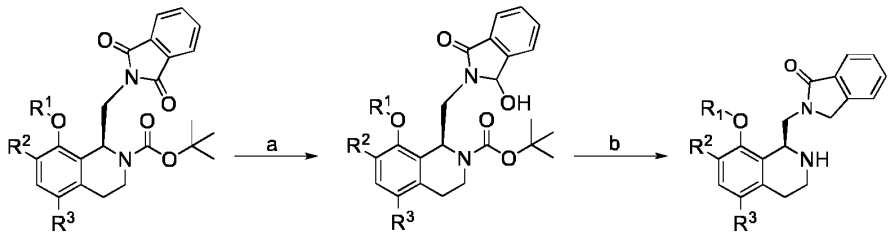
Scheme 2: a) H_2, 10% Pd/C, THF, EtOH; b) BBr_3, DCM; c) Boc_2O, DCM; d) NCS, DMF.

[00144] As shown in Scheme 3, the conversion of the bromo R^3 substituent into a suitable boronate or boronic acid allows preparation of the fluoro and trifluoro derivatives. The bromo can be converted to an alkyl group through reaction with a suitable alkyl boronate with a suitable palladium catalyst; for example, where alkyl is methyl, a suitable boronate is 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane and a suitable palladium catalyst is $Pd(dppf)Cl_2$. Compounds wherein R^3 is cyano can be prepared from bromo derivatives by treatment with a cyanating agent such as $Zn(CN)_2$ with a palladium catalyst such as $Pd(PPh_3)_4$.



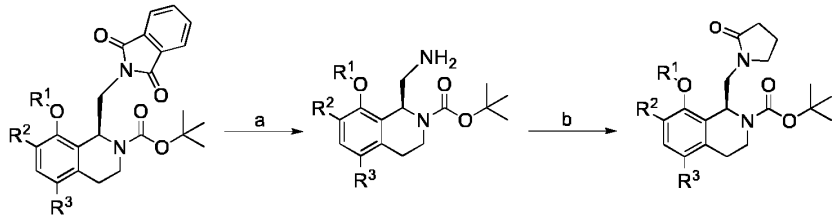
Scheme 3: a) dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane, X-phos Pd, hypoboric acid; b) CF_3SO_3Ag, SelectFluor®; c) bis(pinacolato)diboron, $Pd(dppf)Cl_2$; d) potassium trimethoxy(trifluoromethyl)boranide, $Cu(OAc)_2$; e) $Pd(dppf)Cl_2$, alkyl borane; f) $Zn(CN)_2$, $Pd(PPh_3)_4$.

[00145] Compounds of the invention wherein $-NR^4R^5$ represents an indolinone may be prepared by reduction of the corresponding phthalimide sequentially with sodium borohydride and then triethylsilane, according to Scheme 4.



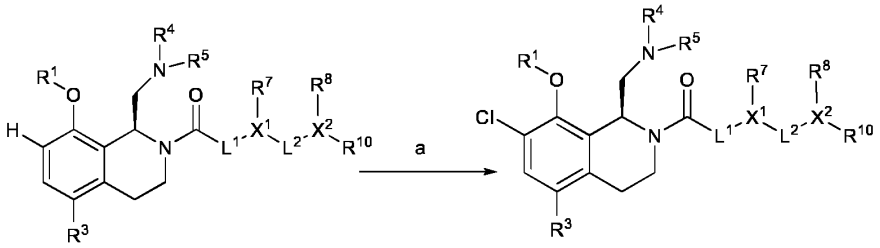
Scheme 4: a) $NaBH_4$, MeOH; b) TFA, Et_3SiH.

[00146] Compounds of the invention wherein the group $-NR^4R^5$ represents a pyrrolidinone may be prepared from intermediates wherein $-NR^4R^5$ represents a phthalimide group by removal of the phthalimide group with hydrazine, followed by conversion of the resulting primary amine to a pyrrolidinone by reaction with an appropriate lactone or ω-halo ester, or to an indolinone according to the routes outlined in Scheme 5.



Scheme 5: a) N_2H_4, EtOH; b) methyl 4-bromobutanoate, Et_3N, PhMe.

[00147] Compounds of the invention wherein R^2 is a halo substituent may be prepared from intermediates or Examples of the invention wherein R^2 is hydrogen by treatment with a suitable halogenating agent, such as *N*-chlorosuccinimide, as shown in Scheme 6.

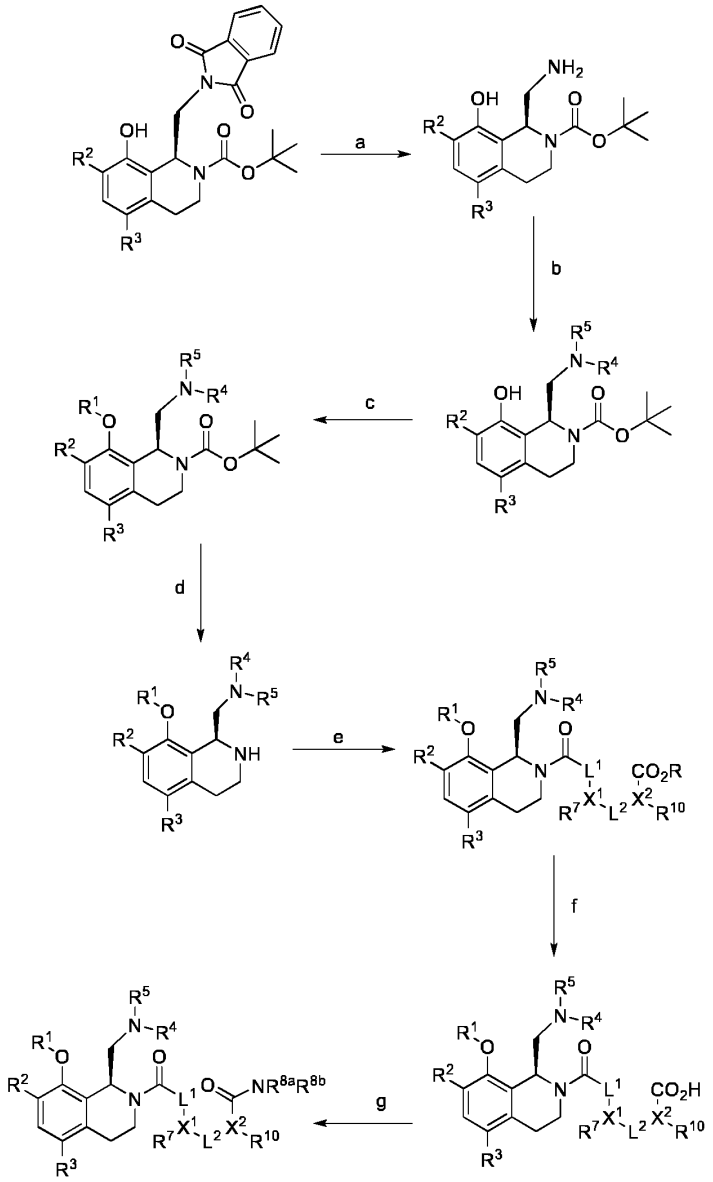


Scheme 6: a) NCS, DCM/DMF.

General Method A

[00148] In a typical synthetic procedure the phthalimide, when used as a protecting group, is removed using typical reagents (e.g. hydrazine) and the amine is reacted with appropriate reagents to install the desired substitution NR^4R^5. A third step involves installation of the required ether through conventional methods such as alkylation with an alkyl halide or activated alcohol (e.g. mesylate, triflate) or Mitsunobu reaction using reagents such as DBAD or DEAD and an appropriate phosphine. The Boc protecting group is then removed typically by treatment with HCl. The $L^1X^1(R^7)L^2X^2(CO_2R)R^{10}$ group may be

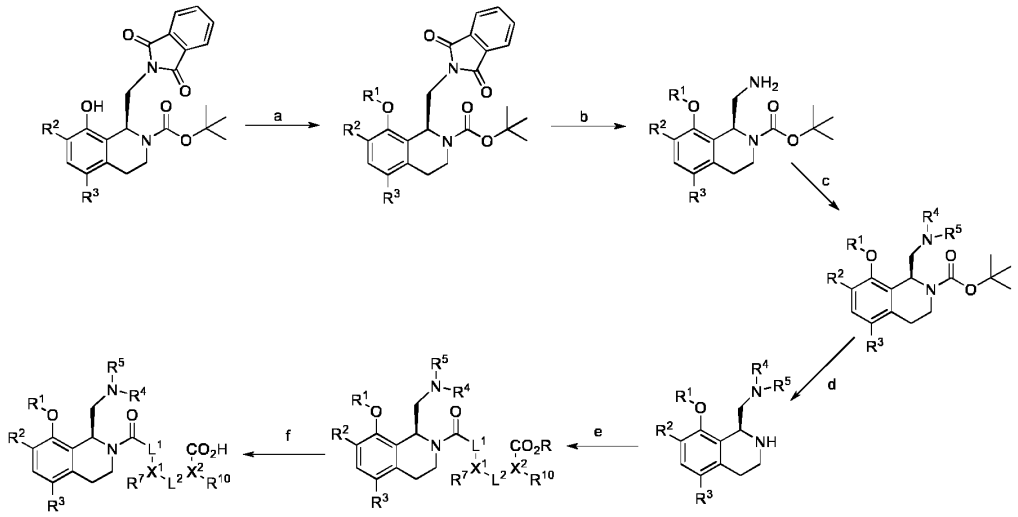
introduced from the appropriately substituted and protected bis-acid derivative; ideally where one of the acid groups is activated for reaction with the amine of the tetrahydroisoquinoline (THIQ) scaffold and the other acid group is suitably protected, for example as a benzyl or dimethoxybenzyl ester, or by ring opening of an appropriate cyclic anhydride, or by reaction with an acid chloride. Typical amide coupling reagents such as HATU are used to effect acid activation.



[00149] In a penultimate step, the protecting group is removed by the appropriate methodology such as hydrolysis, hydrogenolysis, strong acid such as HCl or TFA or lewis acid such as BBr_3 to give the carboxylic acid. In a final step the carboxylic acid is converted

to a primary, secondary or tertiary amide using amide coupling reactions and agents well known in the art, such as HATU and 1,1'-carbonyldiimidazole (CDI).

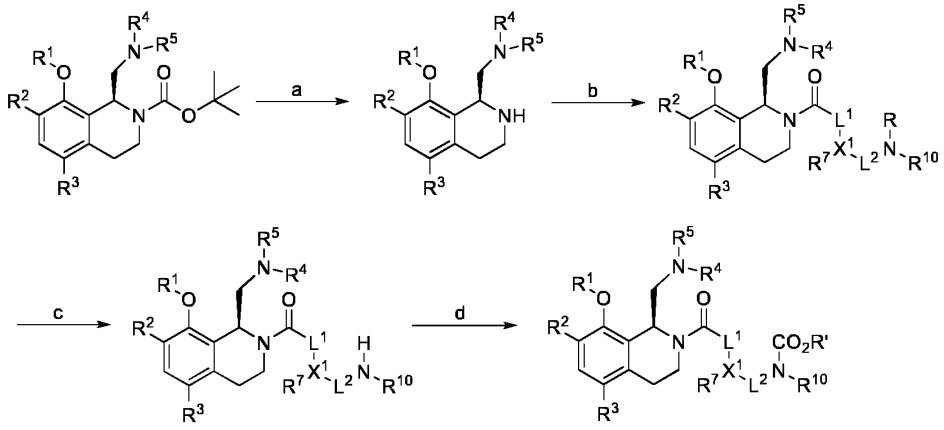
General Method B



[00150] In a further typical procedure, the order of steps can be altered compared with general method A. The required ether is installed in a first step, again through conventional methods as described in the above General Method A. The phthalimide protecting group is removed in a second step and the amine is reacted with appropropriate reagents to install the desired substitution NR^4R^5. The Boc protecting group is then removed and the $L^1X^1(R^7)L^2X^2(CO_2R)R^{10}$ group may then be introduced in a fifth step. The final step comprises removal of the carboxylic acid protecting group as described in the above general methods.

[00151] Syntheses of example carboxylic acid compounds are described in the co-pending application PCT/GB2019/053012 (WO2020/084300).

General Method C



In a further typical procedure the $L^1X^1(R^7)L^2N(R)R^{10}$ group may be introduced from the appropriately substituted and protected mono-acid derivative; ideally where the acid group is activated for reaction with the amine of the tetrahydroisoquinoline (THIQ) scaffold and the amine group is suitably protected, for example as a *tert*-butoxycarbonyl, or by reaction with an appropriate acid chloride.

Pharmaceutical Compositions

[00152] The compounds of the invention will normally, but not necessarily, be formulated into pharmaceutical compositions prior to administration to a patient. Therefore, according to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, diluent or carrier.

[00153] The pharmaceutical compositions of the invention may be prepared and packaged in bulk form wherein a safe and effective amount of a compound of the invention can be extracted and then given to the patient such as with powders or syrups. Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged in unit dosage form wherein each physically discrete unit contains a safe and effective amount of a compound of the invention. When prepared in unit dosage form, the pharmaceutical compositions of the invention typically contain from 1 mg to 1000 mg.

[00154] The compositions of the invention may be in a form suitable for oral use (for example as tablets, capsules, caplets, pills, troches, powders, syrups, elixirs, suspensions, solutions, emulsions, sachets, and cachets), for topical use (for example as creams, ointments, lotions, solutions, pastes, sprays, foams, and gels), for transdermal administration such as *via* transdermal patches, for administration by inhalation (for example as a dry powders, aerosols, suspensions, and solutions), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

[00155] As used herein, "pharmaceutically-acceptable excipient" means a pharmaceutically acceptable material, composition or vehicle involved in giving form or consistency to the pharmaceutical composition. Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would substantially reduce the efficacy of the compound of the invention when administered to a patient and interactions which would result in pharmaceutical

compositions that are not pharmaceutically acceptable are avoided. In addition, each excipient must be of sufficiently high purity to render it pharmaceutically-acceptable.

[00156] Suitable pharmaceutically-acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically-acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the carrying or transporting of the compound or compounds of the invention once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically-acceptable excipients may be chosen for their ability to enhance patient compliance.

[00157] Suitable pharmaceutically-acceptable excipients include the following types of excipients: diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anticaking agents, humectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents. The person skilled in the art will appreciate that certain pharmaceutically-acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

[00158] Persons skilled in the art possess the knowledge and skill to enable them to select suitable pharmaceutically-acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically-acceptable excipients and may be useful in selecting suitable pharmaceutically-acceptable excipients. Examples include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

[00159] The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

[00160] The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

[00161] The size of the dose for therapeutic or prophylactic purposes of a compound of the formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

[00162] In using a compound of the invention for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general, lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous or intraperitoneal administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration may also be suitable, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

Routes of Administration

[00163] The compounds of the invention or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/peripherally or topically (i.e. at the site of desired action).

[00164] Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eyedrops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., *via* an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

[00165] In a preferred embodiment, a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, is administered orally or *via* inhalation.

Therapeutic Uses and Applications

[00166] The compounds of the invention are activators of Nrf2. As a consequence, they are potentially useful therapeutic agents for the treatment of diseases or conditions mediated by Nrf2 activation.

[00167] Thus, in one aspect, the present invention relates to a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in therapy.

[00168] In another aspect, the present invention relates to a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of diseases or disorders mediated by Nrf2 activation.

[00169] In another aspect, the present invention relates to the use of a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of diseases or disorders mediated by Nrf2 activation.

[00170] In another aspect, the present invention relates to a method of treating a disease or disorders mediated by Nrf2 activation, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound of the invention as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00171] Examples of particular diseases or conditions that the compounds of formula (I) and their pharmaceutically acceptable salts may be used to treat include, but are not limited to, any one of the following: chronic obstructive pulmonary disease, acute, chronic and severe asthma, acute lung injury/acute respiratory distress syndrome with or without accompanying multi organ dysfunction syndrome, pulmonary fibrosis including idiopathic pulmonary fibrosis, cystic fibrosis, COVID-19, diabetes, atherosclerosis, hypertension, heart failure, myocardial infarction and repair, cardiac remodelling, cardiac arrhythmias, cardiac hypertrophy, heart failure with preserved ejection fraction, diabetic cardiomyopathy, sarcopenia, obesity, metabolic syndrome, diabetes mellitus, insulin resistance, pulmonary arterial hypertension, subarachnoid haemorrhage, intracerebral haemorrhage, ischemic stroke, beta-thalassemia, sickle cell disease, rheumatoid arthritis,

irritable bowel disorder, ulcerative colitis, Crohn's disease, psoriasis, radiation-induced dermatitis, atopic dermatitis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, toxin-induced liver disease, viral hepatitis and cirrhosis, chronic kidney disease, diabetic nephropathy, autosomal dominant polycystic kidney disease, CKD associated with type 1 diabetes (T1D), IgA nephropathy (IgAN), Alport Syndrome, focal segmental glomerulosclerosis, Huntington's disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal dementia, multiple sclerosis, Friedreich's ataxia, chronic pain, schizophrenia, lung cancer, breast cancer, colon cancer, age related macular degeneration (AMD), Fuchs Endothelial Corneal Dystrophy, uveitis or preeclampsia.

[00172] In particular, the compounds of the invention (including pharmaceutically acceptable salts) may be used in the treatment of chronic obstructive pulmonary disease, asthma, pulmonary arterial hypertension, diabetes mellitus, chronic kidney disease, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Friedreich's ataxia, sickle cell disease or non-alcoholic steatohepatitis.

[00173] In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of chronic obstructive pulmonary disease, acute, chronic and severe asthma, acute lung injury/acute respiratory distress syndrome with or without accompanying multi organ dysfunction syndrome, pulmonary fibrosis including idiopathic pulmonary fibrosis, cystic fibrosis, COVID-19, diabetes, atherosclerosis, hypertension, heart failure, myocardial infarction and repair, cardiac remodelling, cardiac arrhythmias, cardiac hypertrophy, heart failure with preserved ejection fraction, diabetic cardiomyopathy, sarcopenia, obesity, metabolic syndrome, diabetes mellitus, insulin resistance, pulmonary arterial hypertension, subarachnoid haemorrhage, intracerebral haemorrhage, ischemic stroke, beta-thalassemia, sickle cell disease, rheumatoid arthritis, irritable bowel disorder, ulcerative colitis, Crohn's disease, psoriasis, radiation-induced dermatitis, atopic dermatitis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, toxin-induced liver disease, viral hepatitis and cirrhosis, chronic kidney disease, diabetic nephropathy, autosomal dominant polycystic kidney disease, CKD associated with type 1 diabetes (T1D), IgA nephropathy (IgAN), Alport Syndrome, focal segmental glomerulosclerosis, Huntington's disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal dementia, multiple sclerosis, Friedreich's ataxia, chronic pain, schizophrenia, lung cancer, breast cancer, colon cancer, age related macular degeneration (AMD), Fuchs Endothelial Corneal Dystrophy, uveitis or preeclampsia.

[00174] In another aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of chronic obstructive pulmonary disease, asthma, pulmonary arterial hypertension, diabetes mellitus, chronic kidney disease, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Friedreich's ataxia, sickle cell disease or non-alcoholic steatohepatitis.

[00175] In another aspect, the present invention provides the use of a compound, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease, acute, chronic and severe asthma, acute lung injury/acute respiratory distress syndrome with or without accompanying multi organ dysfunction syndrome, pulmonary fibrosis including idiopathic pulmonary fibrosis, cystic fibrosis, COVID-19, diabetes, atherosclerosis, hypertension, heart failure, myocardial infarction and repair, cardiac remodelling, cardiac arrhythmias, cardiac hypertrophy, heart failure with preserved ejection fraction, diabetic cardiomyopathy, sarcopenia, obesity, metabolic syndrome, diabetes mellitus, insulin resistance, pulmonary arterial hypertension, subarachnoid haemorrhage, intracerebral haemorrhage, ischemic stroke, beta-thalassemia, sickle cell disease, rheumatoid arthritis, irritable bowel disorder, ulcerative colitis, Crohn's disease, psoriasis, radiation-induced dermatitis, atopic dermatitis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, toxin-induced liver disease, viral hepatitis and cirrhosis, chronic kidney disease, diabetic nephropathy, autosomal dominant polycystic kidney disease, CKD associated with type 1 diabetes (T1D), IgA nephropathy (IgAN), Alport Syndrome, focal segmental glomerulosclerosis, Huntington's disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal dementia, multiple sclerosis, Friedreich's ataxia, chronic pain, schizophrenia, lung cancer, breast cancer, colon cancer, age related macular degeneration (AMD), Fuchs Endothelial Corneal Dystrophy, uveitis or preeclampsia.

[00176] In another aspect, the present invention provides the use of a compound, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease, asthma, pulmonary arterial hypertension, diabetes mellitus, chronic kidney disease, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Friedreich's ataxia, sickle cell disease or non-alcoholic steatohepatitis.

[00177] In another aspect, the present invention provides a method of treating chronic obstructive pulmonary disease, acute, chronic and severe asthma, acute lung injury/acute respiratory distress syndrome with or without accompanying multi organ dysfunction syndrome, pulmonary fibrosis including idiopathic pulmonary fibrosis, cystic fibrosis,

COVID-19, diabetes, atherosclerosis, hypertension, heart failure, myocardial infarction and repair, cardiac remodelling, cardiac arrhythmias, cardiac hypertrophy, heart failure with preserved ejection fraction, diabetic cardiomyopathy, sarcopenia, obesity, metabolic syndrome, diabetes mellitus, insulin resistance, pulmonary arterial hypertension, subarachnoid haemorrhage, intracerebral haemorrhage, ischemic stroke, beta-thalassemia, sickle cell disease, rheumatoid arthritis, irritable bowel disorder, ulcerative colitis, Crohn's disease, psoriasis, radiation-induced dermatitis, atopic dermatitis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, toxin-induced liver disease, viral hepatitis and cirrhosis, chronic kidney disease, diabetic nephropathy, autosomal dominant polycystic kidney disease, CKD associated with type 1 diabetes (T1D), IgA nephropathy (IgAN), Alport Syndrome, focal segmental glomerulosclerosis, Huntington's disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal dementia, multiple sclerosis, Friedreich's ataxia, chronic pain, schizophrenia, lung cancer, breast cancer, colon cancer, age related macular degeneration (AMD), Fuchs Endothelial Corneal Dystrophy, uveitis or preeclampsia, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00178] In another aspect, the present invention provides a method of treating chronic obstructive pulmonary disease, asthma, pulmonary arterial hypertension, diabetes mellitus, chronic kidney disease, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Friedreich's ataxia, sickle cell disease or non-alcoholic steatohepatitis, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00179] In another aspect, the present invention provides a method of activating Nrf2 *in vitro*, said method comprising administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof.

[00180] In another aspect, the present invention provides a method of activating Nrf2 *in vivo*, said method comprising administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof.

[00181] In another aspect, the present invention provides a method of activating Nrf2 *in vitro* and/or *in vivo*, said method comprising contacting a cell with an effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof.

Combination Therapies

[00182] The compounds of the invention may be administered alone as a monotherapy or may administered in combination with one or more additional therapeutic agents. The selection of the one or more additional therapeutic agents will of course vary depending on the disease or condition to be treated and its severity.

[00183] It is commonplace to use combination therapies to treat certain medical conditions.

[00184] According to a particular aspect of the invention there is provided a combination suitable for use in the treatment of a disease or condition in which Nrf2 activation is implicated, comprising a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt thereof, and another therapeutic agent.

[00185] According to this aspect of the invention there is provided a combination suitable for use in the prevention or treatment of chronic obstructive pulmonary disease, acute, chronic and severe asthma, acute lung injury/acute respiratory distress syndrome with or without accompanying multi organ dysfunction syndrome, pulmonary fibrosis including idiopathic pulmonary fibrosis, cystic fibrosis, COVID-19, diabetes, atherosclerosis, hypertension, heart failure, myocardial infarction and repair, cardiac remodelling, cardiac arrhythmias, cardiac hypertrophy, heart failure with preserved ejection fraction, diabetic cardiomyopathy, sarcopenia, obesity, metabolic syndrome, diabetes mellitus, insulin resistance, pulmonary arterial hypertension, subarachnoid haemorrhage, intracerebral haemorrhage, ischemic stroke, beta-thalassemia, sickle cell disease, rheumatoid arthritis, irritable bowel disorder, ulcerative colitis, Crohn's disease, psoriasis, radiation-induced dermatitis, atopic dermatitis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, toxin-induced liver disease, viral hepatitis and cirrhosis, chronic kidney disease, diabetic nephropathy, autosomal dominant polycystic kidney disease, CKD associated with type 1 diabetes (T1D), IgA nephropathy (IgAN), Alport Syndrome, focal segmental glomerulosclerosis, Huntington's disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal dementia, multiple sclerosis, Friedreich's ataxia, chronic pain, schizophrenia, lung cancer, breast cancer, colon cancer, age related macular degeneration (AMD), Fuchs Endothelial Corneal Dystrophy, uveitis or preeclampsia, the combination comprising a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents.

[00186] In a further aspect of the invention there is provided a compound of the invention or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents.

[00187] Herein, where the term "combination" is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention "combination" refers to simultaneous administration. In another aspect of the invention "combination" refers to separate administration. In a further aspect of the invention "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

[00188] According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the invention, or a pharmaceutically acceptable salt thereof in combination with one or more additional therapeutic agents in association with a pharmaceutically acceptable diluent or carrier.

[00189] The one or more additional therapeutic agents may comprise a further compound of the present invention. Therefore, in an embodiment, there is provided a pharmaceutical composition which comprises two compounds of the invention, or pharmaceutically acceptable salts thereof, in association with a pharmaceutically acceptable diluent or carrier.

[00190] According to a particular aspect of the invention there is provided a combination suitable for use in the prevention or treatment of allergic disease, inflammatory disease or autoimmune disease (e.g. asthma or COPD); a cardiovascular or metabolic disease (e.g. diabetes); a neurodegenerative disease; a chronic kidney or liver disease; sickle cell disease; pulmonary arterial hypertension; cancer; or for aiding transplantation.

[00191] According to a particular aspect of the invention there is provided a combination suitable for use in the prevention or treatment of chronic obstructive pulmonary disease, asthma, pulmonary arterial hypertension, diabetes mellitus, chronic kidney disease, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Friedreich's ataxia, sickle cell disease or non-alcoholic steatohepatitis.

[00192] Examples of other therapeutic agents that may be used as part of a combination therapy with a compound of the present invention (e.g. as one of two or more active agents as part of double or triple combinations) include, but are not limited to, the following:

(i) beta2-adrenoreceptor agonists (which may be a racemate or a single enantiomer) including salmeterol, salbutamol, formoterol, salmefamol, fenoterol, carmoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerbuterol, reproterol, bambuterol, indacaterol, terbutaline, vilanterol, olodaterol and salts thereof;

(ii) anticholinergic agents that act as antagonists at the muscarinic receptors that include ipratropium (for example, as the bromide, CAS 22254-24-6, sold under the name Atrovent), oxitropium and tiotropium (for example, as the bromide, CAS 136310-93-5, sold under the name Spiriva), revatropate, LAS- 34273, Aclidinium, Glycopyrronium, Umeclidinium and salts thereof;

(iii) Corticosteroid anti-inflammatory agents. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, fluticasone furoate, beclomethasone esters (for example the 17-propionate ester or the 17,21 -dipropionate ester), budesonide, flunisolide, mometasone esters (for example mometasone furoate), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126;

(iv) Anti-inflammatory agents including non-steroidal anti-inflammatory drugs (NSAIDs). Examples of NSAID's include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (for example, theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, JAK inhibitors, Pi3K inhibitors, inhibitors of leukotriene synthesis (for example montelukast), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (for example chemokine antagonists, such as a CCR3 antagonist) or inhibitors of cytokine synthesis, or 5 -lipoxygenase inhibitors;

(v) Vasodilator and anti-proliferative agents (e.g. prostanoids and PDE5 inhibitors) including Epoprostenol (Flolan), Treprostinil (Remodulin), Iloprost (Ventavis), Treprostinil (Tyvaso), Bosentan (Tracleer), Ambrisentan (Letairis), Sildenafil (Revatio), Tadalafil (Adcirca);

(vi) Anti-diabetic medications including insulins, biguanides (e.g. metformin), sulfonylureas (e.g. glimepiride), meglitinides (e.g. repaglinide), thiazolidinediones (e.g., pioglitazone), dipeptidyl peptidase IV inhibitors (e.g. sitagliptin), incretin mimetics/GLP-1 analogues (e.g. liraglutide, exenatide, dulaglutide), sodium glucose co-transporter-2 (SGLT2) inhibitors (e.g. canagliflozin, dapagliflozin and empagliflozin) and α-glucosidase inhibitors (e.g. acarbose);

(vii) Hydroxyurea and other agents used to treat sickle cell disease such as L-glutamine, NCX1443, GBT440 (voxelotor), pan-Selectin antagonists (GMI-1070, rivipansel), humanized anti-P-Selectin antibody (SelG1, crinalizumab), P-selectin aptamers, sevuparin, Regadenoson, Ticagrelor, N-Acetyl-Cysteine (NAC), phosphodiesterase 9 inhibitors (e.g. PF-04447943, IMR-687, BAY 73-6691, BAY 41-2271); and

(viii) ASK1 inhibitors such as selonsertib, FXR agonists such as obeticholic acid, GS-9674, Px-102, ACC inhibitors such as GS-0976 and PPARα/δ agonists such as Elafibranor.

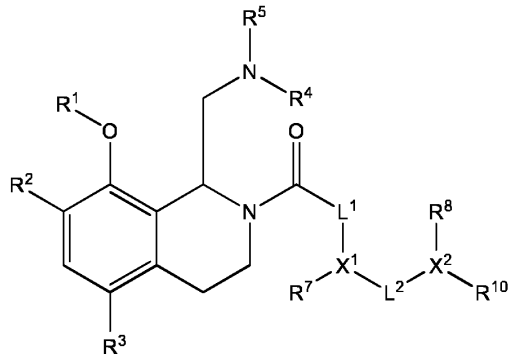
[00193] The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

[00194] Such conjoint/combination treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. In one embodiment, the individual compounds will be administered simultaneously in a combined pharmaceutical formulation.

[00195] Such combination therapies employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent within approved dosage ranges and/or the dosage such as described in the relevant publication reference.

[00196] The following numbered statements 1-30 are not claims, but describe certain aspects and embodiments of the present disclosure.

1. A compound according to Formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

X^1 is nitrogen or a group $-CR^6$;

X^2 is nitrogen or a group $-C^*R^9$;

R^1 is selected from C_{1-4}alkylene-R^{11}, heterocyclyl and 8-10 membered bicyclic heteroaryl, wherein said heterocyclyl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, $-C(O)-R^{12}$, SO_2-R^{13}, C_{1-3}alkylene-OR^{14} and heteroaryl which is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy and cyano; and wherein said 8-10 membered bicyclic heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH and C_{1-3}alkoxy;

R^2 is selected from hydrogen, fluoro, chloro and C_{1-3}alkyl;

R^3 is selected from hydrogen, fluoro, chloro, bromo, C_{1-3}alkoxy, C_{1-3}alkyl, C_{1-3}haloalkyl and cyano;

R^4 is hydrogen or C_{1-4}alkyl;

R^5 is -C(O)-C_{1-4}alkyl, -C(O)-C_{3-7}cycloalkyl, -C(O)-heteroaryl or -C(O)-aryl, wherein said heteroaryl and aryl are optionally substituted with one or more substituents selected from C_{1-4}alkyl, halo, hydroxy, C_{1-3}alkoxy, CO_2R^{15} and cyano; or

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 4-, 5-, or 6-membered heterocyclyl ring, wherein said heterocyclyl ring:

comprises one or more -C(O)- moieties attached to the nitrogen atom;

optionally contains one or more additional heteroatoms selected from oxygen, nitrogen and sulfur;

optionally is fused to an aryl or heteroaryl ring;

optionally is spiro-attached to a C_{3-7}cycloalkyl group or a 3- to 6-membered heterocyclyl ring; and

optionally is substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20};

L^1 and L^2 are independently selected from a bond and -$CR^{21}R^{22}$-, provided that if L^2 is a bond both X^1 and X^2 cannot be nitrogen;

R^6 and R^7 are independently selected from hydrogen, C_{1-4}alkyl, and C_{3-7}cycloalkyl; or

R^6 and R^7, taken together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring;

R^8 is $C(=O)NR^{8a}R^{8b}$ or $-C(=O)R^{8c}$;

R^{8a} is hydrogen or C_{1-6}alkyl;

R^{8b} is hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl, wherein the C_{1-6}alkyl or C_{3-7}cycloalkyl groups are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20}; or

R^{8a} and R^{8b}, taken together with the nitrogen atom to which they are attached, form a 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring, wherein the heterocyclyl ring:

optionally contains one or more additional heteroatoms selected from oxygen, nitrogen and sulfur; and

is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20};

R^{8c} is C_{1-3}alkyl or C_{1-3}haloalkyl;

R^9 is selected from hydrogen, C_{1-4}alkyl, hydroxy, C_{1-3}alkoxy and halo;

R^{10} is selected from hydrogen and C_{1-4}alkyl; or

R^9 and R^{10}, taken together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring; or

L^2 is a bond and R^7 and R^{10}, taken together with the atoms to which they are attached, form a 4-, 5-, 6- or 7-membered cycloalkyl or heterocyclyl ring, wherein:

said heterocyclyl ring contains 1 or 2 heteroatoms independently selected from nitrogen, oxygen and sulfur;

said cycloalkyl ring optionally comprises 1 or 2 carbon-carbon double bonds and is optionally bridged by a C_{1-3}alkylene group connecting two carbon atoms of the ring, or R^9 is optionally a C_{1-3}alkylene group connecting C* to a carbon atom of the ring;

said cycloalkyl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl and deuterium; and

said cycloalkyl and heterocyclyl rings are optionally spiro-attached to a C_{3-7}cycloalkyl group;

R^{11} is selected from $-C(O)-R^{24}$, $-SO_2-R^{25}$, $-NR^{26}C(O)-R^{27}$, $-NR^{28}SO_2-R^{29}$, heterocyclyl, aryl and heteroaryl, wherein said aryl and heteroaryl groups are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocyclyl and cyano; and said heterocyclyl group is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, oxo and cyano;

R^{12} is selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, OR^{31}, $NR^{32}R^{33}$, aryl and heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy and cyano;

R^{13} is selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl and $NR^{34}R^{35}$, wherein said heteroaryl and heterocyclyl are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy and cyano;

R^{17} is selected from hydrogen, C_{1-4}alkyl, $C(O)C_{1-3}$alkyl and $C(O)NR^{36}R^{37}$;

R^{18}, R^{19} and R^{20} are independently selected from C_{1-4}alkyl, OH, C_{1-3}alkoxy and $NR^{38}R^{39}$;

R^{24} is selected from C_{1-4}alkyl, $NR^{40}R^{41}$ and OR^{42};

R^{25} is selected from C_{1-4}alkyl and $NR^{43}R^{44}$;

R^{27} is selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-3}haloalkyl, heterocyclyl, aryl and heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{45}, halo, OH, C_{1-3}alkoxy and cyano;

R^{29} is selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-3}haloalkyl, aryl and heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{46} halo, OH, C_{1-3}alkoxy and cyano;

R^{30} is selected from hydroxy, C_{1-3}alkoxy, C_{3-7}cycloalkyl, cyano and $NR^{47}R^{48}$;

R^{40} is selected from hydrogen and C_{1-4}alkyl;

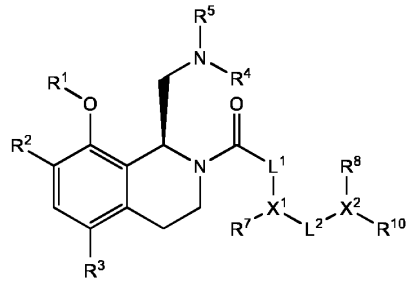
R^{41} is selected from hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-3}alkoxy, aryl and heteroaryl; or

R^{40} and R^{41}, taken together with the nitrogen atom to which they are attached, form a 4-, 5-, or 6-membered heteroaryl or heterocyclyl ring, wherein said heteroaryl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{3-7}cycloalkyl and cyano;

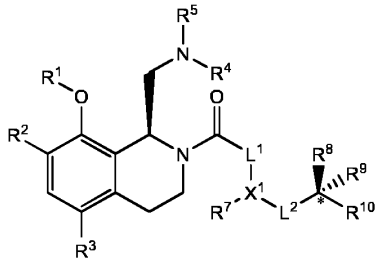
R^{45} and R^{46} are independently selected from hydroxy, C_{1-3}alkoxy and C_{3-7}cycloalkyl; and

R^{14}, R^{15}, R^{16}, R^{21}, R^{22}, R^{23}, R^{26}, R^{28}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{42}, R^{43}, R^{44}, R^{47} and R^{48} are independently selected from hydrogen, C_{1-4}alkyl and C_{3-7}cycloalkyl.

2. A compound according to statement 1, wherein said compound has the structural formula IA or IB shown below



(IA)



(IB)

wherein L^1, L^2, X^1, X^2 and R^1 to R^{10} are as defined in statement 1.

3. A compound according to statement 1 or statement 2, wherein L^2 is a bond and R^7 and R^{10}, taken together with the atoms to which they are attached, form a 4-, 5- or 6-membered cycloalkyl or heterocyclyl ring, wherein:

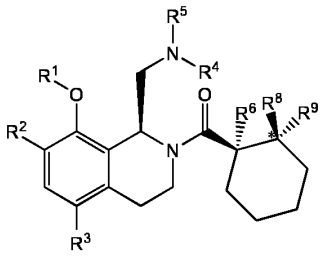
said heterocyclyl ring contains 1 or 2 heteroatoms independently selected from nitrogen, oxygen and sulfur;

said cycloalkyl ring optionally comprises 1 or 2 carbon-carbon double bonds and is optionally bridged by a C_{1-3}alkylene group connecting two carbon atoms of the ring, or R^9 is optionally a C_{1-3}alkylene group connecting C* to a carbon atom of the ring;

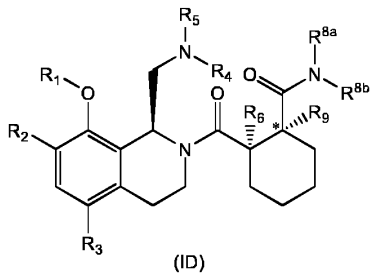
said cycloalkyl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy and deuterium; and

said cycloalkyl and heterocyclyl rings are optionally spiro-attached to a C_{3-7}cycloalkyl group.

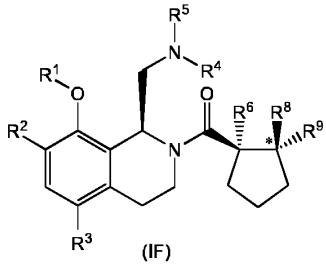
4. A compound according to statement 1, wherein said compound has one of the structural formulae IC, ID, IF, IG, IJ, IK, IL, IM or IN shown below:



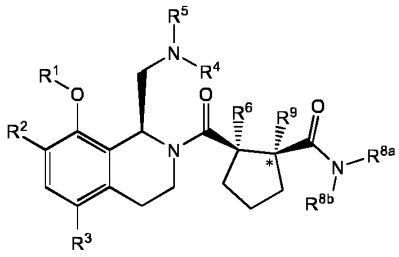
(IC)



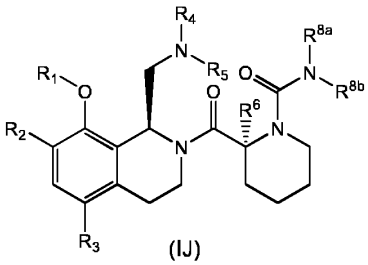
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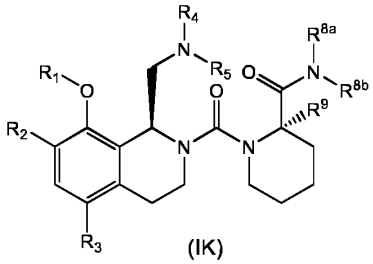
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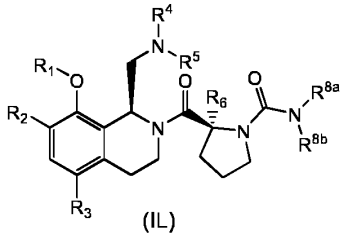
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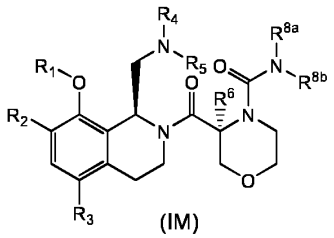
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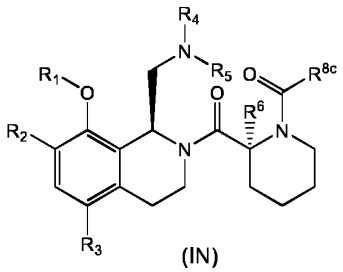
(IK)



(IL)



(IM)



(IN)

wherein R^1 to R^6, R^8, R^{8a}, R^{8b}, R^{8c} and R^9 are as defined in statement 1 and the cyclohexyl, cyclopentyl, piperidinyl, pyrrolidinyl or morpholinyl ring:

is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy and deuterium; and

is optionally spiro-attached to a C_{3-7}cycloalkyl group.

5. A compound according to any one of statements 1 to 4, wherein R^1 is C_{1-4}alkylene-R^{11}, such as CH_2-R^{11}.

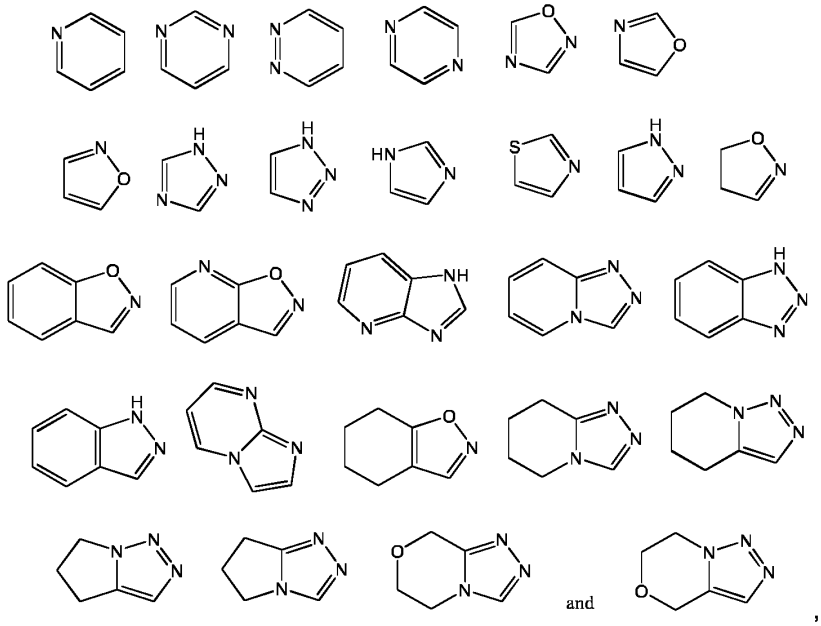
6. A compound according to any one of statements 1 to 5, wherein R^{11} is selected from -C(O)-R^{24}, -SO_2-R^{25}, -NR^{26}C(O)-R^{27}, -$NR^{28}SO_2$-R^{29} and heteroaryl, wherein said heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocyclyl and cyano.

7. A compound according to any one of statements 1 to 6, wherein R^{11} is heteroaryl optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocyclyl and cyano.

8. A compound according to any one of statements 1 to 7, wherein R^{11} is heteroaryl optionally substituted with one or more substituents independently selected from methyl, ethyl, isopropyl, difluoromethyl, trifluoromethyl, chloro, fluoro, cyclopropyl, methoxy, CH_2-R^{30} and CH_2CH_2-R^{30}.

9. A compound according to any one of statements 1 to 7, wherein R^{11} is pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, oxazolyl, isoxazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, indazolyl, benzotriazolyl, benzisoxazolyl, isoxazolopyridinyl, imidazopyridinyl or triazolopyridinyl, each optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocyclyl and cyano.

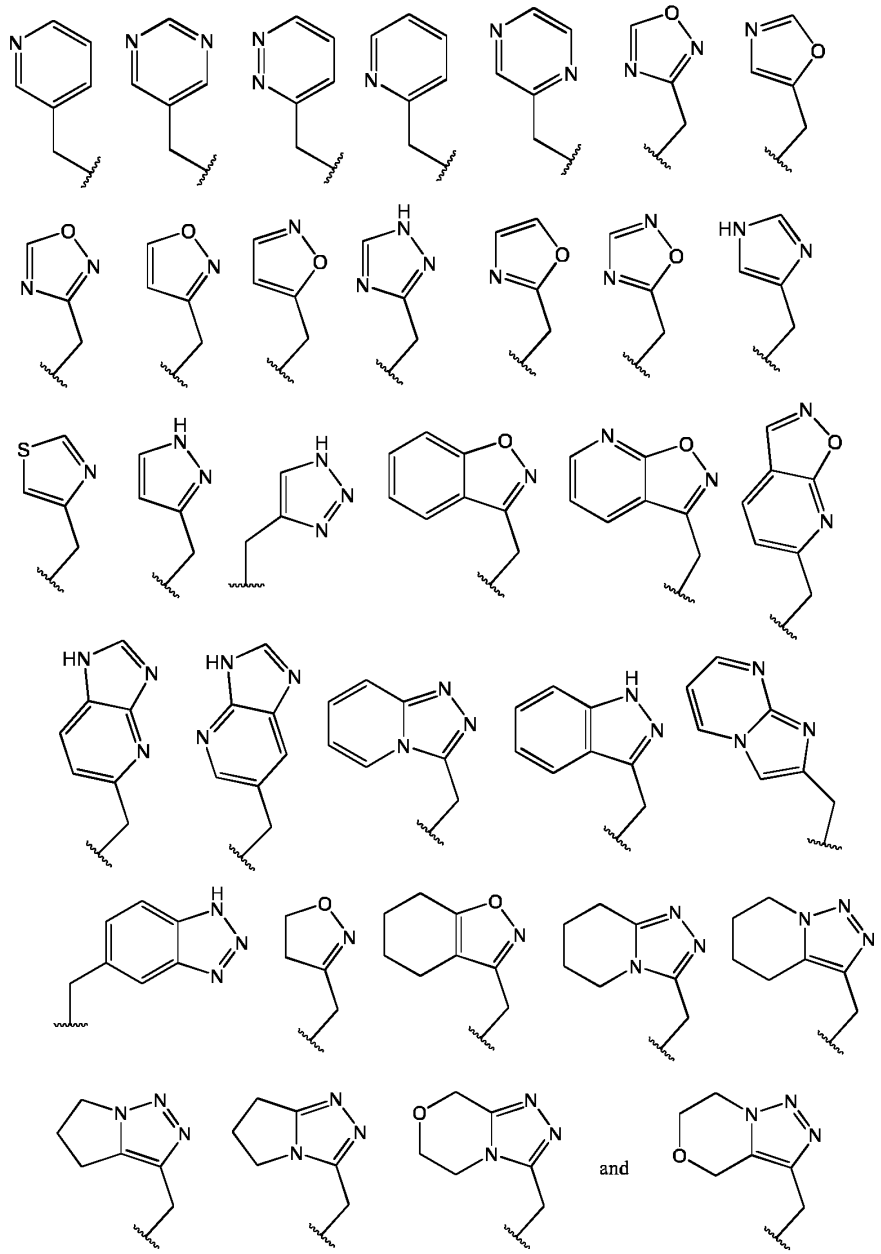
10. A compound according to any one of statements 1 to 7, wherein R^{11} is heteroaryl selected from:



and

each heteroaryl being optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocyclyl and cyano.

11. A compound according to any one of statements 1 to 4, wherein R^1 is selected from one of the following groups:



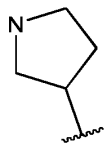
wherein ~~~ represents the point of attachment of the group to the oxygen atom of the rest of the compound and wherein each group is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocyclyl and cyano.

12. A compound according to any one of statements 1 to 4, wherein R^1 is heterocyclyl optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, -C(O)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy and cyano.

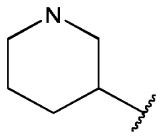
13. A compound according to any one of statements 1 to 4, wherein R^1 is piperidinyl or pyrrolidinyl, each optionally substituted with one or more substituents independently selected from -C(O)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy and cyano.

14. A compound according to statement 13, wherein R^1 is pyrrolidinyl optionally substituted with one or more substituents independently selected from -C(O)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl is optionally substituted with C_{1-4}alkyl or C_{3-7}cycloalkyl.

15. A compound according to any one of statements 1 to 4, wherein R^1 is selected from one of the following groups:



and



,

wherein ~~~ represents the point of attachment of the group to the oxygen atom of the rest of the compound and wherein each group is optionally substituted with one or more substituents independently selected from -C(O)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl is optionally substituted with C_{1-4}alkyl or C_{3-7}cycloalkyl.

16. A compound according to any one of statements 1 to 15, wherein R^2 is hydrogen or fluoro.

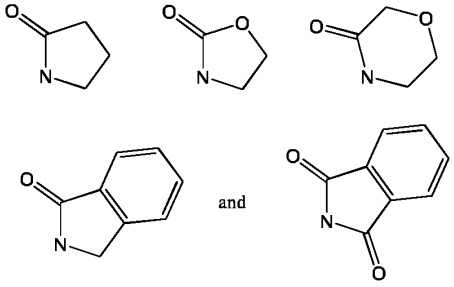
17. A compound according to any one of statements 1 to 16, wherein R^3 is hydrogen or chloro.

18. A compound according to any one of statements 1 to 17, wherein R^4 is hydrogen and R^5 is -C(O)-C_{1-4}alkyl, -C(O)-C_{3-7}cycloalkyl, or -C(O)-aryl, wherein said aryl is optionally substituted with one or more substituents selected from C_{1-4}alkyl, halo, hydroxy, C_{1-3}alkoxy, CO_2R^{15} and cyano.

19. A compound according to any one of statements 1 to 17, wherein R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 5-, or 6-membered heterocyclyl ring, wherein said heterocyclyl ring:
    comprises one or more -C(O)- moieties attached to the nitrogen atom;
    optionally contains one or more additional heteroatoms selected from oxygen, nitrogen and sulfur;
    optionally is fused to an aryl ring;

optionally is spiro-attached to a C_{3-7}cycloalkyl group or a 3- to 5-membered heterocyclyl ring; and
optionally is substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20}.

20. A compound according to any one of statements 1 to 17, wherein R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a heterocyclic moiety selected from one of the following:



wherein the saturated ring of the heterocyclic moiety is optionally spiro-attached to a C_{3-7}cycloalkyl group, and wherein said heterocyclic moiety is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo and OH.

21. A compound according to any one of statements 1 to 20, wherein R^8 is $C(=O)NR^{8a}R^{8b}$.

22. A compound according to statement 21, wherein R^{8a} is hydrogen.

23. A compound according to statement 21 or 22, wherein R^{8b} is hydrogen, C_{1-4}alkyl or C_{3-5}cycloalkyl, wherein the C_{1-4}alkyl group is optionally substituted with one or more substituents independently selected from halo, OH, C_{1-3}alkoxy, C_{3-7}cycloalkyl and cyano.

24. A compound according to statement 21, wherein R^{8a} and R^{8b}, taken together with the nitrogen atom to which they are attached, form a 4-, or 5-membered heterocyclyl ring, wherein the heterocyclyl ring is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20}.

25. A compound according to any one of statements 1 to 20, wherein R^{8c} is C_{1-3}fluoroalkyl.

26. A compound according to any one of statements 1 to 25, wherein R^9 is hydrogen or methyl.

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

(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(4-(methylamino)-4-oxobutoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;

N-(2-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(ethylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-5-methylisoxazole-3-carboxamide;
(1*S*,2*R*)-2-((*S*)-1-(cyclopropanecarboxamidomethyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;
(1*S*,2*R*)-2-((*S*)-8-((1*H*-pyrazol-5-yl)methoxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;
(1*S*,2*R*)-2-((*S*)-1-(acetamidomethyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide;
(1*S*,2*R*)-*N*-methyl-2-((*S*)-1-((2-oxooxazolidin-3-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;
4-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)butanoic acid;
(*R*)-1-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylpiperidine-2-carboxamide;
(*S*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylpyrrolidine-1-carboxamide;
1-(((*S*)-5-chloro-2-((*S*)-1-(2,2-difluoroacetyl)piperidine-2-carbonyl)-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)pyrrolidin-2-one;
(*S*)-6-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methyl-5-azaspiro[2.4]heptane-5-carboxamide;
(1*R*,2*S*)-2-((*R*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(4-oxo-4-(pyrrolidin-1-yl)butoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;
5-cyclopropyl-N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)isoxazole-3-carboxamide;
N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-4,5-dimethylisoxazole-3-carboxamide;
(1S,2R)-2-((S)-8-(((S)-1-acetylpyrrolidin-3-yl)oxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
N-(2-(((S)-2-((1R,2S)-2-(cyclopropylcarbamoyl)cyclohexane-1-carbonyl)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-5-methylisoxazole-3-carboxamide;

N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(3-hydroxyazetidine-1-carbonyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-5-methylisoxazole-3-carboxamide;
N-(2-(((S)-2-((1R,2S)-2-(cyclobutylcarbamoyl)cyclohexane-1-carbonyl)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-5-methylisoxazole-3-carboxamide;
5-cyclopropyl-N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)isoxazole-3-carboxamide;
N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)benzo[d]oxazole-2-carboxamide;
N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)benzo[d]isoxazole-3-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(2-((5-methylisoxazole)-4-sulfonamido)ethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(pyrimidine-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-nicotinoylpyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-((5-methylisoxazol-4-yl)sulfonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
N-(2-(((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1R,2S)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)thiazole-2-carboxamide;
(1S,2R)-2-((S)-8-(((S)-1-(cyclopropanecarbonyl)pyrrolidin-3-yl)oxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(5-methylisoxazole-3-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(oxazol-5-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(2-methylthiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-8-(((S)-1-(2,4-dimethylthiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(2-methylthiazole-4-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(R)-4-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinolin-2(1H)-yl)-N,3-dimethyl-4-oxobutanamide;
(1S,2R)-N-methyl-2-((S)-1-((2-oxopyrrolidin-1-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(pyrazin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(S)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylpiperidine-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-propylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(2-methoxyethyl)cyclohexane-1-carboxamide;
(1S,2R)-N-(2,2-difluoroethyl)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(2,2,2-trifluoroethyl)cyclohexane-1-carboxamide;
(1S,2R)-N-(cyanomethyl)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;
(1S,2R)-N-(2,2-difluoro-3-hydroxypropyl)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(2-hydroxyethyl)cyclohexane-1-carboxamide;
1-((S)-1-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinolin-2(1H)-yl)-1-oxopropan-2-yl)-3-methylurea;
(1S,2R)-2-((S)-8-(((S)-1-acetylpyrrolidin-3-yl)oxy)-5-chloro-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
5-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinolin-2(1H)-yl)-N-methyl-5-oxopentanamide;
4-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinolin-2(1H)-yl)-N-methyl-4-oxobutanamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-ethylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(3-hydroxypropyl)cyclohexane-1-carboxamide;
(1S,2R)-N-methyl-2-((S)-1-(propionamidomethyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;
(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-((1-methyl-1H-pyrazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-8-(((S)-1-acetylpyrrolidin-3-yl)oxy)-5-bromo-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
methyl (S)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)pyrrolidine-1-carboxylate;
(1S,2R)-2-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-ethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-bromo-8-((5-isopropyl-1,2,4-oxadiazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-bromo-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-isopropyl-1,2,4-oxadiazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(2R,3R)-4-((S)-5-chloro-8-((5-isopropyl-1,2,4-oxadiazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)-N,2,3-trimethyl-4-oxobutanamide;
(1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyridin-3-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyridazin-3-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyrazin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyrimidin-5-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclopentane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-(2-(1-methyl-1H-1,2,3-triazol-4-yl)ethoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((3-methyl-3H-imidazo[4,5-b]pyridin-6-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-(isoxazolo[5,4-b]pyridin-3-ylmethoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((3-methylisoxazolo[5,4-b]pyridin-6-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-8-([1,2,4]triazolo[4,3-a]pyridin-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-(imidazo[1,2-a]pyrimidin-2-ylmethoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-8-([1,2,4]triazolo[4,3-a]pyridin-3-ylmethoxy)-5-chloro-1-((1-oxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(2,2-difluoro-3-hydroxypropyl)cyclohexane-1-carboxamide;
(S)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylpiperidine-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((3-methyl-3H-imidazo[4,5-b]pyridin-5-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-indazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;

3-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methyltetrahydrofuran-2-carboxamide;
(1S,2R)-2-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclopentane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((4,5-dimethyl-4H-1,2,4-triazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
(S)-3-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylmorpholine-4-carboxamide;
(S)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylpyrrolidine-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((1,5-dimethyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(S)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylpiperidine-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclopentane-1-carboxamide;
(1S,2R)-2-((1S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclopentane-1-carboxamide;
(1S,2R)-2-((1S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;

(1S,2R)-2-((S)-5-chloro-8-((1,5-dimethyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-(methoxymethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((3-oxomorpholino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-7-fluoro-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-8-((4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridin-3-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((1,5-dimethyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide;
(1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N,1-dimethylcyclohexane-1-carboxamide; or
(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-methylcyclohexane-1-carboxamide;
or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising a compound according to any one of statements 1 to 27, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

29. A compound according to any one of statements 1 to 27, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to statement 28, for use in therapy.

30. A compound according to any one of statements 1 to 27, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to statement 28, for use in the treatment of chronic obstructive pulmonary disease, acute, chronic and severe asthma, acute lung injury/acute respiratory distress syndrome with or without accompanying multi organ dysfunction syndrome, pulmonary fibrosis including idiopathic pulmonary fibrosis, cystic fibrosis, COVID-19, diabetes, atherosclerosis, hypertension, heart failure, myocardial infarction and repair, cardiac remodelling, cardiac arrhythmias, cardiac hypertrophy, heart failure with preserved ejection fraction, diabetic cardiomyopathy, sarcopenia, obesity, metabolic syndrome, diabetes mellitus, insulin resistance, pulmonary arterial hypertension, subarachnoid haemorrhage, intracerebral haemorrhage, ischemic stroke, beta-thalassemia, sickle cell disease, rheumatoid arthritis, irritable bowel disorder, ulcerative colitis, Crohn's disease, psoriasis, radiation-induced dermatitis, atopic dermatitis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, toxin-induced liver disease, viral hepatitis and cirrhosis, chronic kidney disease, diabetic nephropathy, autosomal dominant polycystic kidney disease, CKD associated with type 1 diabetes (T1D), IgA nephropathy (IgAN), Alport Syndrome, focal segmental glomerulosclerosis, Huntington's disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal dementia, multiple sclerosis, Friedreich's ataxia, chronic pain, schizophrenia, lung cancer, breast cancer, colon cancer, age related macular degeneration (AMD), Fuchs Endothelial Corneal Dystrophy, uveitis or preeclampsia.

EXAMPLES

General Procedures:

[00197] Methods for preparing the compounds of this invention are illustrated in the following Examples. Starting materials are made according to procedures known in the art, or as illustrated herein, or are available commercially. Commercial reagents were used without further purification. Where no reaction temperature is included, the reaction was performed at ambient temperature which is typically 18-27°C.

[00198] Where compounds described in the invention are characterized by ^{1}H NMR spectroscopy, spectra were recorded on 500 MHz Bruker, 400 MHz Bruker, 250 MHz Bruker, 300 MHz JEOL or 400 MHz JEOL instruments. Where no temperature is included, the spectra were recorded at ambient temperature. Chemical shift values are expressed in parts per million (ppm). Where NMR spectra are complex due to the presence of interconverting isomers, approximate partial integrations of signals are reported, or characterisation for the major isomer only is reported. The following abbreviations are used for the multiplicity of the NMR signals: s=singlet, b=broad, t=triplet, q=quartet, m=multiplet, d=doublet.

Analytical LCMS

[00199] Where compounds described in the invention are characterized by LCMS data, retention time and molecular weight are determined using the methods listed in the table below. In cases where compounds of the invention appear as slowly interconverting stereoisomers, multiple retention times are reported.

Method	Instrument	Column		Eluents	Gradient
1	Waters Acquity UPLC (diode array 210-350 nm) and SQD mass detector	XBridge BEH C18 (2.5 µm, 2.1 x 50 mm)	40 °C	A: 10 mM ammonium bicarbonate pH 10 B: MeCN	2 - 98% B from 0.0 to 4.0 min
2	Waters Alliance 2695 HPLC (diode array 215-350 nm) and ZQ Mass Spectrometer	XBridge C18 (2.5 µm, 3.0 x 150 mm)	40 °C	A: 0.05% formic acid in water B: MeCN	0 - 95% B from 0.0 to 6.0 min, 95% B to 11.1 min
3	Acquity UPLC (binary pump with PDA detector) and ZQ Mass Spectrometer	Acquity UPLC BEH C18 (1.7 µm, 2.1 x 100 mm)	40 °C	A: 0.1% formic acid in water B: MeCN (containing 0.1% formic acid)	5 - 95% B from 0.4 to 6.0 min
4	Acquity UPLC + Waters DAD + Waters SQD2, single quadrapole UPLC-MS	Acquity UPLC HSS C_{18} (1.8 µm, 2.1 x 100 mm)	40 °C	A: 0.1% formic acid in water B: MeCN (containing 0.1% formic acid)	5 - 95% B from 0.4 to 6.0 min
5	Acquity UPLC + Waters DAD + Waters SQD2, single quadrapole UPLC-MS	Acquity UPLC BEH Shield RP18 (1.7 µm 2.1 x 100 mm)	40 °C	A: 10 mM ammonium bicarbonate pH 10 B: MeCN	5 - 95% B from 0.4 to 6.0 min
6	Waters Acquity UPLC (diode array 210-350 nm) and QDa mass detector	XBridge C18 (2.5 µm, 2.1 x 50 mm)	40 °C	A: 10 mM ammonium bicarbonate pH 10 B: MeCN	2 - 98% B from 0.0 to 4.6 min
7	Waters Acquity UPLC (diode array 210-350 nm) and SQD mass detector	XBridge C18 (2.5 µm, 2.1 x 50 mm)	40 °C	A: water B: MeCN C: 2% ammonia in water	2 - 95% B in A (5% C throughout) from 0.0 to 5.0 min
8	Waters Acquity UPLC (diode array 210-350 nm) and SQD mass detector	XBridge C18 (2.5 µm, 2.1 x 50 mm)	40 °C	A: 10 mM ammonium bicarbonate pH 10 B: MeCN	2 - 95% B in A from 0.0 to 4.0 min, 95% B to 4.7 min
9	Waters Acquity Sample manager (Quaternary pump with PDA 210 – 350 nm and ELS and SQD mass detector)	BEH C18 (1.7 µm, 2.1 x 50 mm)	40 °C	A: water B: MeCN C: 2% ammonia in water	2% B with 5% C and 93% A to 95% B and 5% C from 0.0 to 4.50 min, 95% B 5% C to 5.00 min
10	Waters Acquity UPLC H-Class system (Quaternary	CSH C18 (1.7 µm, 2.1 x 50 mm)	40 °C	A: water B: MeCN	2 - 95% B in A (5% C throughout)

	pump with PDA 210 – 350 nm) and QDa mass detector			C: 2% formic acid in water	from 0.0 to 4.0 min, 95% B 5% C to 4.60 min
11	Waters Acquity UPLC H-Class system (Quaternary pump with PDA 210 – 350 nm) and QDa mass detector	BEH C18 (1.7 µm, 2.1 x 50 mm)	40 °C	A: water B: MeCN C: 2% ammonia in water	2 - 95% B in A (5% C throughout) from 0.0 to 4.0 min, 95% B 5% C to 4.60 min
12	Waters Acquity UPLC H-Class system (Quaternary pump with PDA 210 – 350 nm) and QDa mass detector	CSH C18 (1.7 µm, 2.1 x 50 mm)	40 °C	A: 0.1% formic acid in water B: MeCN containing (0.1% formic acid in water)	3 - 99% B in A from 0.0 to 1.5 min, 95% B 5% A to 1.90 min
13	Waters Acquity Sample manager (Quaternary pump with PDA 210 – 350 nm and ELS and SQD mass detector)	CSH C18 (1.7 µm, 2.1 x 50 mm)	40 °C	A: 0.1% formic acid in water B: MeCN C: 0.1% formic acid in water	2 - 95% B in A (5% C throughout) from 0.0 to 4.5 min, 95% B 5% C to 5.00 min
14	Acquity UPLC (binary pump with PDA detector) and ZQ Mass Spectrometer	Acquity UPLC BEH C18 (1.7 µm, 2.1 x 100 mm)	40 °C	A: 0.1% ammonia in water B: MeCN (containing 0.1% ammonia)	5 - 95% B from 0.4 to 6.0 min
15	Waters Acquity UPLC H-Class system (Quaternary pump with PDA 210 – 350 nm) and QDa mass detector	BEH C18 (1.7 µm, 2.1 x 50 mm)	40 °C	A: 0.1% ammonia in water B: MeCN (containing 0.1% ammonia)	3 - 95% B from 0.2 to 2.2 min
16	Waters Acquity UPLC H-Class system (Quaternary pump with PDA 210 – 350 nm) and QDa mass detector	BEH C18 (1.7 µm, 2.1 x 50 mm)	40 °C	A: water B: MeCN C: 2% ammonia in water	2 - 95% B in A (5% C throughout) from 0.0 to 1.2 min, 95% B 5% C to 1.40 min

Preparative HPLC

[00200] Preparative HPLC was performed using a variety of preparative systems with variable wavelength UV detection or Mass Directed AutoPrep (MDAP) systems as listed in the table below. Collection was triggered by UV, MS or a combination of the two. The UV detection was at a selected wavelength generally 210 nm, 230 nm or 280 nm. Mass spectra were recorded on a mass spectrometer using an alternate-scan positive and negative electrospray ionization.

Method	Instrument	Column		Eluents	Gradient
1	Agilent 1260 infinity purifications system.	XSELECT CSH Prep	rt	A: 0.1% formic acid in water	10% to 95% B over 22 min,

	Agilent 6100 series single Quadrupole LC/MS	C18 (5 µm OBD, 21 x 250 mm)		B: MeCN (containing 0.1% formic acid)	centered around a specific focused gradient
2	Agilent 1260 infinity purifications system. Agilent 6100 series single Quadrupole LC/MS	XBridge Prep C18 (5 µm OBD, 21 x 250 mm)	rt	A: 0.1% ammonia in water B: MeCN (containing 0.1% ammonia)	10% to 95% B over 22 min, centered around a specific focused gradient
3	Waters Fractionlynx preparative HPLC system (2525 pump, 2996/2998 UV/VIS detector, 2767 liquid handler) with Waters Acquity systems with Waters SQD LCMS detection	Waters Sunfire OBD Phenomenex Luna Phenyl Hexyl (10 µm, 19 x 150 mm)	rt	A: MeOH B: MeCN (containing 10mM ammonium bicarbonate)	Gradient as specified

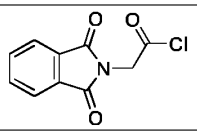
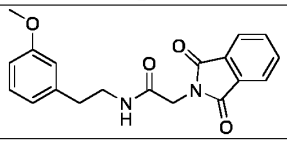
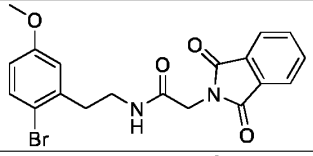
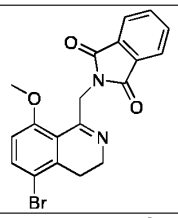
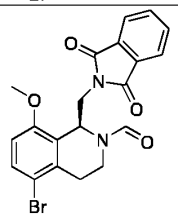
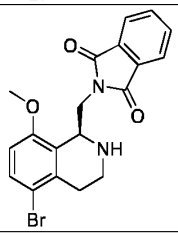
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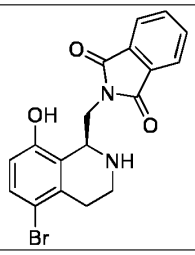
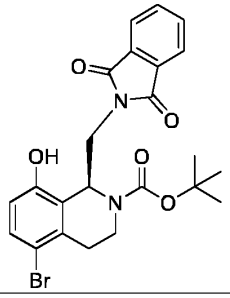
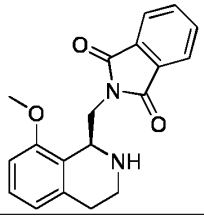
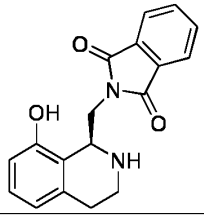
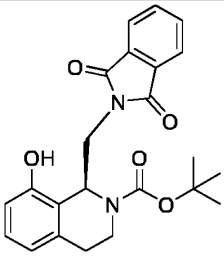
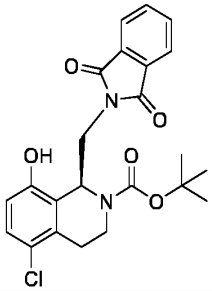
CDI	1,1'-Carbonyldiimidazole
DBAD	Di-*tert*-butyl azodicarboxylate
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDTA	Ethylenediaminetetraacetic acid
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour(s)
HATU	*N*-[(Dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
HPLC	High Performance Liquid Chromatography
IMS	Industrial methylated spirits
LCMS	Liquid Chromatography Mass Spectrometry
MDAP	Mass Directed Auto Purification
MeCN	Acetonitrile
MeOH	Methanol

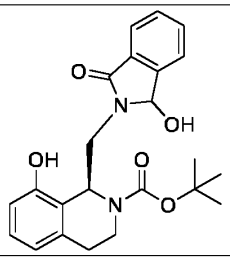
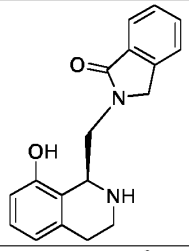
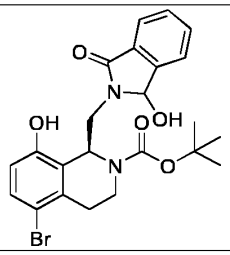
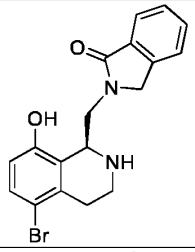
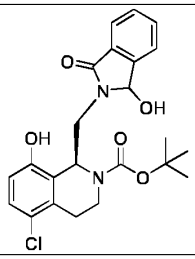
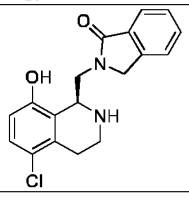
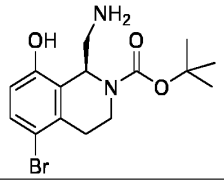
min	Minute(s)
NMR	Nuclear Magnetic Resonance
Pd/C	Palladium on carbon
rt	Room Temperature
TBME	*tert*-Butyl methyl ether
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

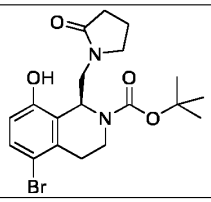
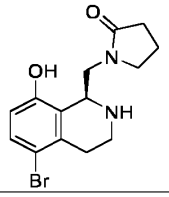
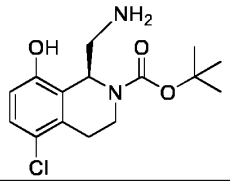
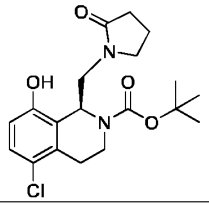
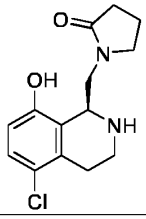
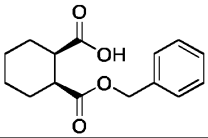
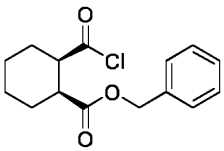
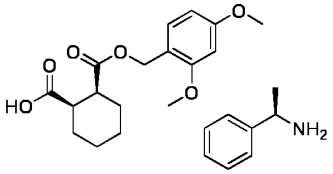
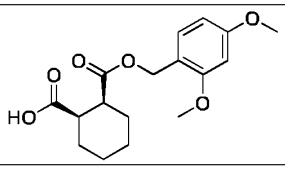
Intermediates

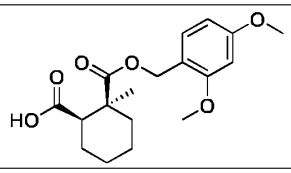
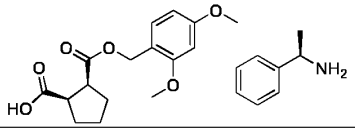
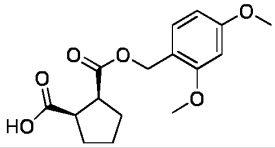
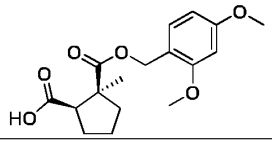
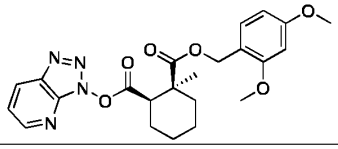
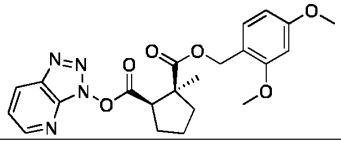
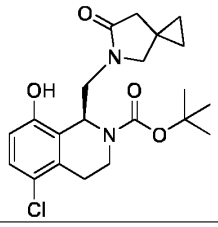
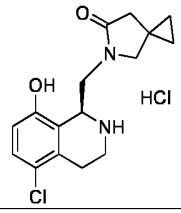
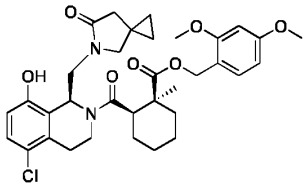
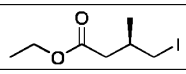
[00201] The following intermediates and their synthetic routes are described in co-pending application PCT/GB2019/053012:

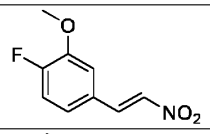
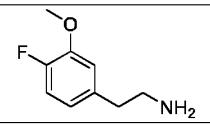
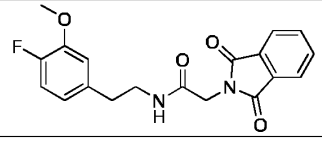
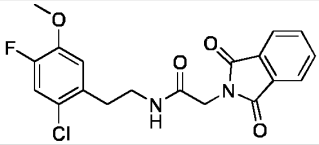
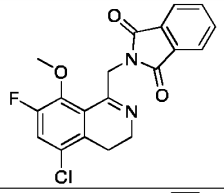
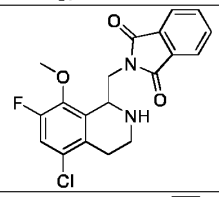
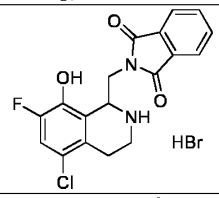
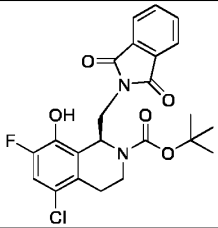
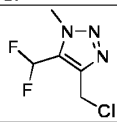
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Intermediate 2		2-(1,3-dioxoisoindolin-2-yl)-*N*-(3-methoxyphenethyl)acetamide
Intermediate 3		*N*-(2-bromo-5-methoxyphenethyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide
Intermediate 4		2-((5-bromo-8-methoxy-3,4-dihydroisoquinolin-1-yl)methyl)isoindoline-1,3-dione
Intermediate 5		(*S*)-5-bromo-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carbaldehyde
Intermediate 6		(*S*)-2-((5-bromo-8-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoindoline-1,3-dione

Intermediate 7		(*S*)-2-((5-bromo-8-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoindoline-1,3-dione
Intermediate 8		*tert*-butyl (*S*)-5-bromo-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate
Intermediate 9		(*S*)-2-((8-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoindoline-1,3-dione
Intermediate 10		(*S*)-2-((8-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoindoline-1,3-dione
Intermediate 11		*tert*-butyl (*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate
Intermediate 12		*tert*-butyl (*S*)-5-chloro-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate

Intermediate 13		*tert*-butyl (1*S*)-8-hydroxy-1-((1-hydroxy-3-oxoisoindolin-2-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate
Intermediate 14		(*S*)-2-((8-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoindolin-1-one
Intermediate 15		*tert*-butyl (1*S*)-5-bromo-8-hydroxy-1-((1-hydroxy-3-oxoisoindolin-2-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate
Intermediate 16		(*S*)-2-((5-bromo-8-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoindolin-1-one
Intermediate 17		*tert*-butyl (1*S*)-5-chloro-8-hydroxy-1-((1-hydroxy-3-oxoisoindolin-2-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate
Intermediate 18		(*S*)-2-((5-chloro-8-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoindolin-1-one
Intermediate 19		*tert*-butyl (*S*)-1-(aminomethyl)-5-bromo-8-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate

Intermediate 20		*tert*-butyl (*S*)-5-bromo-8-hydroxy-1-((2-oxopyrrolidin-1-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate
Intermediate 21		(*S*)-1-((5-bromo-8-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)pyrrolidin-2-one
Intermediate 22		*tert*-butyl (*S*)-1-(aminomethyl)-5-chloro-8-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate
Intermediate 23		*tert*-butyl (*S*)-5-chloro-8-hydroxy-1-((2-oxopyrrolidin-1-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate
Intermediate 24		(*S*)-1-((5-chloro-8-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)pyrrolidin-2-one
Intermediate 25		(1*R*,2*S*)-2-((benzyloxy)carbonyl)cyclohexane-1-carboxylic acid
Intermediate 26		benzyl (1*S*,2*R*)-2-(chlorocarbonyl)cyclohexane-1-carboxylate
Intermediate 27		(1*R*,2*S*)-2-[(2,4-dimethoxyphenyl) methoxycarbonyl] cyclohexane-carboxylic acid; (1*R*)-1-phenylethanamine
Intermediate 28		(1*R*,2*S*)-2-(((2,4-dimethoxybenzyl)oxy) carbonyl)cyclohexane-1-carboxylic acid

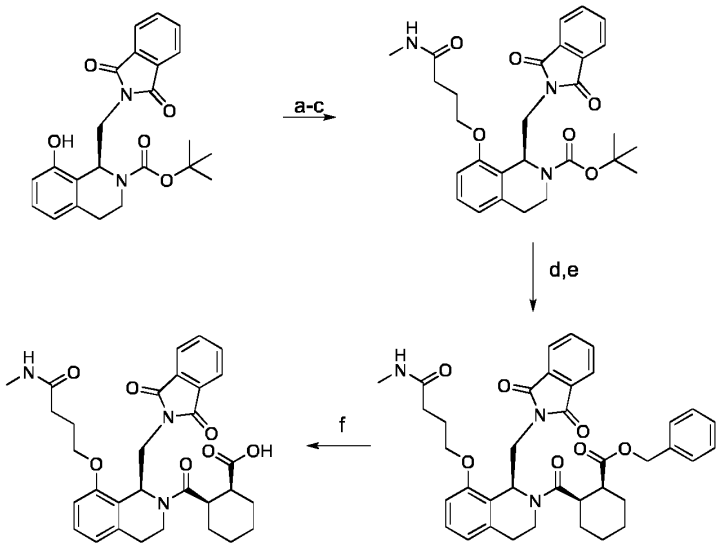
Intermediate 29		(1*R*,2*S*)-2-(((2,4-dimethoxybenzyl)oxy)carbonyl)-2-methylcyclohexane-1-carboxylic acid
Intermediate 30		(1*R*,2*S*)-2-[(2,4-dimethoxyphenyl) methoxycarbonyl]cyclopentane-carboxylic acid; (1*R*)-1-phenylethanamine
Intermediate 31		(1*R*,2*S*)-2-(((2,4-dimethoxybenzyl)oxy)carbonyl) cyclopentane-1-carboxylic acid
Intermediate 32		(1*R*,2*S*)-2-(((2,4-dimethoxybenzyl)oxy)carbonyl)-2-methylcyclopentane-1-carboxylic acid
Intermediate 33		2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl) 1-(2,4-dimethoxybenzyl) (1*S*,2*R*)-1-methylcyclohexane-1,2-dicarboxylate
Intermediate 34		2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl) 1-(2,4-dimethoxybenzyl) (1*S*,2*R*)-1-methylcyclopentane-1,2-dicarboxylate
Intermediate 35		*tert*-butyl (*S*)-5-chloro-8-hydroxy-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate
Intermediate 36		(*S*)-5-((5-chloro-8-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-5-azaspiro[2.4]heptan-6-one hydrochloride
Intermediate 37		2,4-dimethoxybenzyl (1*S*,2*R*)-2-((*S*)-5-chloro-8-hydroxy-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylate
Intermediate 38		ethyl (*R*)-4-iodo-3-methylbutanoate

Intermediate 39		(*E*)-1-fluoro-2-methoxy-4-(2-nitrovinyl)benzene
Intermediate 40		2-(4-fluoro-3-methoxyphenyl)ethan-1-amine
Intermediate 41		2-(1,3-dioxoisoindolin-2-yl)-*N*-(4-fluoro-3-methoxyphenethyl)acetamide
Intermediate 42		*N*-(2-chloro-4-fluoro-5-methoxyphenethyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide
Intermediate 43		2-((5-chloro-7-fluoro-8-methoxy-3,4-dihydroisoquinolin-1-yl)methyl)isoindoline-1,3-dione
Intermediate 44		2-((5-chloro-7-fluoro-8-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoindoline-1,3-dione
Intermediate 45		2-((5-chloro-7-fluoro-8-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoindoline-1,3-dione hydrobromide
Intermediate 46		*tert*-butyl (*S*)-5-chloro-1-((1,3-dioxoisoindolin-2-yl)methyl)-7-fluoro-8-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate
Intermediate 47		4-(chloromethyl)-5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazole

Synthesis of Example Compounds

[00202] For methodology to synthesise the required carboxylic acids, see experimental methods in PCT/GB2019/053012 (WO 2020/084300), and the representative synthesis below:

(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(4-(methylamino)-4-oxobutoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid



[00203] Step a. To a stirred solution of Intermediate 11 (1.0 g, 2.45 mmol) in anhydrous THF (15 mL) was added benzyl 4-hydroxybutanoate (570 mg, 2.94 mmol; CAS: 91970-62-6) and triphenylphosphine (963 mg, 3.67 mmol; CAS: 603-35-0) and to this was added a solution of DBAD (845 mg, 3.67 mmol) in anhydrous THF (5 mL) dropwise over 15 min. The reaction mixture was stirred at rt for 18 h and concentrated *in vacuo*. Flash column chromatography (silica, 20% EtOAc in Heptanes) gave *tert*-butyl (*S*)-8-(4-(benzyloxy)-4-oxobutoxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (1.47 g, assumed quantitative). LCMS (Method 1 with 2 - 98% B in 0.80 min, 98% B to 1.30 min): 1.05 min, 585.5 $[M+H]^+$.

[00204] Step b. A suspension of the above intermediate (1.47 g, 2.51 mmol) and 10% Pd/C (535 mg, 0.251 mmol) in anhydrous THF (20 mL) was stirred under an atmosphere of hydrogen (atmospheric pressure) at rt for 18 h. The reaction mixture was filtered through Celite®, washed with methanol, and the filtrate concentrated *in vacuo*. Flash column chromatography (silica, 30 - 50% EtOAc in Heptanes) gave (*S*)-4-((2-(*tert*-

butoxycarbonyl)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)butanoic acid (1.00 g, 80%). LCMS (Method 1): 1.62 min, 495.2 $[M+H]^+$.

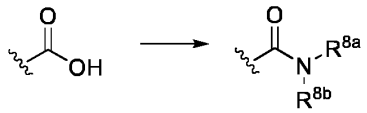
[00205] Step c. To a stirred solution of the above intermediate (200 mg, 0.40 mmol) in anhydrous THF (2 mL) at rt was added CDI (262 mg, 1.62 mmol; CAS: 530-62-1) in one portion. After 1 h, the reaction mixture was cooled to 0 °C and methylamine (2M in THF; 0.40 mL, 1.62 mmol; CAS: 74-89-5) was added. The reaction mixture was stirred for 18 h at rt, diluted with water, extracted with EtOAc and the combined organics washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (silica, EtOAc) gave *tert*-butyl (*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(4-(methylamino)-4-oxobutoxy)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (120 mg, 58%). LCMS (Method 2 with XBridge IS C18 2.5 µm 2.1 x 20 mm column, 0 - 95% B 0.18 to 2.00 min, 95% B to 2.60 min): 1.99 min, 508.2 $[M+H]^+$.

[00206] Step d. To a stirred solution of the above intermediate (120 mg, 0.24 mmol) in 1,4-dioxane (1 mL) was added hydrogen chloride (3 M in dioxane, 2 mL) and the reaction mixture stirred at rt for 3 h. The suspension was concentrated *in vacuo* and triturated from TBME to give (*S*)-4-((1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-*N*-methylbutanamide hydrochloride (105 mg, assumed quantitative), used without further purification. LCMS (Method 2 with XBridge IS C18 2.5 µm 2.1 x 20 mm column, 0 - 95% B 0.18 to 2.00 min, 95% B to 2.60 min): 1.68 min, 408.2 $[M+H]^+$.

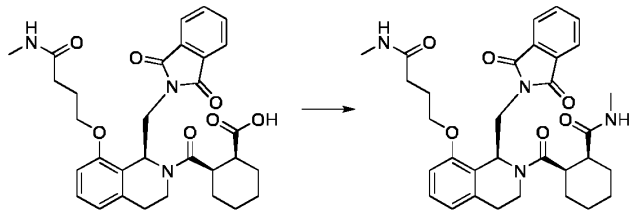
[00207] Step e. To a stirred solution of the above intermediate (120 mg, 0.27 mmol) and triethylamine (0.11 mL, 0.81 mmol) in anhydrous DCM (1.5 mL) at 0 °C was added a solution of Intermediate 26 (83 mg, 0.297 mmol) in DCM (0.5 mL) dropwise. The reaction mixture was stirred for 0.5 h at 0 °C then at rt 1 h. To this was added water, the mixture was extracted with EtOAc and the combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (silica, 20% EtOAc in heptanes, followed by 100% EtOAc) gave benzyl (1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(4-(methylamino)-4-oxobutoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylate (80 mg, 45%). LCMS (Method 1 with 2 - 98% B in 0.80 min, 98% B to 1.30 min): 0.93 min, 652.6 $[M+H]^+$.

[00208] Step f. A suspension of the above intermediate (80 mg, 0.12 mmol) and 10% Pd/C (26 mg, 0.12 mmol) in anhydrous THF (2 mL) was stirred under an atmosphere of hydrogen (atmospheric pressure) at rt for 24 h. The reaction mixture was filtered through Celite®, washed with methanol, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (0 - 10% MeOH in DCM) gave the title compound (6.1 mg, 9%). LCMS (Method 1): 1.56 min, 562.4 $[M+H]^+$.

Amide Coupling Methods

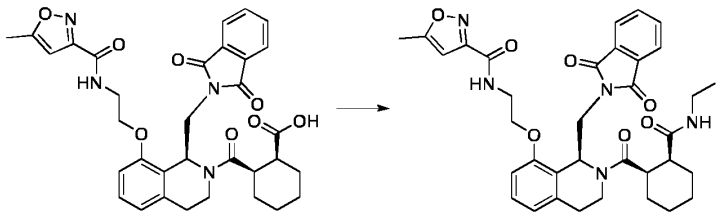


Amide Coupling Method A: Example 2: (1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(4-(methylamino)-4-oxobutoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide



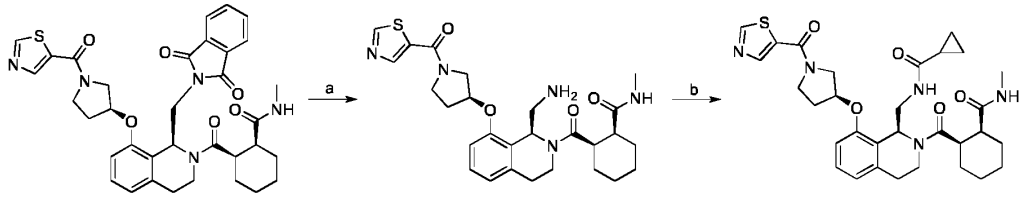
[00209] To a stirred solution of (1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(4-(methylamino)-4-oxobutoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid (50 mg, 0.09 mmol; synthesis above) in THF (5 mL) was added 1,1'-carbonyldiimidazole (58 mg, 0.36 mmol; CAS: 530-62-1) and the reaction mixture was heated to 50 °C for 2 h. The reaction mixture was cooled to 0 °C and to this was added methylamine (2M in THF; 0.9 mL, 1.8 mmol; CAS: 74-89-5). After 45 min, the the mixture was diluted with 0.5 M aqueous HCl (8 mL), the mixture extracted with EtOAc (2 x 10 mL) and the combined organics dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by reverse phase column chromatography (15 - 80 % MeCN in pH10 ammonium hydrogen carbonate aqueous buffer solution, 12 g C18 cartridge) to give the title compound (16 mg, 31%). LCMS (Method 1): 2.01 min, 575.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.89-7.77 (m, 4H), 7.71 (m, 1H), 7.23-7.13 (m, 2H), 6.86 (d, 1H), 6.78 (d, 1H), 6.01 (dd, 1H), 4.18-4.03 (m, 2H), 3.98 (m, 1H), 3.85 (m, 1H), 3.76 (dd, 1H), 3.63 (m, 1H), 3.26 (m, 1H), 2.96 (m, 1H), 2.76 (m, 1H), 2.59 (d, 3H), 2.55-2.37 (m, 2H), 2.35 (d, 3H), 2.15 (m, 2H), 2.04 (m, 1H), 1.92 (m, 1H), 1.53 (m, 1H), 1.41 (m, 1H), 1.35-1.19 (m, 2H), 0.93 (m, 1H), 0.66 (m, 1H), 0.17 (m, 1H).

Amide Coupling Method B: Example 6: *N*-(2-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)-methyl)-2-((1*R*,2*S*)-2-(ethylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-5-methylisoxazole-3-carboxamide



[00210] To a stirred solution of (1*S*,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(2-(5-methylisoxazole-3-carboxamido)ethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid (50 mg, 0.08 mmol) in THF (1 mL) was added ethylamine solution (2M in THF; 0.08 mL, 0.16 mmol), triethylamine (0.01 mL, 0.72 mmol) and HATU (37 mg, 0.096 mmol) and the reaction mixture stirred at rt for 18 h. To this was added 10% aqueous citric acid (1 mL), the mixture was extracted with EtOAc, tthe combined organics were dried ($MgSO_4$) and concentrated in vacuo. Purification by reverse phase column chromatography (30 – 80% MeCN in pH10 ammonium hydrogen carbonate aqueous buffer solution, 12 g spherical bead C18 cartridge) to give the title compound (23 mg, 44%). LCMS (Method 1): 2.36 min, 642.5 $[M+H]^+$. ^1H NMR (300 MHz, DMSO) δ 8.76 (t, 1H), 7.91-7.76 (m, 4H), 7.24-7.12 (m, 2H), 6.89 (d, 1H), 6.80 (d, 1H), 6.54 (m, 1H), 6.03 (dd, 1H), 4.25-4.04 (m, 3H), 4.02-3.70 (m, 4H), 3.62 (m, 1H), 3.25 (m, 1H), 3.03-2.67 (m, 4H), 2.35 (s, 3H), 2.10-1.82 (m, 2H), 1.58-1.38 (m, 2H), 1.37-1.15 (m, 2H), 0.94 (m, 1H), 0.82-0.63 (m, 4H), 0.23 (m, 1H).

Example 38: (1*S*,2*R*)-2-((*S*)-1-(cyclopropanecarboxamidomethyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide

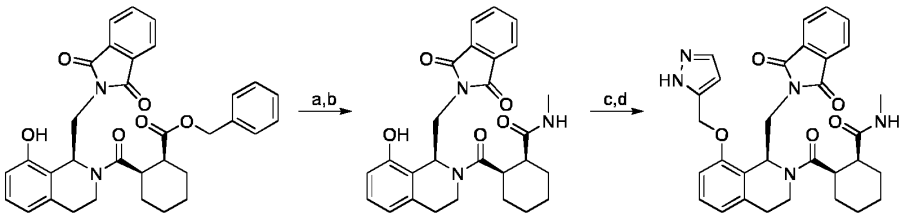


[00211] Step a. To a stirred solution of Example 17 (58 mg, 0.088 mmol) in IMS (1 mL) under argon was added hydrazine hydrate (6 uL, 0.18 mmol; CAS: 10217-52-4) and the reaction mixture was heated at 80 °C for 2h. The cooled reaction mixture was diluted with water, extracted with EtOAc, the combined organics concentrated *in vacuo* to give (1*S*,2*R*)-2-((*S*)-1-(aminomethyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide (46 mg, assumed quantitative). The crude product was used without further purification.

[00212] Step b. To a stirred solution of the above intermediate (46 mg, 0.088 mmol) and triethylamine (25 uL, 0.18 mmol) in DCM (1 mL) under argon at 0 °C was added a solution of cyclopropanecarbonyl chloride (9 uL, 0.098 mmol; CAS: 4023-34-1) in DCM (0.5 mL) dropwise. The reaction mixture was allowed to warm to rt and stirred at rt for 18 h. The mixture was diluted with water, extracted with DCM, the combined organics passed through a phase separator and concentrated *in vacuo*. Purification by MDAP (Method 1) provided the title compound (6 mg, 11%). ^1H NMR (400 MHz, DMSO-d_6; rotamers

observed, all reported) δ 9.30-9.14 (m, 1H), 8.59-8.03 (m, 2H), 7.48 (m, 0.4H), 7.29-7.11 (m, 1.6H), 7.10-6.85 (m, 1H), 6.84-6.71 (m, 1H), 5.80-5.65 (m, 0.6H), 5.39-5.21 (m, 0.5H), 5.20-5.08 (m, 0.5H), 5.06-4.93 (m, 0.4H), 4.54-2.97 (m, 9H), 2.97-2.04 (m, 9H), 2.00-0.77 (m, 8H), 0.76-0.47 (m, 4H).

Example 39: (1*S*,2*R*)-2-((*S*)-8-((1*H*-pyrazol-5-yl)methoxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide



[00213] Step a. To a solution of benzyl (1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-hydroxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylate (527 mg, 0.95 mmol; PCT/GB2019/053012 Example 2, step a) in THF (15 mL) was added Pd/C (10%; 200 mg). The mixture was stirred at rt under an atmosphere of hydrogen for 18 h at atmospheric pressure. The mixture was then filtered through a pad of Celite® and the filtrate was concentrated *in vacuo* to give (1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-hydroxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid (392 mg, 89%).

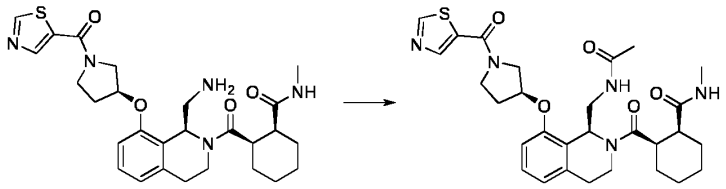
[00214] Step b. (1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-hydroxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide (541 mg, assumed quantitative) was prepared from the above intermediate (392 mg, 0.85 mmol) using a procedure similar to that described for Example 92, step g. LCMS (Method 12): 1.27 min, 476.2 $[M+H]^+$.

[00215] Step c. *tert*-Butyl 5-((((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)methyl)-1*H*-pyrazole-1-carboxylate (110 mg, 54%) was prepared from the above intermediate (156 mg, 0.32 mmol) and *tert*-butyl 5-(bromomethyl)-1*H*-pyrazole-1-carboxylate (107 mg, 0.41 mmol; CAS: 186551-69-9) using a procedure similar to that described for Example 67 step a. LCMS (Method 12): 1.61 min, 678.3 $[M+H]^+$.

[00216] Step d. To a stirred solution of the above intermediate (110 mg, 0.17 mmol) in DCM (5 mL) was added TFA (1 mL) and the reaction mixture was stirred at rt for 1 h. The mixture was concentrated in vacuo and azeotroped with toluene. Purification by MDAP (Method 1) provided the title compound (39 mg, 41%). LCMS (Method 3): 4.00 min, 556.2

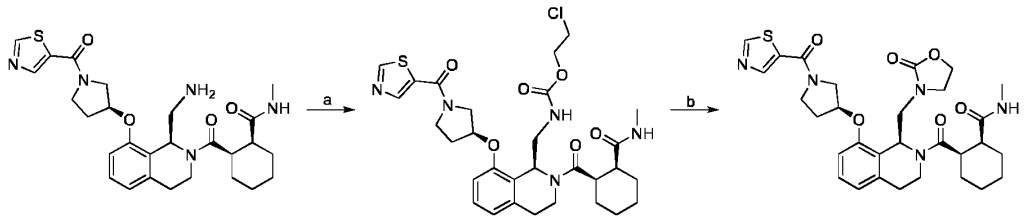
$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.78 (bs, 1H), 7.89-7.66 (m, 5H), 7.19 (t, 1H), 7.14 (m, 1H), 7.05 (d, 1H), 6.80 (d, 1H), 6.65 (bm, 1H), 6.05 (dd, 1H), 5.25 (d, 1H), 5.19 (d, 1H), 4.17 (dd, 1H), 3.81 (m, 1H), 3.73 (dd, 1H), 3.63 (m, 1H), 3.24 (m, 1H), 2.97 (m, 1H), 2.78 (m, 1H), 2.35 (d, 3H), 2.03 (m, 1H), 1.93 (m, 1H), 1.52 (m, 1H), 1.42-1.18 (m, 3H), 0.92 (m, 1H), 0.61 (m, 1H), 0.18 (m, 1H).

Example 44: (1*S*,2*R*)-2-((*S*)-1-(acetamidomethyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide



[00217] To a stirred solution of (1*S*,2*R*)-2-((*S*)-1-(aminomethyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide (50 mg, 0.095 mmol; Example 38 step a) and triethylamine (15 uL, 0.10 mmol) in DCM (1 mL) at 0 °C under argon was added acetyl chloride (8 uL, 0.10 mmol) and the reaction mixture allowed to warm to rt and stirred for 3 h. To this was added water, the mixture was extracted with DCM and the combined organics concentrated *in vacuo*. Purification by MDAP (Method 2) gave the title compound (12 mg, 22%. LCMS (Method 3): 3.05 min, 590.2 $[M+Na]^+$. ^1H NMR (400 MHz, DMSO-d_6; rotamers observed, all reported) δ 9.26 (s, 0.3H), 9.25 (s, 0.3H), 9.23 (s, 0.2H), 9.18 (s, 0.2H), 8.45-8.37 (m, 0.8H), 8.27 (s, 0.2H), 8.05-7.97 (m, 0.5H), 7.95 (m, 0.3H), 7.87 (m, 0.2H), 7.41 (m, 0.5H), 7.27-7.10 (m, 1.5H), 7.00-6.84 (m, 1H), 6.81-6.69 (m, 1H), 5.77-5.61 (m, 0.5H), 5.30 (m, 0.2H), 5.25 (m, 0.3H), 5.19-5.09 (m, 0.5H), 5.08-4.94 (m, 0.5H), 4.43-2.96 (m, 9H), 2.95-1.96 (m, 9H), 1.95-0.73 (m, 10H).

Example 45: (1*S*,2*R*)-*N*-methyl-2-((*S*)-1-((2-oxooxazolidin-3-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide

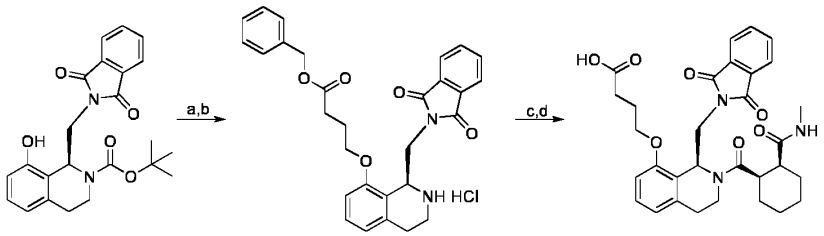


[00218] Step a. 2-Chloroethyl (((*S*)-2-((1*R*,2*S*)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinolin-

1-yl)methyl)carbamate (68 mg, assumed quantitative) was prepared from (1*S*,2*R*)-2-((*S*)-1-(aminomethyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide (50 mg, 0.095 mmol; Example 38 step a) and 2-chloroethyl chloroformate (11 uL, 0.10 mmol; CAS: 627-11-2) using a procedure similar to that described for Example 44.

[00219] Step b. To a mixture of the above intermediate (68 mg, 0.1 mmol) and sodium hydride (60% dispersion in mineral oil; 5 mg, 0.1 mmol) under argon at 0 °C was added anhydrous DMF (1 mL) and the reaction mixture allowed to warm to rt and stirred for 48 h. To the mixture was added saturated ammonium chloride solution, the mixture was extracted with DCM and the combined organics passed through a phase separator and concentrated *in vacuo*. Purification by MDAP (Method 2) gave the title compound (14 mg, 24%). LCMS (Method 3): 3.15 min, 618.2 $[M+Na]^+$. ^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 9.26 (s, 0.5H), 9.24 (s, 0.5H), 8.47 (s, 0.5H), 8.40 (s, 0.5H), 7.31-7.14 (m, 2H), 6.99-6.88 (m, 1H), 6.84-6.72 (m, 1H), 5.88-5.73 (m, 1H), 5.35-5.02 (m, 1H), 4.46-3.40 (m, 10H), 3.39-3.24 (m, 2H), 3.15 (m, 1H), 2.92 (m, 1H), 2.73 (m, 1H), 2.59-2.08 (m, 7H), 1.85-1.59 (m, 3H), 1.55-1.06 (m, 4H).

Example 46: 4-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)butanoic acid



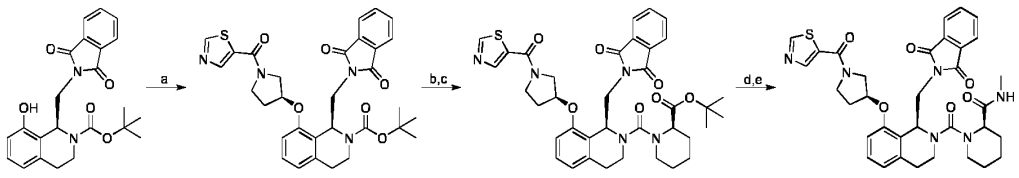
[00220] Step a. To a stirred solution of triphenyl phosphine (6.09 g, 23.2 mmol) in THF (50 mL) at 0 °C was added DIAD (4.5 mL, 23.2 mmol) dropwise and the reaction mixture stirred for 0.5 h. To this was added a solution of benzyl 4-hydroxybutanoate (1.35 g, 6.96 mmol; CAS: 91970-62-6) in THF (10 mL) and stirred at 0 °C for 30 min, followed by addition of Intermediate 11 (1.9 g, 4.64 mmol) in THF (20 mL). The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was diluted with water, extracted with EtOAc and the combined organics dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 0 - 50% EtOAc in n-hexane) gave *tert*-butyl (*S*)-8-(4-(benzyloxy)-4-oxobutoxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (520 mg, 23%).

[00221] Step b. Benzyl (*S*)-4-((1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)butanoate hydrochloride (1.07 g, assumed quantitative) was prepared from the above intermediate (1.14 g, 1.95 mmol) using a procedure similar to that described for Example 67, step b. LCMS (Method 12): 1.11 min, 485 $[M+H]^+$.

[00222] Step c. To a stirred solution of (1*R*,2*S*)-2-(methylcarbamoyl)-cyclohexanecarboxylic acid (43 mg, 0.23 mmol; CAS: 1821740-00-4) in DMF (0.5 mL) at rt under argon was added triethylamine (80 uL, 0.58 mmol) and HATU (88 mg, 0.23 mmol) and the reaction mixture stirred for 10 mins. To this was added a solution of the above intermediate (104 mg, 0.19 mmol) in DMF (1 mL) dropwise and the reaction mixture stirred for 23 h. The mixture was diluted with saturated sodium hydrogen carbonate solution, extracted with EtOAc and the combined organics washed with saturated ammonium chloride, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (12g Puriflash silica cartridge, 0 - 5% MeOH in DCM) to provide benzyl 4-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)butanoate (120 mg, 80%). LCMS (Method 12): 1.63 min, 652 $[M+H]^+$.

[00223] Step d. A solution of the above intermediate (118 mg, 0.18 mmol) in MeOH (0.1 M; 1.8 mL) was passed through an H-Cube® with a 10% Pd/C cartridge at 1 mL/min at 50 °C with hydrogen at 50 bar pressure. The solution was passed through a second time and then concentrated *in vacuo*. Purification by MDAP (Method 1) gave the title compound (23 mg, 23%). LCMS (Method 3): 4.05 min, 584.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.11 (bs, 1H), 7.92-7.75 (m, 4H), 7.26-7.06 (m, 2H), 6.86 (d, 1H), 6.79 (d, 1H), 6.00 (dd, 1H), 4.19-4.06 (m, 2H), 4.01 (m, 1H), 3.85 (m, 1H), 3.76 (m, 1H), 3.63 (m, 1H), 3.26 (m, 1H), 2.97 (m, 1H), 2.82-2.46 (m, 3H), 2.36 (d, 3H), 2.23-2.10 (m, 2H), 2.04 (m, 1H), 1.93 (m, 1H), 1.53 (m, 1H), 1.41 (m, 1H), 1.35-1.19 (m, 2H), 0.93 (m, 1H), 0.66 (m, 1H), 0.17 (m, 1H).

Example 48: (*R*)-1-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylpiperidine-2-carboxamide



[00224] Step a. To a stirred solution of Intermediate 11 (5.0 g, 12.2 mmol) and (*R*)-(3-hydroxypyrrolidin-1-yl)(thiazol-5-yl)methanone (3.16 g, 15.9 mmol, CAS: 1690066-04-6) in anhydrous THF (100 mL) under argon was added tributylphosphine (3.98 mL, 15.9 mmol)

followed by a solution of DBAD (3.66 g, 15.9 mmol; CAS: 870-50-8) in THF (50 mL) over 10 mins. After 2 h of stirring additional protions of tributylphosphine (3.98 mL, 15.9 mmol) and DBAD (3.66 g, 15.9 mmol) in THF (50 mL) were added and the reaction mixture stirred at rt for 18 h. Additional (*R*)-(3-hydroxypyrrolidin-1-yl)(thiazol-5-yl)methanone (3.16 g, 15.9 mmol, CAS: 1690066-04-6), tributylphosphine (3.98 mL, 15.9 mmol) and DBAD (3.66 g, 15.9 mmol) in THF (50 mL) were added sequentially and the reaction mixture stirred for 3 h. To the reaction mixture was added water and the mixture was concentrated *in vacuo*. Purification by flash column chromatography on the Interchim 4125 (330 g silica column Puriflash HP, 0 – 10% MeOH in EtOAc) followed by flash column chromatography on the Interchim 4100 (300 g silica Biotage SNAP, 0 – 10% MeOH in EtOAc) gave *tert*-butyl (*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (6.48 g, 90%). LCMS (Method 3): 1.47 min, 611 $[M+Na]^+$.

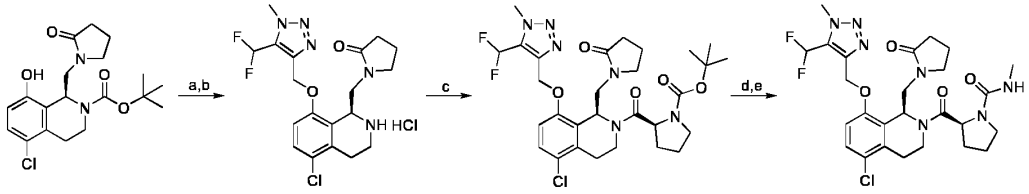
[00225] Step b. 2-(((*S*)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)isoindoline-1,3-dione hydrochloride (498 mg, assumed quantitative) was prepared from the above intermediate (600 mg, 1.02 mmol) using a procedure similar to that described for Example 67, step b.

[00226] Step c. To a stirred solution of the above intermediate (150 mg, 0.29 mmol) in DCM (1.5 mL) under argon was added triethylamine (120 uL, 0.86 mmol) and a solution of triphosgene (34 mg, 0.11 mmol) in DCM (1 mL). The reaction mixture was stirred at rt for 20 min, and to this was added a solution of *tert*-butyl (*R*)-piperidine-2-carboxylate hydrochloride (66mg, 0.30 mmol; CAS: 140646-13-5) in DCM (1.5 mL) and triethylamine (200 uL, 1.43 mmol). The reaction mixture was stirred at rt for 2 h, then heated to 40 °C for 5 days. The mixture was diluted with saturated sodium hydrogen carbonate, extracted with DCM and the combined organics washed with brine, dried over Na2SO4 and concentrated *in vacuo*. Purification by flash column chromatography (12g Puriflash silica cartridge, 0 - 10% MeOH in DCM) gave *tert*-Butyl (*R*)-1-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)piperidine-2-carboxylate (128 mg, 64%). LCMS (Method 12): 1.61 min, 700 $[M+H]^+$.

[00227] Step d. To a stirred solution of the above intermediate (127 mg, 0.18 mmol) in DCM (3 mL) was added TFA (1.5 mL) and the reaction mixture stirred at rt for 2 h 40 mins. The mixture was concentrated in vacuo and azeotroped with toluene to give (*R*)-1-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)piperidine-2-carboxylic acid (117 mg, assumed quantitative), used without further purification.

[00228] Step e. The title compound (50 mg, 42%) was prepared from the above intermediate (117 mg, 0.18 mmol) using a procedure similar to that described for Example 92 step g. LCMS (Method 3): 3.92 min, 657.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 9.24 (s, 1H), 8.42 (s, 0.5H), 8.39 (s, 0.5H), 7.90-7.78 (m, 4H), 7.41 (m, 1H), 7.29-7.16 (m, 1H), 6.97 (d, 0.5H), 6.93 (d, 0.5H), 6.81 (d, 0.5H), 6.79 (d, 0.5H), 5.31-5.17 (m, 2H), 4.37-4.23 (m, 1H), 4.10 (m, 0.5H), 4.02-3.72 (m, 4.5H), 3.65-3.47 (m, 2H), 3.45-3.23 (m, 1H), 2.98 (m, 1H), 2.92-2.63 (m, 3H), 2.58-2.22 (m, 5H), 1.79-1.62 (m, 1H), 1.41-0.79 (m, 5H).

Example 67: (*S*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylpyrrolidine-1-carboxamide



[00229] Step a. To a stirred solution of Intermediate 23 (2.6 g, 6.83 mmol) in DMF (59 mL) was added 4-(chloromethyl)-5-(difluoromethyl)-1-methyl-triazole (1.29 g, 7.09 mmol, CAS: 2138555-23-2) and caesium carbonate (8.01 g, 24.6 mmol) and the reaction mixture stirred under argon at rt for 19 h. The reaction was filtered and the solid washed with EtOAc (20 ml) and the filtrate concentrated *in vacuo*. The residue was partitioned between EtOAc and water, the organics washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on the Teledyne ISCO CombiFlash® Rf+ (80 g silica column Puriflash HC, 0 - 10% MeOH in DCM) to provide *tert*-butyl (*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (0.63 g). The caesium carbonate residue was partitioned between DCM/H_2O, and the aqueous extracted with DCM, the combined organics dried over Mg_2SO_4, filtered and concentrated *in vacuo* to give another crop of the product (2.35 g). The batches were combined to give *tert*-butyl (*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-3,4-dihydroiso-quinoline-2(1*H*)-carboxylate (2.98 g, 83%). LCMS (Method 12): 1.42 min, 548.3 $[M+Na]^+$.

[00230] Step b. To the above intermediate (1.11 g, 2.11 mmol) was added hydrochloric acid (4 M dioxane; 10.55 mL, 42.2 mmol) and the reaction mixture was stirred at rt for 20 min. MeOH was added to the reaction mixture and the mixture concentrated *in vacuo* to give (*S*)-1-((5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-

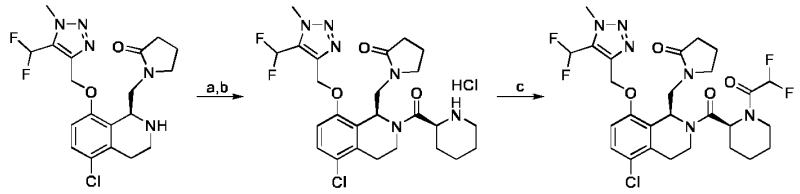
1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)pyrrolidin-2-one (0.99 g, assumed quantitative), used without further purification. LCMS (Method 12): 0.77 min, 426.0 $[M+H]^+$.

[00231] Step c. To a stirred solution of *N*-(*tert*-butoxycarbonyl)-L-proline (78 mg, 0.36 mmol; CAS: 15761-39-4) in anhydrous DMF (1 mL) under argon was added DIPEA (0.17 mL, 0.98 mmol) and HATU (137 mg, 0.36 mmol; CAS: 148893-10-1). The reaction mixture was stirred at rt for 10 min, then to this was added the above intermediate (151 mg, 0.33 mmol) in anhydrous DMF (2 mL) dropwise. The reaction mixture was stirred at rt for 21 h, diluted with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc and the combined organics were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on the Teledyne ISCO CombiFlash® Rf200 (12 g silica column Puriflash HC, 0 - 10% MeOH in DCM) to provide *tert*-butyl (*S*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-pyrrolidine-1-carboxylate (159 mg, 78%). LCMS (Method 12): 1.30 min, 623.3 $[M+H]^+$.

[00232] Step d. To a stirred solution of the above intermediate (158 mg, 0.25 mmol) in anhydrous 1,4-dioxane (4 mL) was added hydrogen chloride (4 M in dioxane; 4.0 mL, 16 mmol). The reaction mixture was stirred at rt for 2.5 h then concentrated *in vacuo* to provide 1-(((*S*)-2-(*L*-prolyl)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)pyrrolidin-2-one hydrochloride (154 mg, assumed quantitative). LCMS (Method 12): 0.84 min, 523.3 $[M+H]^+$.

Step e. To a stirred mixture of the above intermediate (152 mg, 0.27 mmol) in anhydrous DCM (5 mL) was added *N*-methyl-1-imidazolecarboxamide (46 mg, 0.37 mmol; CAS: 72002-25-6), then triethylamine (0.1 mL, 0.73 mmol) and the resulting solution was stirred at rt under argon for 17 h. Additional *N*-methyl-1-imidazolecarboxamide (15 mg, 0.12 mmol) was added and the solution was stirred for a further 7 h. The solution was diluted with saturated $NaHCO_3$ solution, extracted with DCM and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by MDAP (Method 3) to provide the title compound (115 mg, 73%). LCMS (Method 5): 3.03 min, 580.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.58 (t, 1H), 7.41 (d, 1H), 7.18 (d, 1H), 5.99 (m, 1H), 5.67 (dd, 1H), 5.35-5.25 (m, 2H), 4.70 (m, 1H), 4.17 (s, 3H), 4.02 (dd, 1H), 3.87 (dd, 1H), 3.57 (m, 1H), 3.40 (m, 1H), 3.36-3.27 (m, 1H), 3.20 (m, 1H), 2.94 (dd, 1H), 2.87-2.69 (m, 3H), 2.46 (d, 3H), 2.17 (m, 1H), 2.05-1.60 (m, 7H).

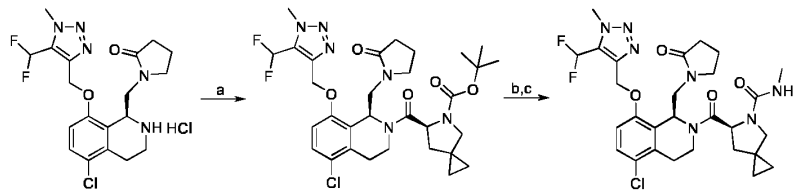
Example 84: 1-(((*S*)-5-chloro-2-((*S*)-1-(2,2-difluoroacetyl)piperidine-2-carbonyl)-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)pyrrolidin-2-one



[00233] Steps a & b. These steps were carried out with (*S*)-(−)-1-(*tert*-butoxycarbonyl)-2-piperidinecarboxylic acid (162 mg, 0.70 mmol; CAS: 26250-84-0) with methods analogous to Example 67 steps c and d.

[00234] Step c. To a stirred solution of 1-(((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-2-((*S*)-piperidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)pyrrolidin-2-one (126 mg, 0.22 mmol) in DCM (1.5 mL) under nitrogen was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.07 mL, 0.26 mmol; CAS: 25952-53-8), 1-hydroxybenzotriazole hydrate (40 mg, 0.26 mmol; CAS: 123333-53-9) and DIPEA (0.15 mL, 0.88 mmol). The reaction mixture was stirred at rt for 10 min and to this was added 2,2-difluoroacetic acid (0.02 mL, 0.26 mmol; CAS: 381-73-7). The reaction mixture was stirred at rt for 3 days, diluted with DCM and directly purified by chromatography on silica (Puriflash 12g, 0 - 50% EtOAc in isohexane) followed by chromatography on silica (Puriflash 12g, 0 - 10% MeOH in DCM) and MDAP (Method 3) to give the title compound (7 mg, 5%). LCMS (Method 3) 4.24 min, 615.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.57 (t, 1H), 7.40 (d, 1H), 7.17 (d, 1H), 6.72 (t, 1H), 5.71 (m, 1H), 5.33-5.25 (m, 2H), 5.22 (m, 1H), 4.17 (s, 3H), 4.00 (m, 1H), 3.87 (dd, 1H), 3.75 (m, 1H), 3.70-3.20 (m, 2H), 2.99 (m, 1H), 2.85 (m, 2H), 2.72 (m, 1H), 2.19 (m, 1H), 2.02 (m, 1H), 1.93-1.53 (m, 7H), 1.50-1.13 (m, 2H).

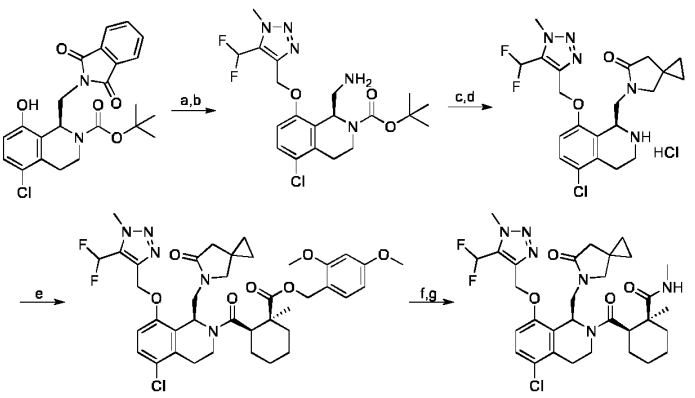
Example 88: (*S*)-6-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methyl-5-azaspiro[2.4]heptane-5-carboxamide



[00235] Steps a, b. These steps were carried out with (*S*)-5-(*tert*-butoxycarbonyl)-5-azaspiro[2.4]heptane-6-carboxylic acid (86 mg, 0.36 mmol; CAS: 1129634-44-1) with methods analogous to Example 67 steps c and d.

[00236] Step c. To a solution of 1-(((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-2-((*S*)-5-azaspiro[2.4]heptane-6-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl)methyl)pyrrolidin-2-onehydrochloride (75 mg, 0.12 mmol) in DCM (1.9 mL) cooled to 2 °C was added triethylamine (0.04 mL, 0.26 mmol) followed by *N*-methylcarbamoyl chloride (13.14 mg, 0.140 mmol; CAS: 6452-47-7). The reaction mixture was warmed to ambient temperature and stirred for 1 h and the mixture was combined with another batch (0.031 mmol). To the combined mixture was added water, the mixture extracted with DCM and the combined organics concentrated *in vacuo*. The crude product was purified by automated reverse phase column chromatography on the Biotage Isolera One™ (200-400 nm diode array detector, 12 g C18 column, 5 - 40% MeCN in pH10 0.1 M NH_4HCO_3 buffer solution) to provide the title compound (50 mg, 54%). LCMS (Method 6): 1.63 min, 606.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.58 (t, 1H), 7.41 (d, 1H), 7.18 (d, 1H), 5.95 (m, 1H), 5.68 (m, 1H), 5.38-5.21 (m, 2H), 4.79 (dd, 1H), 4.17 (s, 3H), 3.98 (m, 1H), 3.86 (dd, 1H), 3.53 (m, 1H), 3.45-3.21 (m, 2H), 3.18 (d, 1H), 2.94 (dd, 1H), 2.86-2.72 (m, 3H), 2.45 (d, 3H), 2.22-2.09 (m, 2H), 1.98 (m, 1H), 1.89-1.66 (m, 2H), 1.52 (dd, 1H), 0.60-0.34 (m, 4H).

Example 98: (1*R*,2*S*)-2-((*R*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide



[00237] Step a. To a stirred solution of Intermediate 12 (16.5 g, 37.3 mmol) and cesium carbonate (43.7g, 134 mmol) in DMF (300 mL) was added 4-(chloromethyl)-5-(difluoromethyl)-1-methyl-triazole hydrochloride (8.12 g, 37.3 mmol) and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with water and the precipitate isolated. The solid was azeotroped with MeOH, dissolved in Et_2O and concentrated *in vacuo* to give *tert*-butyl (*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (18.5 g, 84%) LCMS (Method 16): 1.13 min, 488.2 $[M-CO_2{}^tBu+H]^+$.

[00238] Step b. To a solution of the above intermediate (18.5 g, 31.4 mmol) in EtOH (569 mL) was added hydrazine hydrate (7.65 mL, 157 mmol). The reaction mixture was heated at 65 °C for 18 h then cooled to rt. The suspension was filtered and the solid rinsed with EtOH. The combined filtrates were concentrated *in vacuo*. The residue was washed with diethyl ether and filtered. The filtrate was concentrated *in vacuo*, azeotroped with IMS and the precipitate dissolved in DCM. Precipitate was removed by filtration and the combined organics dried over $MgSO_4$, filtered and concentrated *in vacuo* to give *tert*-butyl (*S*)-1-(aminomethyl)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (13.5 g, 94%). LCMS (Method 16): 0.90 min, 458.2 $[M+H]^+$.

[00239] Step c. A stirred mixture of the above intermediate (11.0 g, 22.0 mmol), triethylamine (4.60 mL, 33.0 mmol) and methyl 2-(1-(bromomethyl)-cyclopropyl)acetate (5.92 g, 28.6 mmol, CAS: 855473-50-6) in MeCN (210 mL) was heated at reflux for 72 h. The mixture was concentrated *in vacuo*. Purification by flash column chromatography (silica, 0 – 2% MeOH in DCM) gave *tert*-butyl (*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]-heptan-5-yl)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (11.5 g, 95%). LCMS (Method 16): 1.02 min, 452.2 $[M\text{-}CO_2{}^tBu+H]^+$.

[00240] Step d. (*S*)-5-((5-Chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-5-azaspiro[2.4]heptan-6-one hydrochloride (4.08 g, assumed quantitative) was prepared from the above intermediate (4.54 g, 8.22 mmol) using a procedure similar to that described for Example 67, step b and was used without further purification. LCMS (Method 12): 0.99 min, 452.2 $[M+H]^+$.

[00241] Step e. A mixture of the above intermediate (12.4 g, 25.4 mmol), Intermediate 33 (17.3 g, 38.1 mmol) and DIPEA (8.85 mL, 50.8 mmol) in DMF (30 mL) was stirred under nitrogen at rt for 6 days. The mixture was diluted with water (120 mL) and extracted with EtOAc. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on the Teledyne ISCO CombiFlash® Rf+ (330 g silica column Puriflash HC, 0 - 5% MeOH in DCM) followed by another purification on the Teledyne ISCO CombiFlash® Rf+ (330 g silica column Puriflash HC, 0 - 5% MeOH in DCM) to give 2,4-dimethoxybenzyl (1*S*,2*R*)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylate (14.7 g, 75%). LCMS (Method 3): 1.71 min, 770.5 $[M+H]^+$.

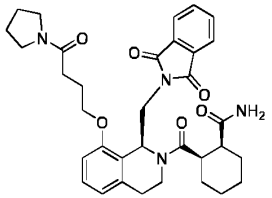
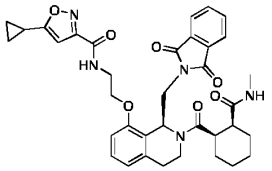
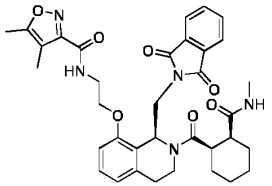
[00242] Step f. A solution of the above intermediate (550 mg, 0.71 mmol) in hydrogen chloride in dioxane (4 M; 17.8 mL, 71.4 mmol) was stirred at rt for 10 mins and concentrated *in vacuo*. The residue was triturtated with methanol, then purified by reverse phase flash column chromatography on the Biotage Isolera (Biotage C18 SNAP 60 g, 20 - 60% MeCN in water, 0.1 % formic acid throughout) to provide (1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]-heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid (250 mg, 56%). LCMS (Method 10): 2.52 min, 620.3 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.84 (bs, 1H), 7.57 (t, 1H), 7.38 (d, 1H), 7.14 (d, 1H), 5.77 (m, 1H), 5.28 (s, 2H), 4.16 (s, 3H), 4.04-3.86 (m, 2H), 3.59 (m, 1H), 3.38-3.24 (m, 1H), 3.06-2.90 (m, 2H), 2.84 (m, 1H), 2.77-2.65 (m, 1H), 2.61 (d, 1H), 2.37-2.15 (m, 2H), 2.10 (d, 1H), 1.75-1.16 (m, 7H), 1.10 (s, 3H), 0.67-0.32 (m, 4H).

[00243] Step f Method 2. To a stirred solution of the above intermediate (14.7 g, 19.1 mmol) in DCM (92 mL) was added triethylsilane (3.05 mL, 19.1 mmol) followed by dropwise addition of TFA (1.76 mL, 22.9 mmol). The resulting solution was stirred for 1.5 h. The precipitate was removed by filtration, and the filtrate was concentrated *in vacuo* to ~5mL. The residue was purified by flash column chromatography on the Teledyne ISCO CombiFlash® Rf^+ (220 g silica column Puriflash HC, 0 - 3% MeOH in DCM). The product was then dissolved in 10mL of warm EtOH and left to cool to rt and the resulting precipitate was collected by filtration and the precipitate was washed with cold EtOH. The material was then slurried in MeCN (30 mL) and collected by filtration to provide (1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methyl-cyclohexane-1-carboxylic acid (9.45 g, 78%). LCMS (Method 3): 4.57 min, 620.4 $[M+H]^+$.

[00244] Step g. To a stirred solution of the above intermediate (100 mg, 0.160 mmol) in DMF (0.5 mL) was added HATU (92 mg, 0.240 mmol; CAS: 148893-10-1), methylamine (2 M in THF; 0.81 mL, 1.61 mmol; CAS: 74-89-5) and DIPEA (0.17 mL, 0.97 mmol) and the reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with water, extracted with EtOAc and the combined organics washed with 10 % citric acid, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification using the Isolera (Biotage C18 SNAP 30 g, 5 - 60 % MeCN in water, 0.1 % formic acid throughout) gave the title compound (18 mg, 17%). LCMS (Method 9): 2.33 min, 633.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (bm, 1H), 7.24 (d, 1H), 6.93 (t, 1H), 6.89 (d, 1H), 5.97 (m, 1H), 5.32-5.18 (m, 2H), 4.17 (s, 3H), 4.07 (dd, 1H), 3.96 (m, 1H), 3.85 (m, 1H), 3.52 (d, 1H), 3.07 (m, 1H), 3.02-2.89 (m, 3H), 2.83 (m, 1H), 2.71 (d, 3H), 2.55 (m, 1H), 2.37 (d, 1H), 2.20 (d, 1H), 1.82-1.31 (m, 6H), 1.22-1.07 (m, 4H), 0.69-0.47 (m, 4H).

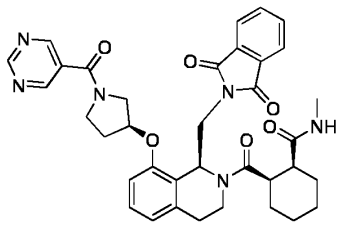
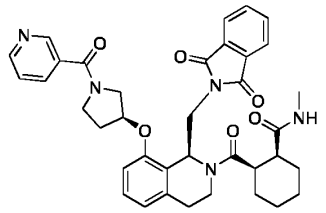
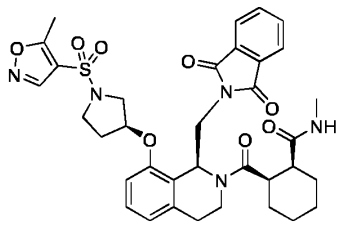
[00245] Compounds in Table 1 were synthesised by methods analogous to the above Examples.

Table 1

Ex.	Structure	Name	Analogous Example	^{1}H NMR δ ppm	LCMS
1		(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(4-oxo-4-(pyrrolidin-1-yl)butoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide	2	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87-7.76 (m, 4H), 7.18 (m, 1H), 6.86 (m, 1H), 6.80-6.72 (m, 2H), 6.51 (bs, 1H), 6.02 (m, 1H), 4.20-4.06 (m, 2H), 4.00 (m, 1H), 3.89-3.71 (m, 2H), 3.64 (m, 1H), 3.52-3.20 (m, 4H), 2.99 (m, 1H), 2.75 (m, 1H), 2.65 (m, 2H), 2.14 (m, 2H), 2.05-1.88 (m, 2H), 1.87-1.69 (m, 4H), 1.49 (m, 1H), 1.44-1.08 (m, 4H), 0.91 (m, 1H), 0.63 (m, 1H), 0.15 (m, 1H)	Method 1: 1.90 min, 601.1 $[M+H]^+$
3		5-cyclopropyl-*N*-(2-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)isoxazole-3-carboxamide	2	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.71 (t, 1H), 7.90-7.77 (m, 4H), 7.25-7.11 (m, 2H), 6.89 (d, 1H), 6.80 (d, 1H), 6.48 (s, 1H), 6.02 (m, 1H), 4.24-4.05 (m, 3H), 4.00-3.73 (m, 4H), 3.60 (m, 1H), 3.39-3.22 (m, 1H), 2.96 (m, 1H), 2.75 (m, 1H), 2.35 (d, 3H), 2.15-1.83 (m, 2H), 1.76 (m, 1H), 1.60-1.39 (m, 2H), 1.37-0.66 (m, 8H), 0.22 (m, 1H).	Method 1: 2.42 min, 654.5 $[M+H]^+$
4		*N*-(2-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-4,5-dimethylisoxazole-3-carboxamide	2	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.69 (t, 1H), 7.91-7.75 (m, 4H), 7.25-7.09 (m, 2H), 6.90 (d, 1H), 6.80 (d, 1H), 6.02 (dd, 1H), 4.22-4.06 (m, 3H), 4.04-3.68 (m, 4H), 3.61 (m, 1H), 3.26 (m, 1H), 2.96 (m, 1H), 2.75 (m, 1H), 2.35 (d, 3H), 2.25 (s, 3H), 2.13-1.79 (m, 5H), 1.59-1.39 (m, 2H), 1.37-0.62 (m, 4H), 0.21 (m, 1H).	Method 1: 2.44 min, 642.5 $[M+H]^+$

5		(1*S*,2*R*)-2-((*S*)-8-(((*S*)-1-acetylpyrrolidin-3-yl)oxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	2	^{1}H NMR (400 MHz, DMSO-d$_6$; rotamers observed, both reported) δ 7.91-7.75 (m, 4H), 7.25-7.10 (m, 2H), 6.89 (m, 1H), 6.81 (m, 1H), 5.92 (m, 1H), 5.16 (m, 0.6H), 5.10 (m, 0.4H), 4.15-3.52 (m, 8H), 3.25 (m, 1H), 2.95 (m, 1H), 2.80-2.70 (m, 1H), 2.60-1.81 (m, 10H), 1.52 (m, 1H), 1.42 (m, 1H), 1.36-1.17 (m, 2H), 1.01-0.76 (m, 1H), 0.75-0.62 (m, 1H), 0.31-0.04 (m, 1H).	Method 1: 1.89 & 1.97 min, 587.5 $[M+H]^+$ (rotamers)
7		*N*-(2-(((*S*)-2-((1*R*,2*S*)-2-(cyclopropylcarbamoyl)cyclohexane-1-carbonyl)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-5-methylisoxazole-3-carboxamide	6	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.77 (m, 1H), 7.91-7.75 (m, 4H), 7.26-7.11 (m, 2H), 6.90 (m, 1H), 6.80 (m, 1H), 6.54 (m, 1H), 6.03 (m, 1H), 4.25-4.05 (m, 3H), 4.03-3.72 (m, 4H), 3.62 (m, 1H), 3.23 (m, 1H), 2.96 (m, 1H), 2.75 (m, 1H), 2.42-2.25 (m, 4H), 2.10-1.79 (m, 2H), 1.53-1.37 (m, 2H), 1.36-1.16 (m, 2H), 0.92 (m, 1H), 0.74 (m, 1H), 0.44-0.02 (m, 5H).	Method 1: 2.37 min, 654.5 $[M+H]^+$
8		*N*-(2-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(3-hydroxyazetidine-1-carbonyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-5-methylisoxazole-3-carboxamide	6	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.78 (t, 1H), 7.98-7.77 (m, 4H), 7.20 (t, 1H), 6.90 (m, 1H), 6.80 (m, 1H), 6.55 (m, 1H), 6.07 (m, 1H), 5.60 (m, 1H), 4.37-3.48 (m, 12H), 3.08-2.66 (m, 3H), 2.44-2.22 (m, 4H), 1.95 (m, 1H), 1.69-0.90 (m, 5H), 0.73 (m, 1H), 0.51 (m, 1H).	Method 1: 2.12 min, 670.6 $[M+H]^+$
9		*N*-(2-(((*S*)-2-((1*R*,2*S*)-2-(cyclobutylcarbamoyl)cyclohexane-1-carbonyl)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)-5-methylisoxazole-3-carboxamide	6	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.77 (t, 1H), 7.91-7.77 (m, 4H), 7.36 (d, 1H), 7.19 (t, 1H), 6.89 (m, 1H), 6.79 (m, 1H), 6.54 (m, 1H), 6.02 (m, 1H), 4.24-4.04 (m, 3H), 4.01-3.71 (m, 5H), 3.62 (m, 1H), 3.24 (m, 1H), 2.96 (m, 1H), 2.74 (m, 1H), 2.35 (s, 3H), 2.13-1.17 (m, 12H), 0.93 (m, 1H), 0.73 (m, 1H), 0.23 (m, 1H).	Method 1: 2.53 min, 668.6 $[M+H]^+$

10		5-cyclopropyl-*N*-(2-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)isoxazole-3-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (t, 1H), 7.89-7.78 (m, 4H), 7.20 (t, 1H), 7.15 (m, 1H), 6.90 (d, 1H), 6.81 (d, 1H), 6.79 (s, 1H), 6.03 (dd, 1H), 4.23 (m, 1H), 4.17-4.08 (m, 2H), 3.94-3.75 (m, 4H), 3.62 (m, 1H), 3.26 (m, 1H), 2.97 (m, 1H), 2.76 (m, 1H), 2.35 (d, 3H), 2.05 (m, 1H), 1.99-1.87 (m, 2H), 1.52 (m, 1H), 1.44 (m, 1H), 1.36-1.21 (m, 2H), 1.02-0.86 (m, 3H), 0.79-0.65 (m, 3H), 0.24 (m, 1H).	Method 1: 2.29 min, 654.6 $[M+H]^+$
11		*N*-(2-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)benzo[*d*]oxazole-2-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (t, 1H), 7.92-7.74 (m, 4H), 7.71 (m, 1H), 7.44 (m, 1H), 7.36-7.26 (m, 2H), 7.21 (t, 1H), 7.16 (m, 1H), 6.92 (d, 1H), 6.81 (d, 1H), 6.08 (dd, 1H), 4.28-4.21 (m, 2H), 4.17 (dd, 1H), 4.02 (m, 1H), 3.94-3.75 (m, 3H), 3.60 (m, 1H), 3.27 (m, 1H), 2.95 (m, 1H), 2.75 (m, 1H), 2.35 (d, 3H), 2.04 (m, 1H), 1.89 (m, 1H), 1.57-1.20 (m, 4H), 0.93 (m, 1H), 0.74 (m, 1H), 0.21 (m, 1H).	Method 1: 2.42 min, 664.6 $[M+H]^+$
12		*N*-(2-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)benzo[*d*]isoxazole-3-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (t, 1H), 8.12 (m, 1H), 7.84-7.77 (m, 4H), 7.75 (m, 1H), 7.66 (m, 1H), 7.46 (m, 1H), 7.21 (t, 1H), 7.17 (m, 1H), 6.93 (d, 1H), 6.81 (d, 1H), 6.04 (dd, 1H), 4.32-4.19 (m, 2H), 4.15 (dd, 1H), 4.06 (m, 1H), 3.95-3.75 (m, 3H), 3.61 (m, 1H), 3.26 (m, 1H), 2.96 (m, 1H), 2.75 (m, 1H), 2.35 (d, 3H), 2.04 (m, 1H), 1.90 (m, 1H), 1.52 (m, 1H), 1.45 (m, 1H), 1.35-1.20 (m, 2H), 0.93 (m, 1H), 0.74 (m, 1H), 0.20 (m, 1H).	Method 1: 2.62 min, 664.6 $[M+H]^+$
13		(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(2-((5-methylisoxazole)-4-sulfonamido)ethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-	6	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (bs, 1H), 7.89-7.76 (m, 4H), 7.19 (t, 1H), 7.15 (m, 1H), 6.83 (d, 1H), 6.78 (d, 1H), 6.13 (t, 1H), 5.96 (dd, 1H), 4.26-4.14 (m, 2H), 3.99 (m, 1H), 3.86 (m, 1H), 3.75 (dd, 1H), 3.62 (m, 1H), 3.45-3.21 (m, 3H), 2.94 (m, 1H), 2.75 (m, 1H), 2.34 (d, 3H), 2.07-1.86 (m, 2H), 1.81 (s, 3H), 1.55-1.39 (m, 2H), 1.35-1.21 (m, 2H), 0.93 (m, 1H), 0.73 (m, 1H), 0.23 (m, 1H).	Method 1: 1.63 min, 664.5 $[M+H]^+$

		methylcyclohexane-1-carboxamide			
14		(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(pyrimidine-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d$_6$; rotamers observed, both reported) δ 9.32 (s, 0.6H), 9.27 (s, 0.4H), 9.09 (s, 1.2H), 9.04 (s, 0.8H), 7.89-7.75 (m, 4H), 7.24 (t, 0.4H), 7.19 (t, 0.6H), 7.14 (m, 0.6H), 7.08 (m, 0.4H), 6.99 (d, 0.4H), 6.88 (d, 0.6H), 6.84 (d, 0.4H), 6.79 (d, 0.6H), 6.01 (dd, 0.4H), 5.87 (dd, 0.6H), 5.25 (m, 0.4H), 5.13 (m, 0.6H), 4.22 (dd, 0.6H), 4.14-3.46 (m, 7.4H), 3.24 (m, 1H), 2.94 (m, 1H), 2.84-2.69 (m, 1H), 2.56-2.20 (m, 5H), 2.15-1.97 (m, 1H), 1.96-1.78 (m, 1H), 1.50 (m, 1H), 1.45-1.35 (m, 1H), 1.33-1.18 (m, 2H), 0.92 (m, 1H), 0.70 (m, 1H), 0.25 (m, 0.4H), 0.13 (m, 0.6H).	Method 1: 1.95 min, 651.6 $[M+H]^+$
15		(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-nicotinoylpyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d$_6$; rotamers observed, both reported) δ 8.82 (m, 0.5H), 8.76 (m, 0.5H), 8.67 (dd, 0.5H), 8.64 (dd, 0.5H), 8.06 (m, 0.5H), 8.00 (m, 0.5H), 7.88-7.76 (m, 4H), 7.52 (dd, 0.5H), 7.45 (dd, 0.5H), 7.27-7.09 (m, 2H), 6.97 (d, 0.5H), 6.86 (d, 0.5H), 6.83 (d, 0.5H), 6.79 (d, 0.5H), 6.01 (dd, 0.5H), 5.89 (dd, 0.5H), 5.23 (m, 0.5H), 5.12 (m, 0.5H), 4.14-3.53 (m, 8H), 3.26 (m, 1H), 2.95 (m, 1H), 2.84-2.69 (m, 1H), 2.59-2.21 (m, 5H), 2.18-1.77 (m, 2H), 1.51 (m, 1H), 1.43 (m, 1H), 1.35-1.17 (m, 2H), 1.01-0.78 (m, 1H), 0.71 (m, 1H), 0.19 (m, 1H).	Method 1: 2.00 min, 650.6 $[M+H]^+$
16		(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-((5-methylisoxazol-4-yl)sulfonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.90-7.75 (m, 5H), 7.24-7.13 (m, 2H), 6.86 (m, 1H), 6.78 (m, 1H), 5.93 (m, 1H), 4.98 (m, 1H), 4.11 (dd, 1H), 4.03 (m, 1H), 3.86 (m, 1H), 3.75 (m, 1H), 3.68-3.29 (m, 4H), 3.25 (m, 1H), 2.95 (m, 1H), 2.74 (m, 1H), 2.35 (d, 3H), 2.26-2.15 (m, 2H), 2.09-1.84 (m, 5H), 1.55-1.38 (m, 2H), 1.35-1.19 (m, 2H), 0.93 (m, 1H), 0.71 (m, 1H), 0.23 (m, 1H).	Method 1: 1.75 min, 690.6 $[M+H]^+$

17		(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 9.26 (s, 0.6H), 9.22 (s, 0.4H), 8.44 (s, 0.6H), 8.39 (s, 0.4H), 7.86-7.74 (m, 4H), 7.27-7.17 (m, 1H), 7.16-7.05 (m, 1H), 6.99-6.90 (m, 1H), 6.85-6.77 (m, 1H), 5.97 (m, 0.4H), 5.91 (m, 0.6H), 5.21 (m, 1H), 4.33 (dd, 0.6H), 4.25-3.69 (m, 6.4H), 3.62 (m, 1H), 3.24 (m, 1H), 2.95 (m, 1H), 2.75 (m, 1H), 2.60-2.22 (m, 5H), 2.14-1.96 (m, 1H), 1.88 (m, 1H), 1.58-1.36 (m, 2H), 1.34-1.05 (m, 2H), 1.02-0.63 (m, 2H), 0.19 (m, 1H).	Method 1: 2.02 min, 656.4 $[M+H]^+$
18		*N*-(2-(((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-2-((1*R*,2*S*)-2-(methylcarbamoyl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)ethyl)thiazole-2-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (t, 1H), 7.96 (d, 1H), 7.91-7.77 (m, 4H), 7.69 (d, 1H), 7.24-7.12 (m, 2H), 6.90 (d, 1H), 6.80 (d, 1H), 6.04 (dd, 1H), 4.22-4.07 (m, 3H), 4.00 (m, 1H), 3.94-3.74 (m, 3H), 3.60 (m, 1H), 3.27 (m, 1H), 2.95 (m, 1H), 2.74 (m, 1H), 2.35 (d, 3H), 2.04 (m, 1H), 1.90 (m, 1H), 1.53 (m, 1H), 1.46 (m, 1H), 1.36-1.19 (m, 2H), 0.95 (m, 1H), 0.76 (m, 1H), 0.22 (m, 1H).	Method 1: 2.25 min, 630.4 $[M+H]^+$
19		(1*S*,2*R*)-2-((*S*)-8-(((*S*)-1-(cyclopropanecarbonyl)pyrrolidin-3-yl)oxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	6	ND	Method 1: 2.14 min, 613.5 $[M+H]^+$
20		(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(5-methylisoxazole-3-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 7.87-7.75 (m, 4H), 7.26-7.17 (m, 1H), 7.14 (m, 1H), 6.94 (m, 0.4H), 6.89 (m, 0.6H), 6.85-6.77 (m, 1H), 6.55 (m, 0.4H), 6.51 (m, 0.6H), 5.93 (m, 0.4H), 5.88 (m, 0.6H), 5.18 (m, 1H), 4.20-3.70 (m, 7H), 3.61 (m, 1H), 3.25 (m, 1H), 3.16 (m, 3H), 2.94 (m, 1H), 2.75 (m, 1H), 2.60-2.23 (m, 5H), 2.17-1.81 (m,	Method 1: 2.24 & 2.35 min, 654.6 $[M+H]^+$ (rotamers)

	methylcyclohexane-1-carboxamide		2H), 1.60-1.36 (m, 2H), 1.33-1.17 (m, 2H), 1.02-0.77 (m, 1H), 0.69 (m, 1H), 0.17 (m, 1H).	
21		(1S,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(oxazol-5-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 7.85-7.75 (m, 4H), 7.52 (s, 1H), 7.23 (t, 1H), 7.14 (m, 1H), 7.07 (d, 1H), 6.84 (d, 1H), 5.98 (dd, 1H), 5.33 (d, 1H), 5.25 (d, 1H), 4.08 (dd, 1H), 3.83 (m, 1H), 3.73 (dd, 1H), 3.62 (m, 1H), 3.24 (m, 1H), 2.97 (m, 1H), 2.77 (m, 1H), 2.35 (d, 3H), 2.03 (m, 1H), 1.91 (m, 1H), 1.52 (m, 1H), 1.42-1.19 (m, 3H), 0.92 (m, 1H), 0.63 (m, 1H), 0.16 (m, 1H).	Method 1: 2.07 min, 557.4 $[M+H]^+$
22		(1S,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(2-methylthiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 8.14 (s, 0.6H), 8.12 (s, 0.4H), 7.90-7.74 (m, 4H), 7.26-7.16 (m, 1H), 7.11 (m, 1H), 6.99-6.87 (m, 1H), 6.86-6.77 (m, 1H), 5.99-5.86 (m, 1H), 5.27-5.09 (m, 1H), 4.29 (dd, 0.6H), 4.24-3.70 (m, 6.4H), 3.61 (m, 1H), 3.24 (m, 1H), 2.94 (m, 1H), 2.82-2.60 (m, 4H), 2.56-2.20 (m, 5H), 2.13-1.96 (m, 1H), 1.88 (m, 1H), 1.50 (m, 1H), 1.42 (m, 1H), 1.34-1.18 (m, 2H), 0.92 (m, 1H), 0.70 (m, 1H), 0.18 (m, 1H).	Method 1: 2.07 min, 670.4 $[M+H]^+$
23		(1S,2*R*)-2-((*S*)-8-(((*S*)-1-(2,4-dimethylthiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96-7.71 (m, 4H), 7.28-7.08 (m, 2H), 6.97-6.74 (m, 2H), 5.93 (m, 1H), 5.17 (m, 1H), 4.16-3.52 (m, 8H), 3.25 (m, 1H), 2.96 (m, 1H), 2.75 (m, 1H), 2.61 (m, 3H), 2.45-2.16 (m, 8H), 2.15-1.81 (m, 2H), 1.59-1.38 (m, 2H), 1.35-1.17 (m, 2H), 0.93 (m, 1H), 0.71 (m, 1H), 0.19 (m, 1H).	Method 1: 2.16 min, 684.2 $[M+H]^+$

24		(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(2-methylthiazole-4-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 8.07 (s, 0.4H), 8.04 (s, 0.6H), 7.97-7.74 (m, 4H), 7.27-7.17 (m, 1H), 7.14 (m, 1H), 6.93 (d, 0.4H), 6.89 (d, 0.6H), 6.82 (d, 0.4H), 6.79 (d, 0.6H), 5.94 (dd, 0.4H), 5.88 (dd, 0.6H), 5.19 (m, 0.6H), 5.14 (m, 0.4H), 4.32-3.69 (m, 7H), 3.61 (m, 1H), 3.24 (m, 1H), 3.02-2.86 (m, 1H), 2.83-2.58 (m, 4H), 2.55-2.09 (m, 5H), 2.02 (m, 1H), 1.88 (m, 1H), 1.60-1.47 (m, 1H), 1.46-1.36 (m, 1H), 1.33-1.18 (m, 2H), 0.91 (m, 1H), 0.69 (m, 1H), 0.16 (m, 1H).	Method 1: 2.20 min, 670.4 $[M+H]^+$
25		(*R*)-4-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,3-dimethyl-4-oxobutanamide	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 9.28-9.18 (m, 1H), 8.42 (s, 0.5H), 8.38 (s, 0.5H), 7.87-7.72 (m, 4H), 7.51 (m, 1H), 7.28-7.17 (m, 1H), 7.00-6.88 (m, 1H), 6.86-6.76 (m, 1H), 5.93 (m, 0.5H), 5.88 (m, 0.5H), 5.22 (m, 1H), 4.35-3.74 (m, 7H), 3.65 (m, 1H), 3.10-2.75 (m, 3H), 2.55-2.22 (m, 5H), 2.14 (m, 1H), 1.83 (m, 1H), 0.56 (d, 3H).	Method 1: 1.78 min, 616.3 $[M+H]^+$
26		(1*S*,2*R*)-*N*-methyl-2-((*S*)-1-((2-oxopyrrolidin-1-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 9.26 (s, 1H), 8.46 (s, 0.5H), 8.42 (s, 0.5H), 7.31-7.11 (m, 2H), 6.91 (d, 1H), 6.82-6.71 (m, 1H), 5.80 (m, 0.5H), 5.74 (m, 0.5H), 5.17 (m, 0.5H), 5.12 (m, 0.5H), 4.34-3.22 (m, 9H), 3.11-2.80 (m, 3H), 2.71 (m, 1H), 2.46-1.51 (m, 14H), 1.50-1.32 (m, 2H), 1.31-1.08 (m, 2H).	Method 1: 1.42 min, 594.3 $[M+H]^+$

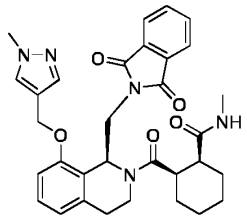
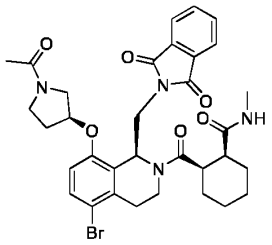
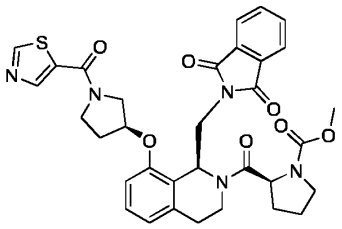
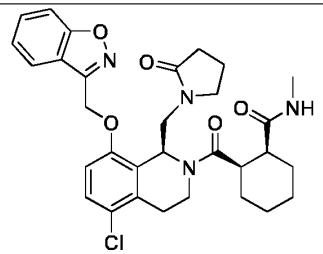
27		(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(pyrazin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (m, 1H), 8.71-8.67 (m, 2H), 7.86-7.78 (m, 4H), 7.25 (t, 1H), 7.15 (m, 1H), 7.08 (d, 1H), 6.87 (d, 1H), 6.14 (dd, 1H), 5.41 (d, 1H), 5.33 (d, 1H), 4.18 (dd, 1H), 3.90-3.75 (m, 2H), 3.67 (m, 1H), 3.40-3.20 (m, 1H), 3.00 (m, 1H), 2.82 (m, 1H), 2.36 (d, 3H), 2.05 (m, 1H), 1.93 (m, 1H), 1.53 (m, 1H), 1.44-1.15 (m, 3H), 0.92 (m, 1H), 0.60 (m, 1H), 0.17 (m, 1H).	Method 3: 4.16 min, 568.2 $[M+H]^+$
28		(*S*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylpiperidine-1-carboxamide	67	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 9.25 (s, 0.6H), 9.23 (s, 0.4H), 8.43 (s, 0.6H), 8.39 (s, 0.4H), 7.86-7.79 (m, 4H), 7.23 (m, 1H), 6.95 (m, 1H), 6.82 (m, 1H), 6.23 (m, 1H), 5.88 (m, 1H), 5.25-5.18 (m, 1H), 4.99-4.92 (m, 1H), 4.32 (dd, 0.6H), 4.25-3.92 (m, 3.4H), 3.92-3.77 (m, 4H), 3.65 (m, 1H), 3.42-3.23 (m, 1H), 3.04-2.91 (m, 2H), 2.79 (m, 1H), 2.47-2.24 (m, 4H), 1.47-1.37 (m, 2H), 1.24 (m, 1H), 1.07 (m, 1H), 0.91 (m, 1H), 0.31 (m, 1H).	Method 3: 3.91 min, 657.2 $[M+H]^+$
29		(1S,2R)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-propylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 9.25 (s, 0.6H), 9.23 (s, 0.4H), 8.41 (s, 0.6H), 8.39 (s, 0.4H), 7.86-7.75 (m, 4H), 7.21 (m, 1H), 7.03 (m, 1H), 6.93 (m, 1H), 6.80 (m, 1H), 5.97 (dd, 0.4H), 5.91 (dd, 0.6H), 5.26-5.15 (m, 1H), 4.31 (dd, 0.6H), 4.25-3.69 (m, 6.4H), 3.62 (m, 1H), 3.22 (m, 1H), 2.92 (m, 1H), 2.82-2.63 (m, 3H), 2.56-2.24 (m, 2H), 2.09-1.87 (m, 2H), 1.48-1.37 (m, 2H), 1.35-1.20 (m, 2H), 1.12-0.85 (m, 3H), 0.72 (m, 1H), 0.46 (t, 1.2H), 0.37 (t, 1.8H), 0.24 (m, 1H).	Method 3: 4.38 min, 684.2 $[M+H]^+$

30		(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-(2-methoxyethyl)cyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d$_6$; rotamers observed, both reported) δ 9.25 (s, 0.6H), 9.23 (s, 0.4H), 8.42 (s, 0.6H), 8.39 (s, 0.4H), 7.84-7.75 (m, 4H), 7.22 (m, 1H), 7.13 (m, 1H), 6.93 (m, 1H), 6.81 (m, 1H), 5.98 (dd, 0.4H), 5.92 (dd, 0.6H), 5.25-5.16 (m, 1H), 4.32 (dd, 0.6H), 4.24-3.70 (m, 6.4H), 3.62 (m, 1H), 3.22 (m, 1H), 3.01-2.87 (m, 8H), 2.76 (m, 1H), 2.59-2.24 (m, 2H), 2.05 (m, 1H), 1.92 (m, 1H), 1.50-1.38 (m, 2H), 1.35-1.20 (m, 2H), 0.93 (m, 1H), 0.72 (m, 1H), 0.24 (m, 1H).	Method 3: 4.13 min, 700.2 $[M+H]^+$
31		(1*S*,2*R*)-*N*-(2,2-difluoroethyl)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d$_6$; rotamers observed, both reported) δ 9.25 (s, 0.6H), 9.23 (s, 0.4H), 8.42 (s, 0.6H), 8.38 (s, 0.4H), 7.85-7.74 (m, 4H), 7.57 (m, 1H), 7.27-7.17 (m, 1H), 6.99-6.89 (m, 1H), 6.86-6.76 (m, 1H), 5.97 (m, 0.4H), 5.91 (m, 0.6H), 5.80-5.42 (m, 1H), 5.27-5.16 (m, 1H), 4.32 (dd, 0.6H), 4.27-3.71 (m, 6.4H), 3.63 (m, 1H), 3.45-2.84 (m, 4H), 2.76 (m, 1H), 2.58-2.24 (m, 2H), 2.19-2.06 (m, 1H), 1.92 (m, 1H), 1.63-1.39 (m, 2H), 1.38-1.20 (m, 2H), 1.04-0.87 (m, 1H), 0.75 (m, 1H), 0.26 (m, 1H).	Method 3: 4.42 min, 706.2 $[M+H]^+$
32		(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-(2,2,2-trifluoroethyl)cyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d$_6$; rotamers observed, both reported) δ 9.25 (s, 0.6H), 9.23 (s, 0.4H), 8.42 (s, 0.6H), 8.38 (s, 0.4H), 7.89-7.72 (m, 5H), 7.28-7.16 (m, 1H), 6.99-6.89 (m, 1H), 6.86-6.75 (m, 1H), 5.97 (m, 0.4H), 5.91 (m, 0.6H), 5.21 (m, 1H), 4.38-3.43 (m, 10H), 3.21 (m, 1H), 2.89 (m, 1H), 2.76 (m, 1H), 2.55-2.22 (m, 2H), 2.16 (m, 1H), 1.94 (m, 1H), 1.62-1.41 (m, 2H), 1.37-1.21 (m, 2H), 0.97 (m, 1H), 0.76 (m, 1H), 0.25 (m, 1H).	Method 3: 4.60 min, 724.2 $[M+H]^+$

33		(1*S*,2*R*)-*N*-(cyanomethyl)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d$_6$; rotamers observed, both reported) δ 9.26 (s, 0.6H), 9.23 (s, 0.4H), 8.42 (s, 0.6H), 8.39 (s, 0.4H), 7.98-7.88 (m, 1H), 7.85-7.76 (m, 4H), 7.22 (m, 1H), 6.94 (m, 1H), 6.82 (m, 1H), 5.96 (m, 0.4H), 5.90 (m, 0.6H), 5.27-5.14 (m, 1H), 4.32 (dd, 0.6H), 4.22-3.56 (m, 9.4H), 3.22-3.20 (m, 1H), 2.94 (m, 1H), 2.77 (m, 1H), 2.57-2.24 (m, 2H), 2.15 (m, 1H), 1.89 (m, 1H), 1.60-1.42 (m, 2H), 1.36-1.22 (m, 2H), 0.95 (m, 1H), 0.74 (m, 1H), 0.17 (m, 1H).	Method 3: 4.23 min, 681.2 $[M+H]^+$
34		(1*S*,2*R*)-*N*-(2,2-difluoro-3-hydroxypropyl)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d$_6$; rotamers observed, both reported) δ 9.25 (s, 0.6H), 9.23 (s, 0.4H), 8.42 (s, 0.6H), 8.38 (s, 0.4H), 7.85-7.76 (m, 4H), 7.56 (t, 1H), 7.21 (m, 1H), 6.94 (m, 1H), 6.80 (m, 1H), 6.02-5.88 (m, 1H), 5.22 (m, 1H), 5.04 (m, 1H), 4.32 (dd, 0.6H), 4.23-3.71 (m, 6.4H), 3.71-3.55 (m, 1H), 3.42-3.18 (m, 5H), 2.89 (m, 1H), 2.76 (m, 1H), 2.57-2.25 (m, 2H), 2.16 (m, 1H), 1.93 (m, 1H), 1.58-1.41 (m, 2H), 1.36-1.22 (m, 2H), 0.97 (m, 1H), 0.76 (m, 1H), 0.29 (m, 1H).	Method 3: 4.27 min, 736.2 $[M+H]^+$
35		(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-(2-hydroxyethyl)cyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d$_6$; rotamers observed, both reported) δ 9.25 (s, 0.6H), 9.22 (s, 0.4H), 8.44 (s, 0.6H), 8.39 (s, 0.4H), 7.84-7.75 (m, 4H), 7.22 (m, 1H), 7.08 (m, 1H), 6.94 (m, 1H), 6.81 (m, 1H), 5.98 (m, 0.4H), 5.92 (m, 0.6H), 5.21 (m, 1H), 4.39 (m, 1H), 4.33 (dd, 0.6H), 4.23-3.69 (m, 6.4H), 3.62 (m, 1H), 3.23 (m, 1H), 3.18-3.09 (m, 2H), 3.01-2.88 (m, 2H), 2.82 (m, 1H), 2.73 (m, 1H), 2.58-2.22 (m, 2H), 2.06 (m, 1H), 1.92 (m, 1H), 1.55-1.37 (m, 2H), 1.33-1.20 (m, 2H), 0.93 (m, 1H), 0.71 (m, 1H), 0.23 (m, 1H).	Method 3: 3.87 min, 686.2 $[M+H]^+$

36		1-((*S*)-1-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)-1-oxopropan-2-yl)-3-methylurea	67	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 9.26-9.22 (m, 1H), 8.42 (s, 0.5H), 8.38 (s, 0.5H), 7.88-7.75 (m, 4H), 7.30-7.17 (m, 1H), 6.99 (d, 0.5H), 6.95 (d, 0.5H), 6.88-6.77 (m, 1H), 6.00-5.82 (m, 2H), 5.62 (m, 1H), 5.25 (m, 1H), 4.46 (m, 1H), 4.35-4.22 (m, 1H), 4.21-3.56 (m, 7H), 2.96-2.75 (m, 2H), 2.57-2.24 (m, 5H), 0.77-0.68 (m, 3H).	Method 3: 3.52 min, 617.1 $[M+H]^+$
37		(1*S*,2*R*)-2-((*S*)-8-(((*S*)-1-acetylpyrrolidin-3-yl)oxy)-5-chloro-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 7.88-7.78 (m, 4H), 7.39 (d, 0.4H), 7.37 (d, 0.6H), 7.19 (m, 0.6H), 7.13 (m, 0.4H), 7.02-6.96 (m, 1H), 5.97-5.89 (m, 1H), 5.20-5.15 (m, 0.6H), 5.15-5.10 (m, 0.4H), 4.08 (m, 1H), 4.01-3.54 (m, 7H), 3.27 (m, 1H), 2.90-2.70 (m, 2H), 2.55-2.26 (m, 4.4H), 2.19 (m, 0.6H), 2.13-1.81 (m, 5H), 1.52 (m, 1H), 1.41 (m, 1H), 1.34-1.21 (m, 2H), 0.93 (m, 1H), 0.69 (m, 1H), 0.31-0.08 (m, 1H).	Method 3: 4.40 min, 621.3 $[M+H]^+$
40		5-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-methyl-5-oxopentanamide	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 9.26 (s, 0.5H), 9.24 (s, 0.5H), 8.41 (s, 0.5H), 8.39 (s, 0.5H), 7.89-7.75 (m, 4H), 7.49 (m, 1H), 7.28-7.18 (m, 1H), 7.00-6.91 (m, 1H), 6.87-6.78 (m, 1H), 5.93 (m, 0.5H), 5.88 (m, 0.5H), 5.23 (m, 1H), 4.35-4.16 (m, 1H), 4.13-3.97 (m, 2H), 3.96-3.73 (m, 4H), 3.65 (m, 1H), 2.92-2.77 (m, 2H), 2.58-2.23 (m, 5H), 2.10 (t, 2H), 1.81 (t, 2H), 1.46-1.17 (m, 2H).	Method 3: 3.52 min, 616.2 $[M+H]^+$
41		4-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-methyl-4-oxobutanamide	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 9.25 (s, 0.5H), 9.24 (s, 0.5H), 8.41 (s, 0.5H), 8.38 (s, 0.5H), 7.86-7.77 (m, 4H), 7.53 (m, 1H), 7.28-7.18 (m, 1H), 6.96 (d, 0.5H), 6.93 (d, 0.5H), 6.87-6.78 (m, 1H), 5.91 (dd, 0.5H), 5.85 (dd, 0.5H), 5.22 (m, 1H), 4.35-3.75 (m, 7H), 3.74-3.60 (m, 1H), 2.93-2.81 (m, 2H), 2.49-2.19 (m, 7H), 2.10-1.84 (m, 2H).	Method 3: 3.49 min, 602.2 $[M+H]^+$

42		(1S,2*R*)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-ethylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 9.25 (s, 0.6H), 9.23 (s, 0.4H), 8.42 (s, 0.6H), 8.39 (s, 0.4H), 7.84-7.76 (m, 4H), 7.26-7.16 (m, 1H), 7.13-7.02 (m, 1H), 6.95 (d, 0.4H), 6.92 (d, 0.6H), 6.86-6.85 (m, 1H), 5.97 (dd, 0.4H), 5.91 (dd, 0.6H), 5.21 (m, 1H), 4.31 (dd, 0.6H), 4.24-3.69 (m, 6.4H), 3.62 (m, 1H), 3.25-3.19 (m, 1H), 2.94 (m, 1H), 2.85-2.69 (m, 3H), 2.57-2.23 (m, 2H), 2.01 (m, 1H), 1.91 (m, 1H), 1.50-1.38 (m, 2H), 1.34-1.28 (m, 2H), 0.92 (m, 1H), 0.76-0.60 (m, 4H), 0.24 (m, 1H).	Method 3: 4.23 min, 670.3 $[M+H]^+$
43		(1S,2*R*)-2-((S)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-(3-hydroxypropyl)cyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 9.25 (s, 0.6H), 9.23 (s, 0.4H), 8.43 (s, 0.6H), 8.39 (s, 0.4H), 7.85-7.73 (m, 4H), 7.27-7.16 (m, 1H), 7.11 (m, 1H), 6.99-6.88 (m, 1H), 6.85-6.76 (m, 1H), 5.97 (m, 0.4H), 5.92 (m, 0.6H), 5.21 (m, 1H), 4.32 (m, 0.6H), 4.27-3.53 (m, 7.4H), 3.23 (m, 1H), 3.18-3.06 (m, 2H), 3.00-2.20 (m, 6H), 2.04 (m, 1H), 1.92 (m, 1H), 1.56-1.36 (m, 2H), 1.35-1.14 (m, 4H), 0.93 (m, 1H), 0.71 (m, 1H), 0.22 (m, 1H).	Method 3: 3.91 min, 700.3 $[M+H]^+$
47		(1S,2*R*)-*N*-methyl-2-((*S*)-1-(propionamidomethyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide	38	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, all reported) δ 9.26 (s, 0.3H), 9.24 (s, 0.3H), 9.23 (s, 0.2H), 9.18 (s, 0.2H), 8.46-8.37 (m, 0.8H), 8.28 (s, 0.2H), 7.99-7.90 (m, 0.6H), 7.80 (m, 0.2H), 7.73 (m, 0.2H), 7.42 (m, 0.4H), 7.28-7.09 (m, 1.6H), 7.00-6.69 (m, 2H), 5.76-5.64 (m, 0.5H), 5.30 (m, 0.2H), 5.26 (m, 0.3H), 5.19-5.09 (m, 0.5H), 5.02 (m, 0.3H), 4.97 (m, 0.2H), 4.42-2.96 (m, 9H), 2.96-1.90 (m, 11H), 1.90-0.75 (m, 10H).	Method 3: 3.23 min, 582.3 $[M+H]^+$

49		(1*S*,2*R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-((1-methyl-1*H*-pyrazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	46	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (m, 1H), 7.88-7.75 (m, 4H), 7.64 (m, 1H), 7.20 (t, 1H), 7.14 (m, 1H), 7.02 (d, 1H), 6.80 (d, 1H), 6.03 (dd, 1H), 5.14 (d, 1H), 5.06 (d, 1H), 4.12 (dd, 1H), 3.84 (m, 4H), 3.72 (dd, 1H), 3.63 (m, 1H), 3.24 (m, 1H), 2.96 (m, 1H), 2.78 (m, 1H), 2.35 (d, 3H), 2.03 (m, 1H), 1.93 (m, 1H), 1.53 (m, 1H), 1.44-1.15 (m, 3H), 0.92 (m, 1H), 0.61 (m, 1H), 0.18 (m, 1H).	Method 3: 4.23 min, 570.3 $[M+H]^+$
50		(1*S*,2*R*)-2-((*S*)-8-(((*S*)-1-acetylpyrrolidin-3-yl)oxy)-5-bromo-1-((1,3-dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	6	^{1}H NMR (400 MHz, DMSO-d_6; rotamers observed, both reported) δ 7.89-7.76 (m, 4H), 7.58-7.50 (m, 1H), 7.19 (m, 0.6H), 7.13 (m, 0.4H), 6.98-6.90 (m, 1H), 5.99-5.88 (m, 1H), 5.18 (m, 0.6H), 5.13 (m, 0.4H), 4.12-4.03 (m, 1H), 4.02-3.53 (m, 7H), 3.49-3.19 (m, 1H), 2.88-2.64 (m, 2H), 2.58-2.14 (m, 5H), 2.13-1.79 (m, 5H), 1.52 (m, 1H), 1.46-1.35 (m, 1H), 1.35-1.18 (m, 2H), 0.93 (m, 1H), 0.69 (m, 1H), 0.20 (m, 1H).	Method 3: 4.45 min, 665.3 $[M+H]^+$
51		methyl (*S*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-8-(((*S*)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)pyrrolidine-1-carboxylate	67	^{1}H NMR (400 MHz, $CDCl_3$; rotamers observed, all reported) δ 8.94-8.84 (m, 1H), 8.43 (s, 0.1H), 8.41 (s, 0.4H), 8.38 (s, 0.2H), 8.35 (s, 0.3H), 7.90-7.59 (m, 4H), 7.28-7.11 (m, 1H), 6.87-6.62 (m, 2H), 6.19-5.36 (m, 1H), 5.23-5.01 (m, 1H), 4.65-3.71 (m, 9H), 3.51 (s, 1.8H), 3.46-3.35 (m, 1.2H), 3.34-2.49 (m, 5H), 2.47-0.68 (m, 5H).	Method 3: 4.00 min, 644.4 $[M+H]^+$
52		(1*S*,2*R*)-2-((*S*)-8-(benzo[*d*]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (m, 1H), 7.83 (m, 1H), 7.72 (m, 1H), 7.47 (m, 1H), 7.43 (d, 1H), 7.26 (m, 1H), 7.20 (d, 1H), 5.85 (dd, 1H), 5.71 (d, 1H), 5.62 (d, 1H), 3.94 (dd, 1H), 3.86 (dd, 1H), 3.68-3.51 (m, 1H), 3.38-3.29 (m, 1H), 3.25 (m, 1H), 2.98 (dd, 1H), 2.89-2.70 (m, 2H), 2.59 (m, 1H), 2.42 (d, 3H), 2.24-2.04 (m, 3H), 1.95 (m, 1H), 1.77-1.59 (m, 5H), 1.51-1.31 (m, 2H), 1.29-1.07 (m, 2H).	Method 3: 4.33 min, 579.1 $[M+H]^+$

53		(1S,2*R*)-2-((*S*)-8-(benzo[*d*]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-ethylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.04 (m, 1H), 7.83 (m, 1H), 7.72 (m, 1H), 7.47 (m, 1H), 7.42 (d, 1H), 7.26 (t, 1H), 7.19 (d, 1H), 5.87 (dd, 1H), 5.71 (d, 1H), 5.62 (d, 1H), 3.98-3.80 (m, 2H), 3.60 (m, 1H), 3.36-3.22 (m, 2H), 3.02-2.72 (m, 5H), 2.60 (m, 1H), 2.24-2.04 (m, 3H), 1.96 (m, 1H), 1.75-1.60 (m, 5H), 1.51-1.33 (m, 2H), 1.32-1.10 (m, 2H), 0.79 (t, 3H).	Method 3: 4.56 min, 593.1 $[M+H]^+$
54 (Ref. Cpd)		(1S,2*R*)-2-((*S*)-8-(benzo[*d*]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.06 (m, 1H), 7.83 (m, 1H), 7.72 (m, 1H), 7.48 (m, 1H), 7.41 (d, 1H), 7.18 (d, 1H), 6.85 (bs, 1H), 6.55 (bs, 1H), 5.87 (dd, 1H), 5.70 (d, 1H), 5.61 (d, 1H), 3.94 (m, 1H), 3.86 (dd, 1H), 3.59 (m, 1H), 3.37 (m, 1H), 3.24 (m, 1H), 2.97 (dd, 1H), 2.90-2.75 (m, 2H), 2.58 (m, 1H), 2.27-2.04 (m, 3H), 1.94 (m, 1H), 1.75-1.59 (m, 5H), 1.52-1.33 (m, 2H), 1.28-1.11 (m, 2H).	Method 3: 4.18 min, 565.1 $[M+H]^+$
55		(1S,2*R*)-2-((*S*)-5-bromo-8-((5-isopropyl-1,2,4-oxadiazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.55 (d, 1H), 7.26 (m, 1H), 7.06 (d, 1H), 5.86 (dd, 1H), 5.36 (d, 1H), 5.29 (d, 1H), 4.00-3.83 (m, 2H), 3.65-3.53 (m, 2H), 3.39-3.33 (m, 2H), 3.15 (m, 1H), 3.07 (dd, 1H), 2.83-2.65 (m, 2H), 2.42 (d, 3H), 2.18 (m, 3H), 2.02 (m, 1H), 1.94-1.77 (m, 2H), 1.77-1.65 (m, 3H), 1.52-1.37 (m, 2H), 1.36-1.31 (m, 6H), 1.30-1.12 (m, 2H).	Method 3: 4.27 min, 616.2 $[M+H]^+$

56		(1S,2R)-2-((S)-5-bromo-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77-7.49 (m, 5H), 7.43 (m, 1H), 7.21-7.13 (m, 2H), 5.90 (dd, 1H), 5.40-5.30 (m, 2H), 4.50 (d, 1H), 4.22 (s, 3H), 4.14 (dd, 1H), 4.03-3.92 (m, 2H), 3.68 (m, 1H), 3.43 (dd, 1H), 3.27 (m, 1H), 2.86-2.66 (m, 2H), 2.38 (d, 3H), 2.03 (m, 1H), 1.90 (m, 1H), 1.53 (m, 1H), 1.39-1.12 (m, 3H), 0.89 (m, 1H), 0.53 (m, 1H), 0.15 (m, 1H).	Method 3: 4.28 min, 687.2 $[M+H]^+$
57		(1S,2R)-2-((S)-5-chloro-8-((5-isopropyl-1,2,4-oxadiazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 (d, 1H), 7.26 (m, 1H), 7.11 (d, 1H), 5.86 (dd, 1H), 5.36 (d, 1H), 5.29 (d, 1H), 3.96 (dd, 1H), 3.88 (dd, 1H), 3.65-3.52 (m, 2H), 3.41-3.25 (m, 2H), 3.21-3.11 (m, 1H), 3.08 (dd, 1H), 2.87-2.69 (m, 2H), 2.41 (d, 3H), 2.26-2.10 (m, 3H), 2.02 (m, 1H), 1.94-1.77 (m, 2H), 1.77-1.66 (m, 3H), 1.52-1.38 (m, 2H), 1.37-1.31 (m, 6H), 1.31-1.12 (m, 2H).	Method 3: 4.23 min, 572.4 $[M+H]^+$
58		(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (t, 1H), 7.39 (d, 1H), 7.26 (m, 1H), 7.16 (d, 1H), 5.75 (dd, 1H), 5.29 (s, 2H), 4.18 (s, 3H), 3.93 (dd, 1H), 3.82 (dd, 1H), 3.56 (m, 1H), 3.43-3.26 (m, 2H), 2.95 (dd, 1H), 2.85 (m, 1H), 2.81-2.68 (m, 2H), 2.41 (d, 3H), 2.23-2.10 (m, 3H), 1.99 (m, 1H), 1.90-1.64 (m, 5H), 1.50-1.36 (m, 2H), 1.29-1.12 (m, 2H).	Method 3: 3.87 min, 615.3 $[M+Na]^+$

59		(2*R*,3*R*)-4-((*S*)-5-chloro-8-((5-isopropyl-1,2,4-oxadiazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,2,3-trimethyl-4-oxobutanamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (m, 1H), 7.39 (d, 1H), 7.10 (d, 1H), 5.82 (dd, 1H), 5.36 (d, 1H), 5.29 (d, 1H), 4.03 (dd, 1H), 3.90 (dd, 1H), 3.66-3.52 (m, 2H), 3.38-3.25 (m, 1H), 3.18-3.06 (m, 2H), 2.97-2.69 (m, 3H), 2.43 (m, 1H), 2.36 (d, 3H), 2.16 (m, 1H), 1.98 (m, 1H), 1.92-1.69 (m, 2H), 1.36-1.30 (m, 6H), 1.00 (d, 3H), 0.93 (d, 3H).	Method 4: 3.13 min, 546.4 $[M+H]^+$
60		(1*S*,2*R*)-2-((*S*)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyridin-3-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, 1H), 8.60 (dd, 1H), 7.97 (m, 1H), 7.49 (m, 1H), 7.40 (d, 1H), 7.27 (m, 1H), 7.09 (d, 1H), 5.84 (dd, 1H), 5.22 (d, 1H), 5.14 (d, 1H), 3.95 (dd, 1H), 3.87 (dd, 1H), 3.59 (m, 1H), 3.42-3.26 (m, 2H), 3.00 (dd, 1H), 2.88-2.69 (m, 3H), 2.41 (d, 3H), 2.26-2.08 (m, 3H), 1.99 (m, 1H), 1.87-1.62 (m, 5H), 1.52-1.32 (m, 2H), 1.29-1.10 (m, 2H).	Method 4: 2.69 min, 539.4 $[M+H]^+$
61		(1*S*,2*R*)-2-((*S*)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyridazin-3-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (m, 1H), 7.94 (m, 1H), 7.84 (dd, 1H), 7.39 (d, 1H), 7.26 (m, 1H), 7.12 (d, 1H), 5.89 (m, 1H), 5.47 (d, 1H), 5.41 (d, 1H), 3.96 (dd, 1H), 3.86 (dd, 1H), 3.61 (m, 1H), 3.43 (m, 1H), 3.39-3.26 (m, 1H), 3.10 (dd, 1H), 2.94 (dd, 1H), 2.87-2.71 (m, 2H), 2.41 (d, 3H), 2.23-2.10 (m, 3H), 2.00 (m, 1H), 1.90-1.65 (m, 5H), 1.52-1.36 (m, 2H), 1.31-1.12 (m, 2H).	Method 3: 3.34 min, 562.2 $[M+Na]^+$
62		(1*S*,2*R*)-2-((*S*)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyrazin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (d, 1H), 8.72 (dd, 1H), 8.68 (d, 1H), 7.39 (d, 1H), 7.27 (m, 1H), 7.10 (d, 1H), 5.90 (dd, 1H), 5.33 (d, 1H), 5.28 (d, 1H), 3.96 (dd, 1H), 3.88 (dd, 1H), 3.61 (m, 1H), 3.45 (m, 1H), 3.39-3.26 (m, 1H), 3.11 (dd, 1H), 2.96 (m, 1H), 2.88-2.70 (m, 2H), 2.41 (d, 3H), 2.23-2.11 (m, 3H), 2.01 (m, 1H), 1.92-1.66 (m, 5H), 1.53-1.37 (m, 2H), 1.32-1.12 (m, 2H).	Method 3: 3.57 min, 562.2 $[M+Na]^+$

63		(1*S*,2*R*)-2-((*S*)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.62 (m, 1H), 7.91 (m, 1H), 7.63 (m, 1H), 7.42-7.33 (m, 2H), 7.26 (m, 1H), 7.05 (d, 1H), 5.92 (dd, 1H), 5.27-5.16 (m, 2H), 3.96 (dd, 1H), 3.88 (dd, 1H), 3.61 (m, 1H), 3.49 (m, 1H), 3.38-3.29 (m, 1H), 3.13 (dd, 1H), 2.99 (m, 1H), 2.87-2.70 (m, 2H), 2.41 (d, 3H), 2.28-2.10 (m, 3H), 2.01 (m, 1H), 1.91-1.66 (m, 5H), 1.53-1.37 (m, 2H), 1.22 (m, 2H).	Method 3: 3.46 min, 561.3 $[M+Na]^+$
64		(1*S*,2*R*)-2-((*S*)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyrimidin-5-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.23 (s, 1H), 9.02 (s, 2H), 7.41 (d, 1H), 7.27 (m, 1H), 7.10 (d, 1H), 5.84 (dd, 1H), 5.26 (d, 1H), 5.17 (d, 1H), 3.96 (dd, 1H), 3.86 (dd, 1H), 3.60 (m, 1H), 3.41-3.25 (m, 2H), 3.01 (dd, 1H), 2.89-2.70 (m, 3H), 2.41 (d, 3H), 2.24-2.10 (m, 3H), 1.99 (m, 1H), 1.87-1.65 (m, 5H), 1.51-1.36 (m, 2H), 1.28-1.13 (m, 2H).	Method 3: 3.40 min,562.2 $[M+Na]^+$
65		2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclopentane-1-carboxamide (isomer 1)	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.58 (t, 1H), 7.39 (d, 1H), 7.27 (m, 1H), 7.16 (d, 1H), 5.70 (dd, 1H), 5.29 (s, 2H), 4.17 (s, 3H), 3.96 (dd, 1H), 3.81 (dd, 1H), 3.57 (m, 1H), 3.44-3.24 (m, 2H), 2.92 (dd, 1H), 2.88-2.61 (m, 4H), 2.38 (d, 3H), 2.14 (m, 1H), 2.02-1.49 (m, 9H).	Method 3: 3.67 min, 601.3 $[M+Na]^+$
66		(1*S*,2*R*)-2-((*S*)-5-chloro-8-(2-(1-methyl-1*H*-1,2,3-triazol-4-yl)ethoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.91 (s, 1H), 7.33 (d, 1H), 7.28 (m, 1H), 6.96 (d, 1H), 5.79 (dd, 1H), 4.38 (m, 1H), 4.22 (m, 1H), 4.00 (s, 3H), 3.93 (dd, 1H), 3.77 (dd, 1H), 3.58 (m, 1H), 3.47 (m, 1H), 3.41-3.24 (m, 1H), 3.16 (t, 2H), 3.08 (m, 1H), 2.90 (dd, 1H), 2.84-2.71 (m, 2H), 2.42 (d, 3H), 2.24-2.12 (m, 3H), 2.02 (m, 1H), 1.94-1.64 (m, 5H), 1.52-1.37 (m, 2H), 1.32-1.12 (m, 2H).	Method 3: 3.50 min, 579.3 $[M+Na]^+$

68		(1S,2*R*)-2-((*S*)-5-chloro-8-((3-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.57 (d, 1H), 8.47 (s, 1H), 8.28 (d, 1H), 7.39 (d, 1H), 7.26 (m, 1H), 7.14 (d, 1H), 5.84 (dd, 1H), 5.34 (d, 1H), 5.26 (d, 1H), 3.95 (dd, 1H), 3.90-3.81 (m, 4H), 3.58 (m, 1H), 3.41-3.24 (m, 2H), 3.02 (dd, 1H), 2.86-2.69 (m, 3H), 2.41 (d, 3H), 2.21-2.07 (m, 3H), 2.01-1.91 (m, 1H), 1.77-1.61 (m, 5H), 1.50-1.35 (m, 2H), 1.27-1.11 (m, 2H).	Method 3: 3.34 min, 593.4 $[M+H]^+$
69		(1S,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.58 (t, 1H), 7.39 (d, 1H), 7.23 (bm, 1H), 7.16 (d, 1H), 5.72 (dd, 1H), 5.29 (s, 2H), 4.17 (s, 3H), 3.93 (m, 1H), 3.82 (dd, 1H), 3.54 (m, 1H), 3.42-3.26 (m, 1H), 3.01 (m, 1H), 2.95 (dd, 1H), 2.89-2.76 (m, 3H), 2.40 (d, 3H), 2.31 (m, 1H), 2.15 (m, 1H), 1.98 (m, 1H), 1.90-1.68 (m, 2H), 1.67-1.27 (m, 6H), 1.17-0.98 (m, 4H).	Method 4: 3.16 min, 607.4 $[M+H]^+$
70		(1S,2*R*)-2-((*S*)-5-chloro-8-(isoxazolo[5,4-*b*]pyridin-3-ylmethoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.74 (dd, 1H), 8.57 (dd, 1H), 7.59 (dd, 1H), 7.43 (d, 1H), 7.27 (m, 1H), 7.18 (d, 1H), 5.87 (dd, 1H), 5.71 (d, 1H), 5.63 (d, 1H), 3.95 (dd, 1H), 3.86 (dd, 1H), 3.60 (m, 1H), 3.42-3.22 (m, 2H), 3.00 (dd, 1H), 2.88-2.63 (m, 3H), 2.42 (d, 3H), 2.27-2.04 (m, 3H), 1.96 (m, 1H), 1.81-1.57 (m, 5H), 1.53-1.32 (m, 2H), 1.31-1.08 (m, 2H).	Method 4: 3.11 min, 580.4 $[M+H]^+$

71		(1S,2R)-2-((S)-5-chloro-8-((3-methylisoxazolo[5,4-*b*]pyridin-6-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, 1H), 7.71 (d, 1H), 7.37 (d, 1H), 7.27 (m, 1H), 7.05 (d, 1H), 5.98 (dd, 1H), 5.42 (d, 1H), 5.36 (d, 1H), 4.03-3.85 (m, 2H), 3.70-3.51 (m, 2H), 3.40-3.29 (m, 1H), 3.22 (dd, 1H), 3.13 (m, 1H), 2.89-2.72 (m, 2H), 2.59 (s, 3H), 2.41 (d, 3H), 2.25-2.13 (m, 3H), 2.03 (m, 1H), 1.93-1.67 (m, 5H), 1.54-1.38 (m, 2H), 1.33-1.12 (m, 2H).	Method 4: 3.19 min, 594.4 $[M+H]^+$
72		(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (m, 1H), 7.93 (m, 1H), 7.73 (m, 1H), 7.39 (d, 1H), 7.27 (m, 1H), 7.11 (d, 1H), 5.90 (dd, 1H), 5.35 (d, 1H), 5.27 (d, 1H), 4.33 (s, 3H), 4.00-3.83 (m, 2H), 3.61 (m, 1H), 3.41 (m, 1H), 3.37-3.26 (m, 1H), 3.07 (dd, 1H), 2.87 (m, 1H), 2.83-2.70 (m, 2H), 2.41 (d, 3H), 2.25-2.08 (m, 3H), 1.98 (m, 1H), 1.82-1.62 (m, 5H), 1.53-1.35 (m, 2H), 1.29-1.11 (m, 2H).	Method 4: 3.08 min, 593.4 $[M+H]^+$
73		(1S,2R)-2-((S)-8-([1,2,4]triazolo[4,3-a]pyridin-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (m, 1H), 7.87 (m, 1H), 7.48 (m, 1H), 7.44 (d, 1H), 7.30-7.22 (m, 2H), 7.12 (m, 1H), 5.81-5.66 (m, 3H), 3.94 (dd, 1H), 3.80 (dd, 1H), 3.54 (m, 1H), 3.39-3.25 (m, 1H), 3.07 (m, 1H), 2.85-2.68 (m, 3H), 2.41 (d, 3H), 2.34 (m, 1H), 2.21-2.02 (m, 3H), 1.92 (m, 1H), 1.75-1.52 (m, 5H), 1.48-1.32 (m, 2H), 1.26-1.10 (m, 2H).	Method 4: 2.79 min, 579.4 $[M+H]^+$

74		(1S,2R)-2-((S)-5-chloro-8-((1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.36 (d, 1H), 7.25 (m, 1H), 7.13 (d, 1H), 5.78 (dd, 1H), 5.22 (d, 1H), 5.19 (d, 1H), 4.07 (s, 3H), 3.94 (dd, 1H), 3.81 (dd, 1H), 3.56 (m, 1H), 3.47-3.26 (m, 2H), 3.04-2.92 (m, 2H), 2.81-2.69 (m, 2H), 2.41 (d, 3H), 2.23-2.10 (m, 3H), 2.00 (m, 1H), 1.91-1.65 (m, 5H), 1.51-1.36 (m, 2H), 1.30-1.12 (m, 2H).	Method 3: 3.41 min, 565.1 $[M+Na]^+$
75		(1S,2R)-2-((S)-5-chloro-8-(imidazo[1,2-a]pyrimidin-2-ylmethoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (dd, 1H), 8.55 (dd, 1H), 8.04 (s, 1H), 7.36 (d, 1H), 7.26 (m, 1H), 7.14 (d, 1H), 7.07 (dd, 1H), 5.89 (dd, 1H), 5.31 (s, 2H), 3.95 (dd, 1H), 3.85 (dd, 1H), 3.59 (m, 1H), 3.48 (m, 1H), 3.39-3.25 (m, 1H), 3.19 (dd, 1H), 3.05 (m, 1H), 2.85-2.69 (m, 2H), 2.41 (d, 3H), 2.22-2.10 (m, 3H), 2.00 (m, 1H), 1.85-1.66 (m, 5H), 1.52-1.36 (m, 2H), 1.32-1.12 (m, 2H).	Method 3: 3.07 min, 601.2 $[M+Na]^+$
76		(1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77-7.48 (m, 4H), 7.48-7.40 (m, 2H), 7.24-7.15 (m, 2H), 5.90 (dd, 1H), 5.40-5.31 (m, 2H), 4.50 (d, 1H), 4.21 (s, 3H), 4.14 (dd, 1H), 4.04-3.93 (m, 2H), 3.68 (m, 1H), 3.44 (dd, 1H), 3.39-3.23 (m, 1H), 2.83 (dd, 1H), 2.75 (m, 1H), 2.38 (d, 3H), 2.03 (m, 1H), 1.91 (m, 1H), 1.53 (m, 1H), 1.38-1.12 (m, 3H), 0.89 (m, 1H), 0.52 (m, 1H), 0.14 (m, 1H).	Method 3: 4.35 min, 663.3 $[M+Na]^+$

77		(1*S*,2*R*)-2-((*S*)-8-([1,2,4]triazolo[4,3-a]pyridin-3-ylmethoxy)-5-chloro-1-((1-oxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (m, 1H), 7.93 (m, 1H), 7.59-7.48 (m, 3H), 7.46 (d, 1H), 7.41 (t, 1H), 7.37 (d, 1H), 7.32 (d, 1H), 7.21-7.10 (m, 2H), 5.95-5.75 (m, 3H), 4.22 (d, 1H), 4.12 (dd, 1H), 3.98 (dd, 1H), 3.67 (m, 1H), 3.52 (d, 1H), 3.40-3.20 (m, 2H), 2.86 (dd, 1H), 2.75 (m, 1H), 2.38 (d, 3H), 2.03 (m, 1H), 1.89 (m, 1H), 1.52 (m, 1H), 1.36 (m, 1H), 1.30-1.10 (m, 2H), 0.89 (m, 1H), 0.54 (m, 1H), 0.14 (m, 1H).	Method 3: 3.72 min, 649.3 $[M+Na]^+$
78		(1*S*,2*R*)-2-((*S*)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-(2,2-difluoro-3-hydroxypropyl)cyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, 1H), 7.82 (m, 2H), 7.72 (m, 1H), 7.46 (t, 1H), 7.41 (d, 1H), 7.18 (d, 1H), 5.86 (dd, 1H), 5.71 (d, 1H), 5.61 (d, 1H), 5.12 (t, 1H), 3.95-3.78 (m, 2H), 3.67-3.17 (m, 7H), 2.97 (dd, 1H), 2.88-2.70 (m, 2H), 2.59 (m, 1H), 2.35 (m, 1H), 2.17-2.02 (m, 2H), 1.96 (m, 1H), 1.84 (m, 1H), 1.75-1.58 (m, 4H), 1.55-1.13 (m, 4H).	Method 3: 4.64 min, 681.3 $[M+Na]^+$
79		(*S*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylpiperidine-1-carboxamide	67	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (t, 1H), 7.40 (d, 1H), 7.16 (d, 1H), 6.35 (m, 1H), 5.71 (dd, 1H), 5.35-5.22 (m, 2H), 5.04 (m, 1H), 4.17 (s, 3H), 3.93 (dd, 1H), 3.84 (dd, 1H), 3.58 (m, 1H), 3.48 (m, 1H), 3.42-3.21 (m, 2H), 2.97 (dd, 1H), 2.87 (m, 1H), 2.82-2.65 (m, 2H), 2.47 (d, 3H), 2.18 (m, 1H), 2.00 (m, 1H), 1.92-1.72 (m, 2H), 1.72-1.45 (m, 4H), 1.40-1.13 (m, 2H).	Method 3: 3.71 min, 616.1 $[M+Na]^+$

80		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((3-methyl-3*H*-imidazo[4,5-*b*]pyridin-5-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.45 (s, 1H), 8.17 (d, 1H), 7.54 (d, 1H), 7.36 (d, 1H), 7.26 (m, 1H), 7.10 (d, 1H), 5.93 (dd, 1H), 5.36 (d, 1H), 5.30 (d, 1H), 4.00-3.78 (m, 5H), 3.60 (m, 1H), 3.45 (m, 1H), 3.40-3.20 (m, 1H), 3.18 (dd, 1H), 2.90 (m, 1H), 2.86-2.70 (m, 2H), 2.41 (d, 3H), 2.24-2.08 (m, 3H), 1.99 (m, 1H), 1.86-1.63 (m, 5H), 1.54-1.34 (m, 2H), 1.31-1.11 (m, 2H).	Method 3: 3.38 min, 615.4 $[M+Na]^+$
81		(1S,2*R*)-2-((*S*)-5-chloro-8-((1-methyl-1*H*-indazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.91 (d, 1H), 7.67 (d, 1H), 7.44 (m, 1H), 7.39 (d, 1H), 7.29-7.15 (m, 3H), 5.76 (dd, 1H), 5.49 (d, 1H), 5.43 (d, 1H), 4.07 (s, 3H), 3.92 (dd, 1H), 3.80 (dd, 1H), 3.55 (m, 1H), 3.40-3.23 (m, 1H), 3.14 (m, 1H), 2.93 (dd, 1H), 2.86-2.66 (m, 2H), 2.45-2.37 (m, 4H), 2.22-2.02 (m, 3H), 1.92 (m, 1H), 1.78-1.55 (m, 5H), 1.49-1.29 (m, 2H), 1.26-1.08 (m, 2H).	Method 3: 4.40 min, 614.3 $[M+Na]^+$
82		3-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methyltetrahydrofuran-2-carboxamide (isomer 1)	98	^{1}H NMR (400 MHz, DMSO-d$_6$; rotamers observed, both reported) δ 7.62 (t, 0.3H), 7.56 (t, 0.7H), 7.44 (m, 1H), 7.37 (m, 1H), 7.14 (m, 1H), 5.73 (dd, 0.7H), 5.39-5.29 (m, 0.6H), 5.27 (s, 1.4H), 5.15 (m, 0.3H), 4.44 (m, 0.3H), 4.26 (d, 0.7H), 4.21-4.11 (m, 3.6H), 4.03 (m, 0.7H), 3.92 (m, 0.7H), 3.82-3.58 (m, 3.4H), 3.47-3.17 (m, 1.6H), 3.13-2.65 (m, 4H), 2.61-2.43 (m, 3.1H), 2.26 (d, 0.9H), 2.21-1.66 (m, 5H).	Method 3: 3.57 min, 603.3 $[M+Na]^+$

83		(1*S*,2*R*)-2-((*S*)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.03 (m, 1H), 7.83 (m, 1H), 7.72 (m, 1H), 7.47 (m, 1H), 7.43 (d, 1H), 7.24 (bm, 1H), 7.19 (d, 1H), 5.83 (dd, 1H), 5.71 (d, 1H), 5.62 (d, 1H), 3.94 (m, 1H), 3.85 (dd, 1H), 3.57 (m, 1H), 3.25 (m, 1H), 3.06-2.94 (m, 2H), 2.88-2.77 (m, 2H), 2.60 (m, 1H), 2.40 (d, 3H), 2.34 (m, 1H), 2.10 (m, 1H), 1.94 (m, 1H), 1.76-1.56 (m, 3H), 1.56-1.27 (m, 5H), 1.17-0.98 (m, 4H).	Method 3: 4.64 min, 593.3 $[M+H]^+$
85		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclopentane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.57 (t, 1H), 7.39 (d, 1H), 7.16 (d, 1H), 7.03 (m, 1H), 5.66 (dd, 1H), 5.38-5.22 (m, 2H), 4.17 (s, 3H), 3.96 (m, 1H), 3.83 (dd, 1H), 3.51 (m, 1H), 3.44-3.26 (m, 1H), 3.03 (d, 1H), 2.93 (m, 1H), 2.88-2.70 (m, 3H), 2.39 (d, 3H), 2.29 (m, 1H), 2.16 (m, 1H), 2.05-1.89 (m, 2H), 1.88-1.39 (m, 6H), 1.05 (s, 3H).	Method 3: 3.06 min, 593.4 $[M+H]^+$
86		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((4,5-dimethyl-4*H*-1,2,4-triazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.39 (d, 1H), 7.27 (m, 1H), 7.20 (d, 1H), 5.79 (dd, 1H), 5.40-5.25 (m, 2H), 3.95 (dd, 1H), 3.84 (dd, 1H), 3.70-3.50 (m, 4H), 3.50-3.20 (m, 2H), 2.92 (m, 2H), 2.78 (m, 2H), 2.42 (d, 3H), 2.36 (s, 3H), 2.27-2.10 (m, 3H), 2.01 (m, 1H), 1.94-1.62 (m, 5H), 1.54-1.34 (m, 2H), 1.32-1.09 (m, 2H).	Method 3: 2.94 min, 579.3 $[M+Na]^+$

87		(*S*)-3-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylmorpholine-4-carboxamide	67	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (t, 1H), 7.41 (d, 1H), 7.18 (d, 1H), 6.42 (m, 1H), 5.73 (dd, 1H), 5.30 (s, 2H), 4.82 (d, 1H), 4.17 (s, 3H), 3.91 (dd, 1H), 3.87-3.75 (m, 3H), 3.66-3.49 (m, 3H), 3.40-3.24 (m, 3H), 3.00 (dd, 1H), 2.92-2.77 (m, 2H), 2.70 (m, 1H), 2.52-2.45 (m, 3H), 2.19 (m, 1H), 2.05 (m, 1H), 1.77 (m, 2H).	Method 3: 3.40 min, 618.4 $[M+Na]^+$
89		(*S*)-2-((*S*)-5-chloro-8-((1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylpyrrolidine-1-carboxamide	88	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.38 (d, 1H), 7.15 (d, 1H), 5.99 (m, 1H), 5.70 (m, 1H), 5.29-5.16 (m, 2H), 4.70 (m, 1H), 4.09-3.96 (m, 4H), 3.86 (dd, 1H), 3.65-3.39 (m, 2H), 3.38-3.14 (m, 2H), 3.06-2.91 (m, 2H), 2.83-2.75 (m, 1H), 2.58-2.42 (m, 4H), 2.18 (m, 1H), 2.06-1.61 (m, 7H).	Method 6: 1.22 min, 530.2 $[M+H]^+$
90		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((1,5-dimethyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (bm, 1H), 7.23 (d, 1H), 6.91 (d, 1H), 5.96 (m, 1H), 5.14 (d, 1H), 5.07 (d, 1H), 4.05-3.55 (m, 7H), 3.22-2.72 (m, 5H), 2.69 (d, 3H), 2.49 (m, 1H), 2.35-2.09 (m, 5H), 1.97-1.35 (m, 8H), 1.28-1.08 (m, 4H).	Method 7: 1.95 min, 571.4 $[M+H]^+$

91		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-6.76 (m, 2H), 5.97 (m, 1H), 5.31-4.92 (m, 2H), 4.26-3.39 (m, 7H), 3.21-2.37 (m, 9H), 2.35-2.07 (m, 2H), 1.98-0.52 (m, 12H).	Method 7: 2.33 min, 625.4 $[M+H]^+$
92		(*S*)-2-((*S*)-5-chloro-8-((1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylpiperidine-1-carboxamide	88	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.20 (d, 1H), 6.79 (d, 1H), 5.94 (m, 1H), 5.27 (m, 1H), 5.23 (d, 1H), 5.13 (d, 1H), 4.48 (m, 1H), 4.08 (s, 3H), 4.05-3.88 (m, 2H), 3.87-3.44 (m, 3H), 3.31 (m, 1H), 3.15-3.04 (m, 2H), 2.99-2.87 (m, 2H), 2.73 (d, 3H), 2.39-2.06 (m, 2H), 2.00-1.84 (m, 3H), 1.80-1.26 (m, 5H).	Method 8: 1.61 min, 544.4 $[M+H]^+$
93		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.35 (d, 1H), 7.29 (m, 1H), 7.11 (d, 1H), 5.82 (m, 1H), 5.29-5.11 (m, 2H), 4.11-3.98 (m, 4H), 3.81 (dd, 1H), 3.55 (m, 1H), 3.48-3.28 (m, 1H), 3.13 (m, 1H), 3.03-2.86 (m, 2H), 2.80 (m, 2H), 2.61-2.36 (m, 4H), 2.14 (m, 1H), 1.98 (m, 1H), 1.89-1.67 (m, 2H), 1.66-1.36 (m, 6H), 1.35-1.17 (m, 4H).	Method 9 (with CSH column 7 no ammonia): 1.83 min, 557.5 $[M+H]^+$

94		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclopentane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (t, 1H), 7.39 (d, 1H), 7.15 (d, 1H), 7.05 (m, 1H), 5.65 (m, 1H), 5.27 (s, 2H), 4.15 (s, 3H), 4.00 (m, 1H), 3.92 (dd, 1H), 3.52 (m, 1H), 3.39-3.27 (m, 1H), 3.04 (m, 1H), 2.92 (m, 1H), 2.79 (m, 2H), 2.56-2.45 (m, 1H), 2.42-2.24 (m, 4H), 2.17 (d, 1H), 2.08 (d, 1H), 2.01 (m, 1H), 1.79-1.35 (m, 4H), 1.06 (s, 3H), 0.62-0.35 (m, 4H).	Method 11: 1.89 min, 619.3 $[M+H]^+$
95		(1*S*,2*R*)-2-((1*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclopentane-1-carboxamide (isomer 1)	98	^{1}H NMR (300 MHz, $CDCl_3$; rotamers observed, both reported) δ 7.56 (t, 0.3H), 7.27-7.18 (m, 1H), 7.17-6.76 (m, 1.7H), 5.89 (m, 0.7H), 5.72 (m, 0.7H), 5.59 (m, 0.3H), 5.44-5.15 (m, 2H), 4.64 (m, 0.3H), 4.18 (s, 0.9H), 4.18 (s, 2.1H), 4.03-3.87 (m, 2H), 3.84-3.48 (m, 2H), 3.18-2.84 (m, 5H), 2.79 (d, 0.9H), 2.60 (d, 2.1H), 2.43-2.25 (m, 2H), 2.20-1.34 (m, 7H), 1.27-1.13 (m, 3.9H), 1.10 (d, 2.1H).	Method 13: 2.15 min, 607.3 $[M+H]^+$
96		(1*S*,2*R*)-2-((1*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide (isomer 1)	98	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (bm, 1H), 7.28-7.18 (m, 1H), 6.96 (t, 1H), 6.90 (d, 1H), 6.00 (m, 1H), 5.38-5.20 (m, 2H), 4.19 (s, 3H), 4.04-3.76 (m, 3H), 3.54 (m, 1H), 3.10-2.92 (m, 3H), 2.89-2.76 (m, 2H), 2.70 (d, 3H), 2.50 (m, 1H), 2.35 (m, 1H), 2.14 (m, 1H), 1.78-1.01 (m, 14H).	Method 2: 5.67 min, 621.3 $[M+H]^+$

97		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((1-methyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (bm, 1H), 7.23 (d, 1H), 6.95 (d, 1H), 6.00 (dd, 1H), 5.38-5.16 (m, 2H), 4.19 (s, 3H), 4.09 (dd, 1H), 4.02-3.74 (m, 2H), 3.59 (d, 1H), 3.23-2.64 (m, 8H), 2.55 (m, 1H), 2.38 (d, 1H), 2.19 (d, 1H), 1.84-1.32 (m, 6H), 1.25-1.03 (m, 4H), 0.75-0.46 (m, 4H).	Method 9: 2.53 min, 651.2 $[M+H]^+$
99		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-cyclopropyl-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (300 MHz, $CDCl^3$) δ 7.73 (bm, 1H), 7.23 (d, 1H), 6.97 (d, 1H), 5.98 (m, 1H), 5.19-5.07 (m, 2H), 4.16-3.74 (m, 6H), 3.64 (m, 1H), 3.16-3.02 (m, 2H), 3.01-2.71 (m, 3H), 2.69 (d, 3H), 2.51 (m, 1H), 2.35-2.08 (m, 2H), 1.96-1.80 (m, 2H), 1.77-1.32 (m, 7H), 1.27-0.99 (m, 6H), 0.84-0.68 (m, 2H).	Method 10: 1.90 min, 597.3 $[M+H]^+$
100		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide	98	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, 1H), 6.92 (t, 1H), 6.89 (d, 1H), 5.98 (dd, 1H), 5.30-5.15 (m, 2H), 4.17 (s, 3H), 4.08 (dd, 1H), 4.01-3.75 (m, 2H), 3.52 (d, 1H), 3.08 (dd, 1H), 3.03-2.75 (m, 4H), 2.55 (m, 1H), 2.35 (d, 1H), 2.20 (d, 1H), 1.88-1.33 (m, 6H), 1.32-1.13 (m, 4H), 0.69-0.46 (m, 4H).	Method 9: 2.14 min, 619.2 $[M+H]^+$

101		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((1,5-dimethyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (bm, 1H), 7.22 (d, 1H), 6.91 (d, 1H), 5.95 (m, 1H), 5.13 (d, 1H), 5.06 (d, 1H), 4.07 (dd, 1H), 4.00-3.88 (m, 4H), 3.82 (m, 1H), 3.53-3.44 (m, 1H), 3.11 (dd, 1H), 3.01-2.88 (m, 3H), 2.81 (m, 1H), 2.70 (d, 3H), 2.54 (m, 1H), 2.34 (d, 1H), 2.29 (s, 3H), 2.19 (d, 1H), 1.82-1.31 (m, 6H), 1.25-1.01 (m, 4H), 0.68-0.46 (m, 4H).	Method 10: 1.86 min, 597.3 $[M+H]^+$
102		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00-7.32 (m, 2H), 7.21 (d, 1H), 6.81 (d, 1H), 6.00 (dd, 1H), 5.20 (d, 1H), 5.14 (d, 1H), 4.16-3.90 (m, 5H), 3.82 (m, 1H), 3.54 (d, 1H), 3.13 (dd, 1H), 3.05-2.77 (m, 4H), 2.70 (d, 3H), 2.54 (m, 1H), 2.35 (d, 1H), 2.19 (d, 1H), 1.87-1.32 (m, 6H), 1.28-1.04 (m, 4H), 0.69-0.43 (m, 4H).	Method 11: 1.82 min, 583.3 $[M+H]^+$
103		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-cyclopropyl-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (bm, 1H), 7.24 (d, 1H), 6.97 (d, 1H), 5.98 (dd, 1H), 5.22-5.05 (m, 2H), 4.13-4.01 (m, 4H), 3.96 (m, 1H), 3.83 (m, 1H), 3.50 (d, 1H), 3.12 (dd, 1H), 3.02-2.74 (m, 4H), 2.71 (d, 3H), 2.54 (m, 1H), 2.34 (d, 1H), 2.19 (d, 1H), 1.80-0.95 (m, 13H), 0.84-0.67 (m, 2H), 0.66-0.47 (m, 4H).	Method 10: 2.10 min, 623.3 $[M+H]^+$

104		(1S,2*R*)-2-((S)-5-chloro-8-((1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-(((*R*)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (bm, 1H), 7.62 (s, 1H), 7.22 (d, 1H), 6.83 (d, 1H), 5.98 (m, 1H), 5.22 (d, 1H), 5.16 (d, 1H), 4.10 (s, 3H), 4.06-3.74 (m, 3H), 3.29 (m, 1H), 3.22-3.05 (m, 2H), 3.03-2.77 (m, 3H), 2.69 (dd, 3H), 2.59-2.27 (m, 3H), 1.96-1.28 (m, 7H), 1.25-0.99 (m, 7H).	Method 11: 1.64 min, 571.3 $[M+H]^+$
105		(1S,2*R*)-2-((S)-5-chloro-8-((5-(methoxymethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-(((*R*)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (bm, 1H), 7.24 (d, 1H), 6.90 (d, 1H), 5.92 (m, 1H), 5.20 (d, 1H), 5.12 (d, 1H), 4.55 (d, 1H), 4.49 (d, 1H), 4.06 (s, 3H), 4.00 (dd, 1H), 3.93 (m, 1H), 3.83 (m, 1H), 3.33 (s, 3H), 3.22 (dd, 1H), 3.14-3.02 (m, 2H), 2.95 (dd, 1H), 2.87-2.76 (m, 2H), 2.69 (d, 3H), 2.51 (m, 1H), 2.45-2.25 (m, 2H), 1.90-1.20 (m, 7H), 1.17-1.07 (m, 4H), 1.05 (d, 3H).	Method 10: 1.93 min, 615.3 $[M+H]^+$
106		(1S,2*R*)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, 1H), 7.39-7.05 (m, 2H), 5.45-5.35 (m, 2H), 5.20 (m, 1H), 4.12 (s, 3H), 3.97-3.86 (m, 2H), 3.52 (m, 1H), 3.08-2.98 (m, 2H), 2.85 (dd, 1H), 2.80-2.70 (m, 3H), 2.45 (d, 3H), 2.38 (m, 1H), 2.22 (d, 1H), 2.05 (d, 1H), 1.63 (m, 1H), 1.58-1.29 (m, 5H), 1.18 (m, 1H), 1.07 (s, 3H), 0.66-0.44 (m, 4H).	Method 14: 4.51 min, 651.1 $[M+H]^+$

107		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, 1H), 7.29 (t, 1H), 6.91 (bm, 1H), 6.55 (bm, 1H), 5.51 (dd, 1H), 5.40 (m, 1H), 5.22 (m, 1H), 4.14 (s, 3H), 3.98-3.86 (m, 2H), 3.52 (m, 1H), 3.10 (d, 1H), 3.04 (m, 1H), 2.91-2.77 (m, 2H), 2.77-2.68 (m, 2H), 2.46-2.34 (m, 1H), 2.21 (d, 1H), 2.07 (d, 1H), 1.63 (m, 1H), 1.57-1.12 (m, 6H), 1.09 (s, 3H), 0.64-0.44 (m, 4H).	Method 14: 4.32 min, 637.1 $[M+H]^+$
108		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((3-oxomorpholino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, 1H), 7.29 (bm, 1H), 7.23 (m, 1H), 5.49-5.39 (m, 2H), 5.22 (m, 1H), 4.31 (dd, 1H), 4.13 (s, 3H), 3.96 (d, 1H), 3.88 (m, 1H), 3.78 (d, 1H), 3.72 (m, 1H), 3.64 (m, 1H), 3.53 (m, 1H), 3.19 (m, 1H), 3.01 (m, 1H), 2.84 (m, 1H), 2.80-2.70 (m, 3H), 2.45 (d, 3H), 2.36 (m, 1H), 1.63 (m, 1H), 1.58-1.28 (m, 5H), 1.17 (m, 1H), 1.07 (s, 3H).	Method 14: 4.24 min, 641.1 $[M+H]^+$
109		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, 1H), 7.30 (bm, 1H), 7.26 (t, 1H), 5.45-5.36 (m, 2H), 5.22 (m, 1H), 4.13 (s, 3H), 3.93-3.77 (m, 2H), 3.50 (m, 1H), 3.17 (m, 1H), 3.01 (m, 1H), 2.97-2.84 (m, 2H), 2.76 (m, 2H), 2.44 (d, 3H), 2.35 (m, 1H), 2.15 (m, 1H), 2.04-1.79 (m, 2H), 1.78-1.58 (m, 2H), 1.58-1.20 (m, 5H), 1.08 (m, 4H).	Method 14: 4.21 min, 625.1 $[M+H]^+$

110		(1S,2*R*)-2-((*S*)-5-chloro-7-fluoro-8-((1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.52 (d, 1H), 7.30 (bm, 1H), 5.63 (dd, 1H), 5.32-5.20 (m, 2H), 4.04 (s, 3H), 3.98-3.86 (m, 2H), 3.52 (m, 1H), 3.27 (d, 1H), 3.02 (m, 1H), 2.96 (dd, 1H), 2.83-2.68 (m, 3H), 2.43 (d, 3H), 2.38 (m, 1H), 2.22 (d, 1H), 2.09 (d, 1H), 1.63 (m, 1H), 1.57-1.44 (m, 3H), 1.43-1.30 (m, 2H), 1.29-1.14 (m, 1H), 1.05 (s, 3H), 0.65-0.46 (m, 4H).	Method 3: 3.97 min, 601.1 $[M+H]^+$
111		(1S,2*R*)-2-((*S*)-5-chloro-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-8-((4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridin-3-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, 1H), 6.88 (bm, 1H), 6.50 (bm, 1H), 5.62 (dd, 1H), 5.25 (dd, 1H), 5.10 (dd, 1H), 4.28 (m, 2H), 3.99-3.87 (m, 2H), 3.50 (m, 1H), 3.14 (d, 1H), 3.04 (m, 1H), 2.97-2.64 (m, 6H), 2.42 (m, 1H), 2.20 (d, 1H), 2.08 (d, 1H), 1.99 (m, 2H), 1.80 (m, 2H), 1.62 (m, 1H), 1.56-1.42 (m, 3H), 1.42-1.15 (m, 3H), 1.08 (s, 3H), 0.65-0.43 (m, 4H).	Method 14: 4.13 min, 627.1 $[M+H]^+$
112		(1S,2*R*)-2-((*S*)-5-chloro-8-((1,5-dimethyl-1*H*-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide	98	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, 1H), 5.73 (dd, 1H), 5.24 (d, 1H), 5.14 (dd, 1H), 4.04 (dd, 1H), 3.97-3.84 (m, 4H), 3.76 (m, 1H), 3.28 (d, 1H), 3.10 (dd, 1H), 3.01 (d, 1H), 2.96-2.72 (m, 3H), 2.57 (m, 1H), 2.34 (d, 1H), 2.22-2.12 (m, 4H), 1.82-1.36 (m, 6H), 1.27 (m, 1H), 1.18 (s, 3H), 0.68-0.43 (m, 4H).	Method 3: 3.87 min, 601.0 $[M+H]^+$

113		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-cyclopropyl-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-(((*R*)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*,1-dimethylcyclohexane-1-carboxamide	98	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (bm, 1H), 7.24 (d, 1H), 6.96 (d, 1H), 5.96 (m, 1H), 5.13 (s, 2H), 4.10-3.96 (m, 4H), 3.95-3.75 (m, 2H), 3.24 (m, 1H), 3.18-3.03 (m, 2H), 2.95 (m, 1H), 2.87-2.72 (m, 2H), 2.69 (d, 3H), 2.51 (m, 1H), 2.46-2.24 (m, 2H), 1.93-1.24 (m, 8H), 1.19-0.97 (m, 9H), 0.90-0.68 (m, 2H).	Method 9: 2.27 min, 612.47 [M+H]+
114		(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-*N*-methylcyclohexane-1-carboxamide	98	^{1}H NMR (300 MHz, MeOD) δ 7.32 (d, 1H), 7.32 (t, 1H), 7.08 (d, 1H), 5.89 (m, 1H), 5.28 (s, 2H), 4.21 (s, 3H), 4.14-3.98 (m, 2H), 3.74 (m, 1H), 3.50 (m, 1H), 3.44 (d, 1H), 3.16 (dd, 1H), 2.99-2.84 (m, 3H), 2.58 (s, 3H), 2.44-2.17 (m, 4H), 2.07-1.20 (m, 7H), 0.75-0.46 (m, 4H).	Method 9: 2.21 min, 620.6 [M+H]+

Biological Assays

KEAP1 Kelch fluorescence polarization (FP) assay method

[00246] Inhibition of the Kelch domain-NRF2 interaction was determined using a fluorescence polarization-based competition assay in a black 384-well microplate. Compounds were tested at a starting concentration of 10 μM serially diluted 1:3 to generate a 12-point dose response curve on the Biomek FX robot. Each well contained 2 nM FITC-labelled NRF2 peptide (FITC-LDEETGEFL-NH2) and 25nM human KEAP1 (N-term, residues 321−609) enzyme in a final volume of 20 μL of assay buffer (50 mM Tris-HCl pH 8.0, 100 mM NaCl, 5 mM $MgCl_2$, 0.005% Tween-20, 0.005% BSA, 0.5% DMSO) in the presence of varying concentrations of test compound. Unlabelled peptide (LDEETGEFL-NH2) at 50 μM (negative control) and 0.5% DMSO (positive control) was used to determine the assay window.

[00247] After 1 h at room temperature, fluorescence polarization (excitation 470 nm/emission 530 nm) was measured using an Envision plate reader. IC_{50} values were determined by fitting the data to a four parameter logistic fit using XLfit or XE Runner within ActivityBase. The assay limit is such that compounds below 10 nM cannot be differentiated. IC_{50} values for the Example compounds are shown in Table 2.

Table 2

Example No.	IC_{50} (nM)	Example No.	IC_{50} (nM)	Example No.	IC_{50} (nM)
1	901	**39**	3009	**77**	7.2
2	339	**40**	523	**78**	110
3	125	**41**	788	**79**	14
4	161	**42**	53	**80**	371
5	147	**43**	186	**81**	723
6	196	**44**	1169	**82**	4071
7	196	**45**	310	**83**	12
8	1276	**46**	83	**84**	161
9	119	**47**	5332	**85**	7.8
10	38	**48**	728	**86**	14
11	37	**49**	1804	**87**	39
12	56	**50**	72	**88**	67
13	169	**51**	1702	**89**	19
14	183	**52**	38	**90**	7.9
15	93	**53**	47	**91**	9.8
16	366	**54**	31	**92**	12
17	28	**55**	54	**93**	851
18	119	**56**	13	**94**	13
19	196	**57**	112	**95**	23
20	29	**58**	11	**96**	37
21	2253	**59**	533	**97**	8.9

22	32	**60**	72	**98**	6.0
23	606	**61**	34	**99**	7.4
24	294	**62**	82	**100**	6.4
25	292	**63**	340	**101**	6.1
26	61	**64**	41	**102**	12
27	565	**65**	18	**103**	7.1
28	43	**66**	151	**104**	11
29	166	**67**	29	**105**	17
30	215	**68**	13	**106**	6.7
31	539	**69**	14	**107**	6.2
32	2099	**70**	29	**108**	7.3
33	1506	**71**	17	**109**	7.5
34	36	**72**	27	**110**	7.1
35	185	**73**	9.4	**111**	7.2
36	126	**74**	16	**112**	7.0
37	44	**75**	73	**113**	10.9
38	8204*	**76**	11	**114**	9.1

* = one one test occasion >10 μM.

Beas2B NQO1 mRNA cell based assay

[00248] The up regulation of the NRF2 mediated gene NAD(P)H:quinone acceptor oxidoreductase 1 (NQO1) was measured using the following assay method: BEAS-2B cells (ATCC CRL-9609) were plated in 96-well clear plates at 20,000 cells/well in 75μL of cell culture media and incubated overnight (37 °C, 5% CO_2). On day 2, 25μL of compound or controls were added to the cells for 24 h. On day 3, the medium was aspirated from the plate and the Cells-to-CT™ 1-Step TaqMan® Kit (Ambion A25603) was used to perform expression analysis directly from cultured cells without RNA purification according to the manufacturer's instructions.

[00249] Briefly, cells were washed with ice cold PBS and 22.5 μL of room-temperature DNase/Lysis solution was added to the cells and incubated at room temperature for 5 minutes. To stop the reaction, 2.25 μL of stop solution was added to the cell lysate. The samples were diluted 1:5 using nuclease free water and 2.5 μL transferred into the PCR plate. Real-time PCR was performed using the C-1000 Thermal Cycler (Bio-Rad) using human beta actin as the internal control. The cDNA was amplified with a specific primer for NQO1 using the 1-step RT-PCR master mix (Ambion Cells-to-CT™ 1-Step TaqMan® Kit A25603). The primers/probes sets that were used for amplification of cDNA were obtained from TaqMan Gene Expression Assays (Applied Biosystems). The comparative CT (ΔΔCT) relative quantification method was used to calculate the relative mRNA level of the target gene NQO1 as described in the Applied Biosystems Chemistry Guide. The data are expressed as an increase in target gene mRNA compared to vehicle (0.1%

DMSO) control and the EC_{50} values were determined by fitting the data to a four parameter logistic fit using XLfit or XE Runner within ActivityBase. EC_{50} values for the Example compounds are shown in Table 3.

Table 3

Example No.	EC_{50} (nM)	Example No.	EC_{50} (nM)	Example No.	EC_{50} (nM)
1	2027	**39**	ND	**77**	77
2	ND	**40**	ND	**78**	>10,000
3	ND	**41**	ND	**79**	336
4	ND	**42**	580	**80**	2252
5	ND	**43**	ND	**81**	>10,000
6	2358	**44**	ND	**82**	1736
7	ND	**45**	ND	**83**	473
8	ND	**46**	ND	**84**	1531
9	ND	**47**	ND	**85**	330
10	ND	**48**	ND	**86**	2417
11	ND	**49**	ND	**87**	4126
12	ND	**50**	ND	**88**	7563**
13	ND	**51**	ND	**89**	8717
14	ND	**52**	285*	**90**	94
15	ND	**53**	189	**91**	607
16	ND	**54**	135	**92**	565
17	3073	**55**	330	**93**	>10,000
18	ND	**56**	124	**94**	148
19	ND	**57**	3996	**95**	565
20	>500	**58**	206	**96**	3190
21	ND	**59**	ND	**97**	114
22	ND	**60**	650	**98**	41
23	ND	**61**	1083	**99**	109
24	ND	**62**	1462	**100**	26
25	ND	**63**	>10,000	**101**	18
26	ND	**64**	5748	**102**	59
27	ND	**65**	1865	**103**	57
28	ND	**66**	5658	**104**	784
29	ND	**67**	1364	**105**	790
30	ND	**68**	145	**106**	25
31	ND	**69**	239	**107**	37
32	ND	**70**	295	**108**	654
33	ND	**71**	116	**109**	140
34	193	**72**	605	**110**	66
35	ND	**73**	288	**111**	30
36	ND	**74**	334	**112**	99
37	ND	**75**	2171	**113**	299
38	ND	**76**	166	**114**	230

* = one one or more test occasion >0.5 μM, ** = one one or more test occasion 10 μM. ND = not determined

PK/PD Method

[00250] Male Wistar Han rats (Charles River labs) were administered the test item orally or intravenously at the designated dose concentration. The intravenous dose was administered as a slow bolus *via* the tail vein. The oral formulation was administered by gastric gavage into the stomach. Actual dose times were recorded.

[00251] At the designated time points, 2 x 0.25 mL blood samples were collected into K_2EDTA blood tubes via the tail vein. The collected blood samples were then either centrifuged for plasma or decanted into the 1.5 mL PCR RNAlater tubes containing 650 µL of RNAlater.

[00252] Immediately following collection, blood samples were placed on wet ice. As soon as practically possible the 0.25 mL blood samples in K_2EDTA were centrifuged (+4°C, 1500 g, 10 min) and the resulting plasma stored in appropriately labelled polypropylene tubes in a freezer set to maintain a temperature of -80°C until determination of plasma pharmacokinetics. The additional 0.25 mL blood samples in the 1.5 mL PCR RNAlater tubes containing 650 µL of RNAlater were stored in a refrigerator at 4°C until determination of blood pharmacodynamics.

[00253] Following the last sample collection each animal was sacrificed by anesthetic overdose by IP injection of Pentobarbitone Na as soon as practically possible and death was confirmed by cervical dislocation.

[00254] The lungs from each animal were removed and divided into 4 equal pieces immediately after extraction. The first two sections of lung (labelled left and right) were placed in 5 mL RNAlater tissue protect tube containing 5 mL RNAlater stabilisation reagent and stored at 4ºC to allow RNA stabilization (PD analysis). The remaining two sections (labelled left and right) were weighed and snap frozen by immersion in liquid nitrogen in polypropylene tubes (PK analysis).

[00255] The liver was also collected from each animal. Six representative pieces (of a similar size to the lung pieces) from different areas (no more than 0.5 cm thickness) were collected. Four pieces (no more than 0.5 cm thickness) were placed in two separate (two pieces per tube) 5 mL RNAlater tissue protect tubes containing 5 mL RNAlater stabilisation reagent (tissue sections were completely submerged into the RNA later solution) and stored at 4ºC (PD analysis). The remaining two pieces were weighed and snap frozen by immersion in liquid nitrogen in separate polypropylene tubes (a maximum of 0.5 g per tube, PK analysis).

[00256] In some studies, the heart, spleen and brain were also collected from each animal. These tissues were sectioned into four equal sized pieces and two pieces placed in a single 5 mL RNA later tissue protect tube containing 5 mL RNAlater stabilisation reagent and stored at 4ºC. The remaining two pieces were weighed and placed individually into polypropylene tubes and snap frozen by immersion in liquid nitrogen.

[00257] Study sample tubes containing RNAlater RNA Stabilisation Reagent were stored at ca +4 ºC to allow RNA stabilisation reagent to perfuse the tissue. Sections snap frozen were stored in a freezer set to maintain a temperature of -80ºC.

[00258] PK study samples were quantified using a method based on protein precipitation and LC-MS/MS analysis. Prior to analysis defrosted tissue samples were weighed and homogenised following the addition of HPLC grade water using an Omni-Prep Bead Ruptor (Omni Inc., Kennesaw, GA) at 4°C. Plasma and tissue homogenate samples were extracted using protein precipitation with acetonitrile acidified with 0.1% formic acid containing internal standard(s). Samples were mixed and centrifuged at 4000 rpm at 4°C for 30 minutes to remove precipitated proteins, and the supernatant diluted appropriately with HPLC grade water in a 96-well plate. Representative aliquots of plasma and tissue homogenates were assayed for test item by LC-MS/MS using a Waters Xevo TQ-S (Waters, Elstree, UK) against matrix matched calibration curves and quality control standards. The standards were prepared by spiking aliquots of control plasma and tissue homogenate with the test item and extracted as described for the experimental samples.

[00259] RNA extraction and real-time PCR analysis for NQO1 gene expression in in-vivo PD studies was performed as detailed below.

[00260] Total RNA was isolated using RNeasy plus mini RNA isolation kit (Qiagen) or Mouse RiboPure™-Blood RNA Isolation Kit (ThermoFisher Scientific) according to the manufacturer's instructions and quantified using an Agilent RNA 6000 Nano instrument. Real-time PCR was performed using the C-1000 Thermal Cycler (Bio-Rad) using rat beta actin as the internal control. The cDNA was amplified with specific primer for NQO1/Nqo1 using universal master mix (Applied Biosystems). The primers/probes sets used for amplification of cDNA were obtained from TaqMan Gene Expression Assays (Applied Biosystems). The comparative CT (ΔΔCT) relative quantification method is used to calculate the relative mRNA level of the target gene NQO1 as described in the Applied Biosystems Chemistry Guide. The data is expressed as an increase in target gene mRNA compared to vehicle control treated for each tissue type.