

dysfunction, inflammation and oxidative stress, it is currently being studied in these patients suggesting Nrf2 activators will be potentially useful in this disease.

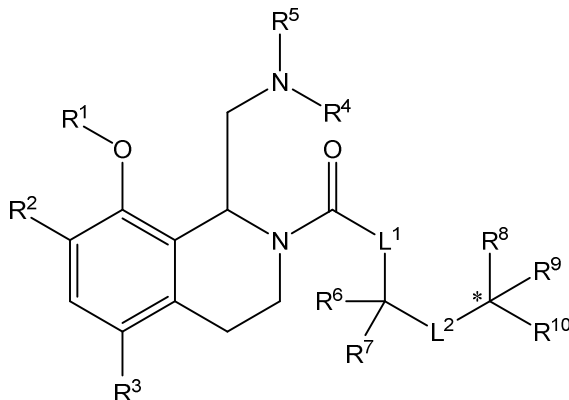
[0012] Oxidative stress plays a critical role in the initiation and progression of cancer (Gorrini, *Nat Rev Drug Discov.*, doi:10.1038/nrd4002). Due to its importance in the maintenance of redox cellular homeostasis, Nrf2 is considered a cytoprotective transcription factor and tumour suppressor. At 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] Therefore, there is an ongoing need for agents capable of Nrf2 activation, given the role of Nrf2 in multiple indications.

SUMMARY

In one aspect, the present disclosure refers to a compound of Formula I



(I)

wherein:

- 5 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;
- 15 R^4 is hydrogen or C_{1-4} alkyl;
- R^5 is $-C(O)-C_{1-4}$ alkyl, $-C(O)-$ 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
- 20 R^4 and R^5 , taken together with the nitrogen atom to which they are attached, form a 4-, 5-, or 6-membered heteroaryl or heterocyclyl ring, wherein:
said heterocyclyl ring comprises one or more $-C(O)-$ moieties attached to the nitrogen atom and is optionally fused to an aryl or heteroaryl ring, or optionally spiro-attached to a C_{3-7} cycloalkyl group; and
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_{1-3} haloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20} ;
- 25 L^1 and L^2 are independently selected from a bond and $-CR^{21}R^{22}-$;
- R^6 and R^7 are independently selected from hydrogen, C_{1-4} alkyl, and C_{3-7} cycloalkyl; or
- 30 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 selected from CO_2R^{23} , $C(O)NHSO_2C_{1-3}$ alkyl, tetrazolyl, 3-trifluoromethyl-1,2,4-triazol-5-yl and a carboxylic acid mimetic group selected from hydroxamic acids, hydroxamic esters, phosphonic acids, phosphinic acids, sulfonic acids, sulfinic acids, sulphonamides, sulfonyl ureas, acyl ureas, thiazolidine dione, oxazolidine dione, oxadiazol-5(4*H*)-one, thiadiazol-
- 35

5(4*H*)-one, oxathiadiazole-2-oxide, oxadiazol-5(4*H*)-thione, isoxazole, tetramic acid, cyclopentane-1,3-diones and cyclopentane-1,2-diones;

R⁹ is selected from hydrogen, C₁₋₄alkyl, hydroxy, C₁₋₃alkoxy and halo;

R¹⁰ is selected from hydrogen and C₁₋₄alkyl; or

5 R⁹ and R¹⁰, taken together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring; or

L² is a bond and R⁷ and R¹⁰, taken together with the atoms to which they are attached, form a 4-, 5-, 6- or 7-membered cycloalkyl or heterocyclyl ring, wherein:

10 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 C₁₋₃alkylene group connecting two carbon atoms of the ring, or R⁹ is optionally a C₁₋₃alkylene group connecting C* to a carbon atom of the ring; and

15 said cycloalkyl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, halo, OH, C₁₋₃alkoxy, C₁₋₃haloalkyl and deuterium;

20 R¹¹ is selected from -C(O)-R²⁴, -SO₂-R²⁵, -NR²⁶C(O)-R²⁷, -NR²⁸SO₂-R²⁹, heterocyclyl, aryl and heteroaryl; wherein said aryl and heteroaryl groups are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₁₋₃haloalkyl, C₃₋₇cycloalkyl, C₁₋₄alkylene-R³⁰, halo, OH, C₁₋₃alkoxy, heterocyclyl and cyano; and said heterocyclyl group is optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₁₋₃haloalkyl, C₃₋₇cycloalkyl, C₁₋₄alkylene-R³⁰, halo, OH, C₁₋₃alkoxy, oxo and cyano;

30 R¹² is selected from C₁₋₄alkyl, C₃₋₇cycloalkyl, OR³¹, NR³²R³³, aryl and heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, halo, OH, C₁₋₃alkoxy and cyano;

R¹³ is selected from C₁₋₄alkyl, C₃₋₇cycloalkyl, heteroaryl, heterocyclyl and NR³⁴R³⁵, wherein said heteroaryl and heterocyclyl are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, halo, OH, C₁₋₃alkoxy and cyano;

35 R¹⁷ is selected from hydrogen, C₁₋₄alkyl, C(O)C₁₋₃alkyl and C(O)NR³⁶R³⁷;

R¹⁸, R¹⁹ and R²⁰ are independently selected from C₁₋₄alkyl, OH, C₁₋₃alkoxy and NR³⁸R³⁹;

- 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.

[0015] In one example, the present disclosure provides a compound, or a pharmaceutically acceptable salt thereof as defined herein.

[0016] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound of the disclosure as defined herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0017] In another aspect, the present disclosure relates to a compound of the disclosure as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in therapy.

[0017a] In another aspect, the present disclosure refers to a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment of diseases or disorders mediated by Nrf2 activation.

- 5 **[0017b]** In another aspect, present disclosure refers to a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for 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
- 10 syndrome, pulmonary fibrosis including idiopathic pulmonary fibrosis, cystic fibrosis, diabetes, atherosclerosis, hypertension, heart failure, myocardial infarction and repair, cardiac remodelling, cardiac arrhythmias, cardiac hypertrophy, heart failure with preserved ejection fraction, diabetic cardiomyopathy, obesity, metabolic syndrome, diabetes mellitus, insulin resistance, pulmonary arterial hypertension, subarachnoid haemorrhage,
- 15 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,
- 20 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, lung cancer, breast cancer, colon cancer, age related macular degeneration (AMD), Fuchs Endothelial Corneal Dystrophy or uveitis.

[0018] In another example, the present disclosure relates to a compound of the disclosure 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.

5 **[0019]** In another example, the present disclosure relates to the use of a compound of the disclosure 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.

10 **[0020]** In another example, the present disclosure 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 disclosure as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

15 **[0021]** Examples of diseases or disorders mediated by Nrf2 activation include chronic obstructive pulmonary disease, asthma, pulmonary arterial hypertension, diabetes mellitus, chronic kidney disease, Friedreich's ataxia, sickle cell disease and non-alcoholic steatohepatitis.

20 **[0022]** In another example, the present disclosure 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, Friedreich's ataxia, sickle cell disease or non-alcoholic steatohepatitis.

25 **[0023]** In another example, the present disclosure 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, Friedreich's ataxia, sickle cell disease or non-alcoholic steatohepatitis.

30 **[0024]** In another example, the present disclosure provides a method of treating chronic obstructive pulmonary disease, asthma, pulmonary arterial hypertension, diabetes mellitus, chronic kidney 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.

[0025] The present disclosure further provides a method of synthesising a compound, or a pharmaceutically acceptable salt thereof, as defined herein.

[0026] In another example, the present disclosure provides a compound, or a pharmaceutically acceptable salt thereof, obtainable by, or obtained by, or directly
5 obtained by a method of synthesis as defined herein.

[0027] In another example, the present disclosure provides novel intermediates as defined herein which are suitable for use in any one of the synthetic methods set out herein.

[0028] Preferred, suitable, and optional features of any one particular example of the present disclosure are also preferred, suitable, and optional features of any other example.

10 ***DETAILED DESCRIPTION OF THE INVENTION***

Definitions

[0029] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

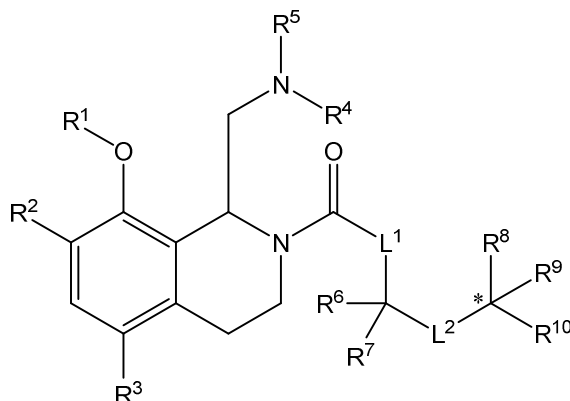
[0030] It is to be appreciated that references to “treating” or “treatment” include
15 prophylaxis as well as the alleviation of established symptoms of a condition. “Treating” or “treatment” of a state, disorder or condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms 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
20 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.

[0031] A “therapeutically effective amount” means the amount of a compound that, when
25 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.

[0032] In this specification the term “alkyl” includes both straight and branched chain alkyl
30 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

CLAIMS

1. A compound of Formula I



(I)

wherein:

R¹ is selected from C₁₋₄alkylene-R¹¹, heterocyclyl and 8-10 membered bicyclic heteroaryl; wherein said heterocyclyl is optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, -C(O)-R¹², SO₂-R¹³, C₁₋₃alkylene-OR¹⁴ and heteroaryl which is optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₃₋₇cycloalkyl, halo, OH, C₁₋₃alkoxy and cyano; and wherein said 8-10 membered bicyclic heteroaryl is optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₃₋₇cycloalkyl, halo, OH and C₁₋₃alkoxy;

R² is selected from hydrogen, fluoro, chloro and C₁₋₃alkyl;

R³ is selected from hydrogen, fluoro, chloro, bromo, C₁₋₃alkoxy, C₁₋₃alkyl, C₁₋₃haloalkyl and cyano;

R⁴ is hydrogen or C₁₋₄alkyl;

R⁵ is -C(O)-C₁₋₄alkyl, -C(O)-heteroaryl or -C(O)-aryl, wherein said heteroaryl and aryl are optionally substituted with one or more substituents selected from C₁₋₄alkyl, halo, hydroxy, C₁₋₃alkoxy, CO₂R¹⁵ and cyano; or

R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a 4-, 5-, or 6-membered heteroaryl or heterocyclyl ring, wherein:

said heterocyclyl ring comprises one or more -C(O)- moieties attached to the nitrogen atom and is optionally fused to an aryl or heteroaryl ring, or optionally spiro-attached to a C₃₋₇cycloalkyl group; and

said heteroaryl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, halo, OH,

C₁₋₃alkoxy, C₁₋₃haloalkyl, cyano, NR¹⁶R¹⁷, C(O)R¹⁸, S(O)R¹⁹ and SO₂R²⁰;

L¹ and L² are independently selected from a bond and -CR²¹R²²-;

R⁶ and R⁷ are independently selected from hydrogen, C₁₋₄alkyl, and C₃₋₇cycloalkyl; or

R⁶ and R⁷, taken together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring;

R⁸ is selected from CO₂R²³, C(O)NHSO₂C₁₋₃alkyl, tetrazolyl, 3-trifluoromethyl-1,2,4-triazol-5-yl and a carboxylic acid mimetic group selected from hydroxamic acids, hydroxamic esters, phosphonic acids, phosphinic acids, sulfonic acids, sulfinic acids, sulphonamides, sulfonyl ureas, acyl ureas, thiazolidine dione, oxazolidine dione, oxadiazol-5(4*H*)-one, thiadiazol-5(4*H*)-one, oxathiadiazole-2-oxide, oxadiazol-5(4*H*)-thione, isoxazole, tetramic acid, cyclopentane-1,3-diones and cyclopentane-1,2-diones;

R⁹ is selected from hydrogen, C₁₋₄alkyl, hydroxy, C₁₋₃alkoxy and halo;

R¹⁰ is selected from hydrogen and C₁₋₄alkyl; or

R⁹ and R¹⁰, taken together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring; or

L² is a bond and R⁷ and R¹⁰, 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 C₁₋₃alkylene group connecting two carbon atoms of the ring, or R⁹ is optionally a C₁₋₃alkylene group connecting C* to a carbon atom of the ring; and

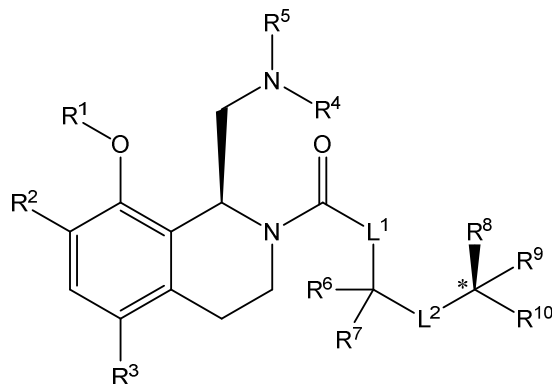
said cycloalkyl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, halo, OH, C₁₋₃alkoxy, C₁₋₃haloalkyl and deuterium;

R¹¹ is selected from -C(O)-R²⁴, -SO₂-R²⁵, -NR²⁶C(O)-R²⁷, -NR²⁸SO₂-R²⁹, heterocyclyl, aryl and heteroaryl; wherein said aryl and heteroaryl groups are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₁₋₃haloalkyl, C₃₋₇cycloalkyl, C₁₋₄alkylene-R³⁰, halo, OH, C₁₋₃alkoxy, heterocyclyl and cyano; and said heterocyclyl group is optionally substituted with one or more substituents independently selected

- from C₁₋₄alkyl, C₁₋₃haloalkyl, C₃₋₇cycloalkyl, C₁₋₄alkylene-R³⁰, halo, OH, C₁₋₃alkoxy, oxo and cyano;
- 5 R¹² is selected from C₁₋₄alkyl, C₃₋₇cycloalkyl, OR³¹, NR³²R³³, aryl and heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, halo, OH, C₁₋₃alkoxy and cyano;
- 10 R¹³ is selected from C₁₋₄alkyl, C₃₋₇cycloalkyl, heteroaryl, heterocyclyl and NR³⁴R³⁵, wherein said heteroaryl and heterocyclyl are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, halo, OH, C₁₋₃alkoxy and cyano;
- R¹⁷ is selected from hydrogen, C₁₋₄alkyl, C(O)C₁₋₃alkyl and C(O)NR³⁶R³⁷;
- R¹⁸, R¹⁹ and R²⁰ are independently selected from C₁₋₄alkyl, OH, C₁₋₃alkoxy and NR³⁸R³⁹;
- 15 R²⁴ is selected from C₁₋₄alkyl, NR⁴⁰R⁴¹ and OR⁴²;
- R²⁵ is selected from C₁₋₄alkyl and NR⁴³R⁴⁴;
- R²⁷ is selected from C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₃haloalkyl, heterocyclyl, aryl and heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₁₋₃haloalkyl, C₃₋₇cycloalkyl, C₁₋₄alkylene-R⁴⁵, halo, OH, C₁₋₃alkoxy and cyano;
- 20 R²⁹ is selected from C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₃haloalkyl, aryl and heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₁₋₃haloalkyl, C₃₋₇cycloalkyl, C₁₋₄alkylene-R⁴⁶, halo, OH, C₁₋₃alkoxy and cyano;
- R³⁰ is selected from hydroxy, C₁₋₃alkoxy, C₃₋₇cycloalkyl, cyano and NR⁴⁷R⁴⁸;
- 25 R⁴⁰ is selected from hydrogen and C₁₋₄alkyl;
- R⁴¹ is selected from hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₃alkoxy, aryl and heteroaryl; or
- R⁴⁰ and R⁴¹, taken together with the nitrogen atom to which they are attached, form a 4-, 5-, or 6-membered heteroaryl or heterocyclyl ring, wherein said
- 30 heteroaryl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, halo, OH, C₁₋₃alkoxy, C₃₋₇cycloalkyl and cyano;
- R⁴⁵ and R⁴⁶ are independently selected from hydroxy, C₁₋₃alkoxy and C₃₋₇cycloalkyl; and
- 35 R¹⁴, R¹⁵, R¹⁶, R²¹, R²², R²³, R²⁶, R²⁸, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R³⁹, R⁴², R⁴³, R⁴⁴, R⁴⁷ and R⁴⁸ are independently selected from hydrogen, C₁₋₄alkyl and C₃₋₇cycloalkyl;

or a pharmaceutically acceptable salt thereof.

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

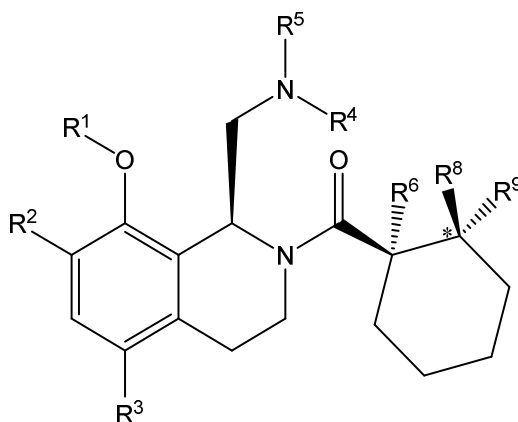


(IA)

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

3. A compound according to claim 1 or claim 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 ring.
4. A compound according to claim 1,

wherein said compound has the structural formula IB shown below



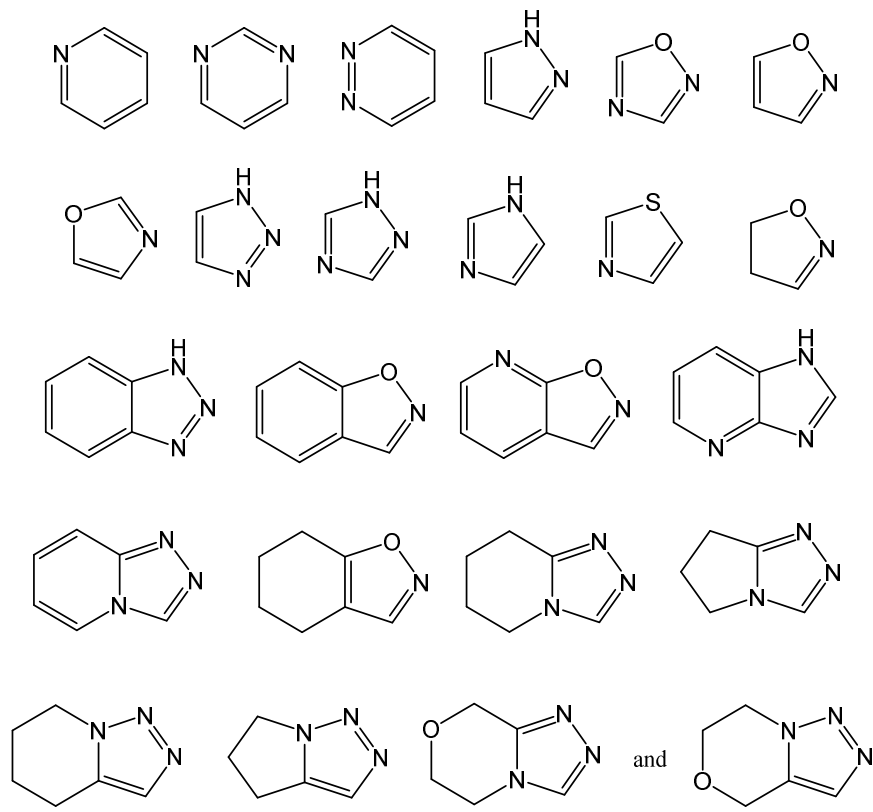
(IB)

- wherein R^1 to R^6 , R^8 and R^9 are as defined in claim 1 and the cyclohexyl 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 the cyclohexyl ring is optionally bridged

by a C₁₋₃alkylene group connecting two carbon atoms of the ring, or R⁹ is optionally a C₁₋₃alkylene group connecting C* to a carbon atom of the ring.

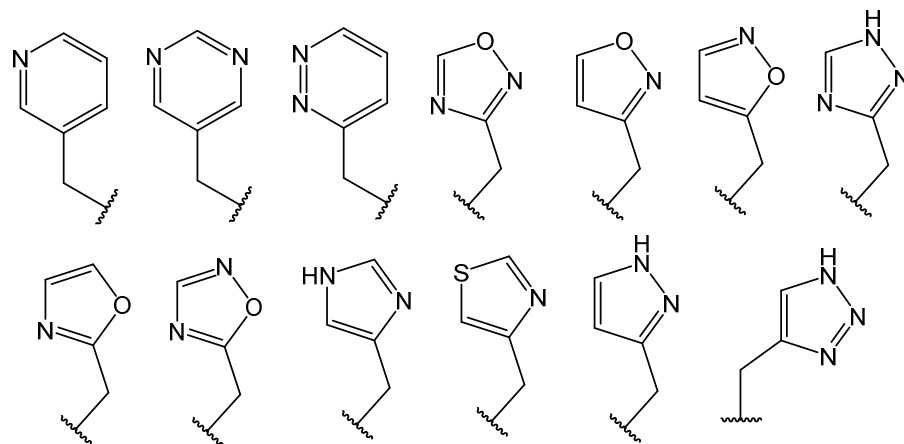
5. A compound according to any one of claims 1 to 4, wherein R⁸ is CO₂R²³ and R²³ is hydrogen.
- 5 6. A compound according to any one of claims 1 to 5, wherein R⁹ is hydrogen or C₁₋₄alkyl.
7. A compound according to any one of claims 1 to 6, wherein R⁹ is hydrogen or methyl.
8. A compound according to any one of claims 1 to 7, wherein R¹ is C₁₋₄alkylene-R¹¹.
9. A compound according to claim 8, wherein R¹ is CH₂-R¹¹.
- 10 10. A compound according to any one of claims 1 to 9, wherein R¹¹ is selected from -C(O)-R²⁴, -NR²⁶C(O)-R²⁷, heterocyclyl, aryl and heteroaryl, wherein said aryl and heteroaryl groups are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₁₋₃haloalkyl, C₃₋₇cycloalkyl, C₁₋₄alkylene-R³⁰, halo, OH, C₁₋₃alkoxy, heterocyclyl and cyano; and said heterocyclyl group is optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₁₋₃haloalkyl, C₃₋₇cycloalkyl, C₁₋₄alkylene-R³⁰, halo, OH, C₁₋₃alkoxy, oxo and cyano.
- 15 11. A compound according to any one of claims 1 to 10, wherein R¹¹ is heteroaryl optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₁₋₃haloalkyl, C₃₋₇cycloalkyl, C₁₋₄alkylene-R³⁰, halo, OH, C₁₋₃alkoxy, heterocyclyl and cyano.
- 20 12. A compound according to any one of claims 1 to 11, wherein R¹¹ is heteroaryl optionally substituted with one or more substituents independently selected from methyl, ethyl, isopropyl, difluoromethyl, trifluoromethyl, chloro, fluoro, cyclopropyl, methoxy, cyano, oxetanyl, CH₂-R³⁰ and C₂H₄-R³⁰.
- 25 13. A compound according to any one of claims 1 to 12, wherein R¹¹ is pyridyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, benzotriazolyl, benzisoxazolyl, isoxazopyridinyl, imidazopyridinyl or triazolopyridinyl, each optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₁₋₃haloalkyl, C₃₋₇cycloalkyl, C₁₋₄alkylene-R³⁰, halo, OH, C₁₋₃alkoxy, heterocyclyl and cyano.
- 30

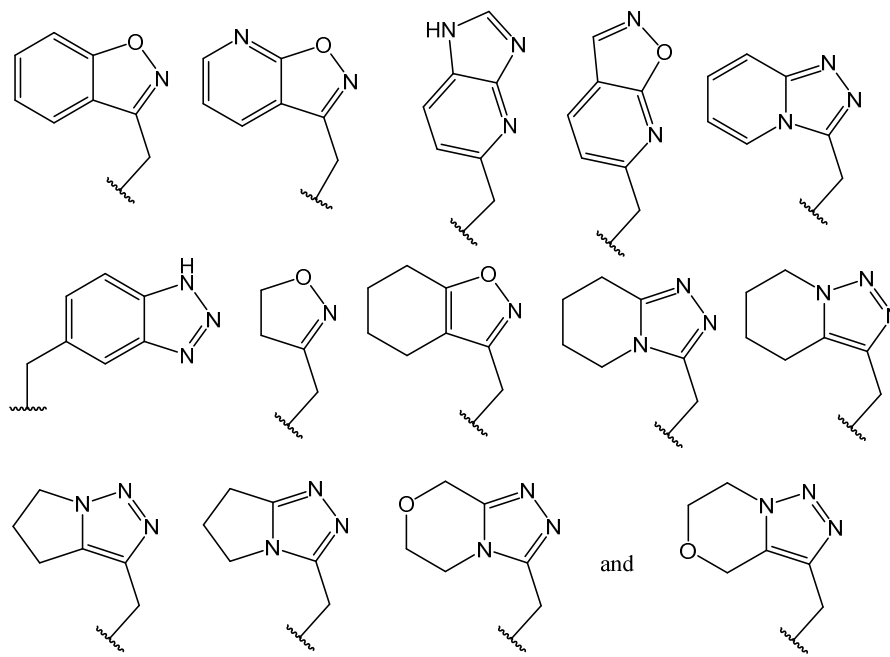
14. A compound according to any one of claims 1 to 12, wherein R¹¹ is heteroaryl selected from:



- 5 each heteroaryl being optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₁₋₃haloalkyl, C₃₋₇cycloalkyl, C₁₋₄alkylene-R³⁰, halo, OH, C₁₋₃alkoxy, heterocyclyl and cyano.

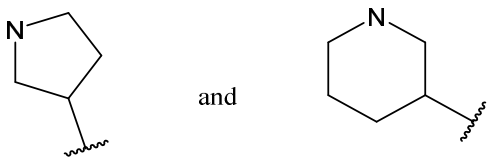
15. A compound according to any one of claims 1 to 7, wherein R¹ is selected from one of the following groups:





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 C₁₋₄alkyl, C₁₋₃haloalkyl, C₃₋₇cycloalkyl, C₁₋₄alkylene-R³⁰, halo, OH, C₁₋₃alkoxy, heterocyclyl and cyano.

16. A compound according to any one of claims 1 to 7, wherein R¹ is heterocyclyl optionally substituted with one or more substituents independently selected from -C(O)-R¹², SO₂-R¹³, heteroaryl and C₁₋₃alkylene-OR¹⁴, wherein said heteroaryl is optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₃₋₇cycloalkyl, halo, OH, C₁₋₃alkoxy and cyano.
17. A compound according to any one of claims 1 to 7, wherein R¹ is piperidinyl or pyrrolidinyl, each optionally substituted with one or more substituents independently selected from -C(O)-R¹², SO₂-R¹³, heteroaryl and C₁₋₃alkylene-OR¹⁴, wherein said heteroaryl is optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, C₃₋₇cycloalkyl, halo, OH, C₁₋₃alkoxy and cyano.
18. A compound according to claim 17, wherein R¹ is pyrrolidinyl optionally substituted with one or more substituents independently selected from -C(O)-R¹², SO₂-R¹³, heteroaryl and C₁₋₃alkylene-OR¹⁴, wherein said heteroaryl is optionally substituted with C₁₋₄alkyl or C₃₋₇cycloalkyl.
19. A compound according to any one of claims 1 to 7, wherein R¹ is selected from one of the following groups:

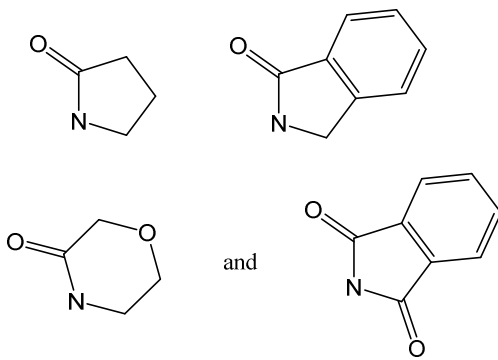


wherein represents the point of attachment of the group to the oxygen atom of the rest of the compound and wherein each group is optionally substituted with one or more substituents independently selected from -C(O)-R¹², SO₂-R¹³, heteroaryl and C₁₋₃alkylene-OR¹⁴, wherein said heteroaryl is optionally substituted with C₁₋₄alkyl or C₃₋₇cycloalkyl.

20. A compound according to any one of claims 1 to 19, wherein R² is hydrogen or fluoro.
21. A compound according to any one of claims 1 to 20, wherein R³ is hydrogen or chloro.
22. A compound according to any one of claims 1 to 21, wherein R⁴ is hydrogen and R⁵ is -C(O)-C₁₋₄alkyl or -C(O)-aryl, wherein said aryl is optionally substituted with one or more substituents selected from C₁₋₄alkyl, halo, hydroxy, C₁₋₃alkoxy, CO₂R¹⁵ and cyano.
23. A compound according to any one of claims 1 to 21, wherein R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a 5-membered heteroaryl or heterocyclyl ring, wherein said heterocyclyl comprises a -C(O)- moiety attached to the nitrogen atom and is optionally fused to an aryl or heteroaryl ring, or optionally spiro-attached to a C₃₋₇cycloalkyl group, and wherein said heteroaryl and heterocyclyl are optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, halo, OH, C₁₋₃alkoxy and cyano.
24. A compound according to claim 23, wherein R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a 5-membered heteroaryl ring, optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, halo and OH.
25. A compound according to claim 24, wherein the 5-membered heteroaryl ring is pyrazolyl.
26. A compound according to claim 23, wherein R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a 5- or 6-membered heterocyclyl ring, wherein said heterocyclyl comprises a -C(O)- moiety attached to the nitrogen atom and is optionally fused to an aryl ring, or optionally spiro-attached to a C₃₋₇cycloalkyl

group, and wherein said heterocyclyl is optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, halo and OH.

27. A compound according to any one of claims 1 to 21, wherein R⁴ and R⁵, 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 C₃₋₇-cycloalkyl group, and wherein said heterocyclic moiety is optionally substituted with one or more substituents independently selected from C₁₋₄alkyl, halo and OH.

28. A compound according to claim 1, which is selected from any one of the following:
- (1S,2R)-2-((S)-1-((1,3-dioxoisindolin-2-yl)methyl)-8-(2-(5-methylisoxazole-3-carboxamido)ethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-8-(2-(Benzo[d]oxazole-2-carboxamido)ethoxy)-1-((1,3-dioxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-8-(((S)-1-Acetylpyrrolidin-3-yl)oxy)-1-((1,3-dioxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-1-((1,3-dioxoisindolin-2-yl)methyl)-8-(((S)-1-(5-methylisoxazole-3-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-1-((1,3-dioxoisindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-1-((1,3-dioxoisindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-1-((1,3-dioxoisindolin-2-yl)methyl)-8-(((S)-1-(2-methylthiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;

- (1S,2R)-2-((S)-1-((1,3-dioxoisindolin-2-yl)methyl)-8-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 5 (1S,2R)-2-((S)-1-((1,3-dioxoisindolin-2-yl)methyl)-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-1-((1,3-dioxoisindolin-2-yl)methyl)-8-((1-methyl-1H-benzo[d]imidazol-5-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 10 (1S,2R)-2-((S)-8-(((S)-1-acetylpyrrolidin-3-yl)oxy)-5-bromo-1-((1,3-dioxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-8-(((S)-1-acetylpyrrolidin-3-yl)oxy)-5-chloro-1-((1,3-dioxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 15 (1S,2R)-2-((S)-8-(((S)-1-acetylpyrrolidin-3-yl)oxy)-5,7-dichloro-1-((1,3-dioxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;;
- (1S,2R)-2-((S)-5-chloro-1-((1,3-dioxoisindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 20 (1S,2R)-2-((S)-1-((1-oxoisindolin-2-yl)methyl)-8-(((S)-1-(thiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-8-([1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)-5-bromo-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-
- 25 carboxylic acid;
- (1S,2R)-2-((S)-8-((1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-8-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-
- 30 carboxylic acid;
- (1S,2R)-2-((S)-8-(((S)-1-acetylpyrrolidin-3-yl)oxy)-5-bromo-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-8-(((S)-1-(2-methylthiazole-5-carbonyl)pyrrolidin-3-yl)oxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-
- 35 carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-8-(((S)-1-(5-methylthiazol-2-yl)pyrrolidin-3-yl)oxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-
- carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-8-(((S)-1-(5-methylpyridazin-3-yl)pyrrolidin-3-yl)oxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-
- 40 carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-8-((4-methyl-4H-1,2,4-triazol-3-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-
- carboxylic acid;

- (1S,2R)-2-((S)-5-bromo-8-((5-methyl-1,2,4-oxadiazol-3-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 5 (1S,2R)-2-((S)-5-Bromo-8-((1-methyl-1H-imidazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-8-((5-methylisoxazol-3-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 10 (1S,2R)-2-((S)-5-bromo-8-((2-ethyl-2H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((1S)-5-bromo-8-((5-methylthiazol-2-yl)methoxy)-1-((1-oxo-1,3,3a,4,5,6-hexahydro-2H-isindol-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 15 (1S,2R)-2-((S)-5-bromo-8-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-1-((1-oxoisindolin-2-yl)methyl)-8-(pyridazin-3-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 20 (1S,2R)-2-((S)-5-bromo-8-((1-(cyclopropylmethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-8-(imidazo[1,2-a]pyridin-7-ylmethoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 25 (1S,2R)-2-((S)-5-bromo-8-((1-methyl-1H-benzo[d]imidazol-5-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-8-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 30 (1S,2R)-2-((S)-5-bromo-8-((1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-8-((5-methyl-1,3,4-oxadiazol-2-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 35 (1S,2R)-2-((S)-5-bromo-8-((7-methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-8-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 40 (1S,2R)-2-((S)-5-bromo-8-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;

- (1S,2R)-2-((S)-5-bromo-8-((1-methyl-1H-1,2,4-triazol-3-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 5 (1S,2R)-2-((S)-5-bromo-8-((1-isopropyl-1H-imidazol-2-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 10 (1S,2R)-2-((S)-5-bromo-8-((4-ethyl-4H-1,2,4-triazol-3-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-8-((5-cyano-1-ethyl-1H-imidazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 15 (1S,2R)-2-((S)-5-bromo-1-((1-oxoisindolin-2-yl)methyl)-8-((5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((1S)-5-bromo-8-(1-(1-methyl-1H-1,2,3-triazol-4-yl)ethoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 20 (1S,2R)-2-((1S)-5-bromo-8-(1-(1-isopropyl-1H-1,2,3-triazol-4-yl)ethoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 25 (1S,2R)-2-((S)-5-chloro-8-((5-methylisoxazol-3-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 30 (1S,2R)-2-((S)-8-([1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)-5-chloro-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-1-((1-oxoisindolin-2-yl)methyl)-8-((1-(2,2,2-trifluoroethyl)-1H-imidazol-2-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 35 (1S,2R)-2-((S)-5-chloro-8-((1-(2,2-difluoroethyl)-1H-imidazol-2-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 40 (1S,2R)-2-((S)-5-chloro-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;

- (1S,2R)-2-((S)-5-chloro-8-((1-ethyl-1H-pyrazol-3-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-imidazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 5 (1S,2R)-2-((S)-5-chloro-8-((1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-fluoro-8-((1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 10 (1S,2R)-2-((S)-8-((1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-5-methyl-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-cyano-8-((1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 15 (1S,2R)-2-((S)-8-((1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-5-methoxy-1-((1-oxoisindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 20 (1S,2R)-2-((S)-8-((1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-oxoisindolin-2-yl)methyl)-5-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-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-carboxylic acid;
- 25 (1S,2R)-2-((S)-8-([1,2,4]triazolo[4,3-a]pyridin-3-ylmethoxy)-5-bromo-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 30 (1S,2R)-2-((S)-5-bromo-8-((5-methylthiazol-2-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (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)cyclohexane-1-carboxylic acid;
- 35 (1S,2R)-2-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-bromo-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-8-(benzo[d]isothiazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 40 (1S,2R)-2-((S)-5-chloro-8-((5-methylisothiazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-(isothiazol-3-ylmethoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;

- (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-carboxylic acid;
- (1S,2R)-2-((1S)-5-bromo-8-((1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 5 (1S,2R)-2-((S)-5-bromo-8-((1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-8-((1-isopropyl-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)cyclohexane-1-carboxylic acid;
- 10 (1S,2R)-2-((S)-5-bromo-8-((1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((S)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyridin-3-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 15 (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-ethyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (R)-4-((S)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-4-oxobutanoic acid;
- 20 1-(((S)-2-((1R,2S)-2-(2H-tetrazol-5-yl)cyclohexane-1-carbonyl)-8-(benzo[d]isoxazol-3-ylmethoxy)-5-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)pyrrolidin-2-one;
- (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)cyclohexane-1-carboxylic acid;
- 25 (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)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((4-methyl-1H-pyrazol-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- 30 (1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyrimidin-5-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;
- (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)cyclopentane-1-carboxylic acid;
- 35 (1R,2S)-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)cyclopentane-1-carboxylic acid;
- 40 (1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-(pyridazin-3-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid;

- (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)cyclohexane-1-carboxylic acid;
- 5 (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)cyclohexane-1-carboxylic acid;
- (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)-1-methylcyclohexane-1-carboxylic acid;
- 10 (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)cyclohexane-1-carboxylic acid;
- (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)cyclohexane-1-carboxylic acid;
- 15 (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)cyclohexane-1-carboxylic acid;
- (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)cyclohexane-1-carboxylic acid;
- 20 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)bicyclo[2.2.1]heptane-2-carboxylic acid;
- 25 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)tetrahydrofuran-2-carboxylic acid;
- (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)cyclohexane-1-carboxylic acid;
- 30 (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)cyclohexane-1-carboxylic acid;
- (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)-1-methylcyclohexane-1-carboxylic acid;
- 35 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)-4,4-difluorocyclopentane-1-carboxylic acid;
- (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)-1-methylcyclopentane-1-carboxylic acid;
- 40 (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)cyclohexane-1-carboxylic acid;

- (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)cyclohexane-1-carboxylic acid;
- 5 (1R,2S)-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)-1-fluorocyclohexane-1-carboxylic acid;
- (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)-1-methylcyclohexane-1-carboxylic acid;
- 10 (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)-1-methylcyclohexane-1-carboxylic acid;
- (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)-1-methylcyclohexane-1-carboxylic acid;
- 15 (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-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)-1-methylcyclopentane-1-carboxylic acid;
- (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-methylcyclopentane-1-carboxylic acid;
- 20 (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-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)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 25 (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclopentane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclopentane-1-carboxylic acid;
- 30 (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((S)-3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclopentane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((S)-3-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 35 (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((S)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclopentane-1-carboxylic acid;
- (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)-1-ethylcyclohexane-1-carboxylic acid;
- 40 (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)-1-ethylcyclopentane-1-carboxylic acid;
- 45 (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)-1-ethylcyclopentane-1-carboxylic acid;

- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-ethyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclopentane-1-carboxylic acid;
- 5 (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-ethyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 10 (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-isopropyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclopentane-1-carboxylic acid;
- (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-carboxylic acid;
- 15 (1S,2R)-2-((S)-5-chloro-8-((4,5-dimethylisoxazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((4-chloro-5-methylisoxazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 20 (1S,2R)-2-((S)-5-chloro-8-((4-methylisoxazol-5-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-(methoxymethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 25 (1S,2R)-2-((S)-5-chloro-8-((5-(2-methoxyethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 30 (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)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-1-(((S)-3-methyl-2-oxopyrrolidin-1-yl)methyl)-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 35 (1S,2R)-2-((S)-5-chloro-1-(((R)-3-methyl-2-oxopyrrolidin-1-yl)methyl)-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 40 (1S,2S)-2-((S)-5-chloro-1-(((R)-4-methyl-2-oxopyrrolidin-1-yl)methyl)-8-((1-methyl-5-(trifluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 45

- (1S,2R)-2-((S)-5-chloro-8-((1-cyclopropyl-5-(difluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 5 (1S,2R)-2-((S)-5-chloro-8-((4-(difluoromethyl)pyrimidin-5-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;
- (1S,2R)-2-((S)-5-chloro-8-((5,5-dimethyl-4,5-dihydroisoxazol-3-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;
- 10 (1S,2R)-2-((S)-5-chloro-8-((4-methylisoxazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-1-((2-oxopyrrolidin-1-yl)methyl)-8-((4,5,6,7-tetrahydrobenzo[d]isoxazol-3-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 15 (1S,2R)-2-((S)-8-((2,5-bis(difluoromethyl)-2H-1,2,3-triazol-4-yl)methoxy)-5-chloro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 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)tetrahydro-2H-pyran-3-carboxylic acid;
- 20 (R)-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)bicyclo[2.2.2]octane-1-carboxylic acid;
- 25 (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-carboxylic-4,4-d₂ acid;
- (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-carboxylic acid;
- 30 (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-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-(2-methoxyethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 35 (1S,2R)-2-((S)-5-chloro-8-((5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-3-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-carboxylic acid;
- 40 (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)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((1-methyl-2-oxo-1,2-dihydropyridin-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;
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- (1S,2S)-2-((S)-5-chloro-8-((5-(difluoromethyl)-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)-1-methylcyclohexane-1-carboxylic acid;
- 5 (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)-1-methylcyclohexane-1-carboxylic acid;
- 1-(((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-2-((1R,2S)-2-methyl-2-(2H-tetrazol-5-yl)cyclohexane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)pyrrolidin-2-one;
- 10 (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((4,4-dimethyl-2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (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)-1-methylcyclopentane-1-carboxylic acid;
- 15 (1S,2R)-2-((S)-5-chloro-8-((5-methyl-4-(trifluoromethyl)isoxazol-3-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;
- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-(2,2,2-trifluoroethyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 20 (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)-1-methylcyclohexane-1-carboxylic acid;
- 25 (1S,2R)-2-((S)-5-chloro-8-((4-(difluoromethyl)-5-methylisoxazol-3-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;
- (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)-1-methylcyclohexane-1-carboxylic acid;
- 30 (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)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-(methoxymethyl)-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-carboxylic acid;
- 35 (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)-1-methylcyclohexane-1-carboxylic acid;
- 40 (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)-1-methylcyclohexane-1-carboxylic acid;
- (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)-1-methylcyclohexane-1-carboxylic acid;
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- (1S,2R)-2-((1S)-5-chloro-8-((7-fluoro-2,7a-dihydrobenzo[d]isoxazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 5 (1S,2R)-2-((S)-5-chloro-8-((6,7-difluorobenzo[d]isoxazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-methylisoxazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 10 (1S,2R)-2-((S)-5-chloro-8-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-methyl-1,2,4-oxadiazol-3-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 15 (1S,2S)-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)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-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-carboxylic acid;
- 20 (1S,2R)-2-((S)-5-chloro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-8-((4-(trifluoromethyl)pyrimidin-5-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((1-cyclopropyl-5-(difluoromethyl)-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-carboxylic acid;
- 25 (1S,2R)-2-((S)-5-chloro-8-((1-(2-(dimethylamino)ethyl)-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-carboxylic acid;
- 30 (1S,2R)-1-methyl-2-((S)-5-methyl-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)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((4-methyl-4H-1,2,4-triazol-3-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;
- 35 (1S,2R)-2-((S)-5-chloro-8-((5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-3-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;
- (1S,2R)-2-((S)-5-chloro-8-((4-cyclopropyl-5-methyl-4H-1,2,4-triazol-3-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;
- 40 (1S,2R)-2-((S)-5-fluoro-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)-1-methylcyclohexane-1-carboxylic acid;
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- (1S,2R)-2-((S)-5-chloro-8-((4,5-dimethyl-4H-1,2,4-triazol-3-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;
- 5 (1S,2R)-2-((S)-5-chloro-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-methylcyclopentane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-3-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;
- 10 (1S,2R)-2-((S)-5-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-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-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;
- 15 (1S,2R)-2-((S)-5-chloro-8-((5-cyclopropyl-4-methyl-4H-1,2,4-triazol-3-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;
- (1S,2R)-2-((S)-5-chloro-8-((1-methyl-1H-imidazol-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;
- 20 (1S,2R)-2-((S)-5-chloro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-8-((5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-(((S)-1-(methylsulfonyl)pyrrolidin-3-yl)oxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 25 (1S,2R)-2-((S)-8-(((S)-1-acetylpyrrolidin-3-yl)oxy)-5-chloro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 30 (1S,2R)-2-((S)-5-chloro-8-((6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-3-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;
- (1S,2R)-1-methyl-2-((S)-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)cyclohexane-1-carboxylic acid;
- 35 (1S,2R)-2-((S)-5-bromo-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)-1-methylcyclohexane-1-carboxylic acid;
- 40 (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-(oxetan-3-yl)-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-carboxylic acid;
- (1S,2R)-2-((S)-8-((1,5-bis(difluoromethyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-chloro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
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- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((R)-2-methyl-5-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 5 (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-(((S)-2-methyl-5-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-1-((3-oxomorpholino)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-carboxylic acid;
- 10 (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)cyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-bromo-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-
- 15 tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((1-methyl-5-(oxetan-3-yl)-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-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((3-oxomorpholino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 20 (1S,6R)-6-((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-methylcyclohex-3-ene-1-carboxylic acid;
- 25 5-(((S)-2-((1R,2S)-2-(1H-tetrazol-5-yl)cyclohexane-1-carbonyl)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-5-azaspiro[2.4]heptan-6-one;
- (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-
- 30 tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((5-(difluoromethyl)thiazol-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;
- (1S,2R)-2-((S)-5-chloro-8-((5-methylthiazol-4-yl)methoxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-
- 35 methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((2-methyl-2H-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;
- 40 (1R,3S,4R,6S)-4-((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)-3-methylbicyclo[4.1.0]heptane-3-carboxylic acid;
- (1S,3S,4R,6R)-4-((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-
- 45 tetrahydroisoquinoline-2-carbonyl)-3-methylbicyclo[4.1.0]heptane-3-carboxylic acid;

- (1S,2R)-2-((1S)-5-chloro-8-((6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-7-yl)oxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- 5 (1S,2R,4S,5R)-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-carboxylic-4,5-d₂ acid;
- (1S,2R)-2-((S)-5-chloro-8-((1-methyl-2-oxo-1,2-dihydropyridin-3-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;
- 10 (1S,2R)-2-((1S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((2-oxo-4-(trifluoromethyl)pyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (1S,2R)-2-((S)-5-chloro-8-((1-methyl-6-oxo-1,6-dihydropyridin-2-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;
- 15 (1S,2R)-2-((1S)-5-chloro-8-((1-methyl-1,4,5,6-tetrahydrocyclopenta[d][1,2,3]triazol-5-yl)oxy)-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
- (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)-4,4-difluoro-1-methylcyclohexane-1-carboxylic acid;
- 20 (1S,2R,4S)-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)-4-fluoro-1-methylcyclohexane-1-carboxylic acid;
- 25 (1S,2R,4R)-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-carboxylic-4-d acid;
- (1S,2R,4S)-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)-4-hydroxy-1-methylcyclohexane-1-carboxylic acid;
- 30 (1S,2R,5S)-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)-5-hydroxy-1-methylcyclohexane-1-carboxylic acid;
- 35 (1S,2R,5R)-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)-5-hydroxy-1-methylcyclohexane-1-carboxylic acid;
- 40 (1S,2R,4R)-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)-4-hydroxy-1-methylcyclohexane-1-carboxylic acid;

- (2S,3R)-3-((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)tetrahydro-2H-pyran-2-carboxylic acid;
- 5 (1R,2R,6S)-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)-6-hydroxy-1-methylcyclohexane-1-carboxylic acid;
- 10 (1R,2R,6R)-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)-6-hydroxy-1-methylcyclohexane-1-carboxylic acid;
- 15 (1S,2S,3R)-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)-3-hydroxy-1-methylcyclohexane-1-carboxylic acid; and
- (1S,2S,3S)-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)-3-hydroxy-1-methylcyclohexane-1-carboxylic acid;
- 20 or a pharmaceutically acceptable salt thereof.
29. A pharmaceutical composition comprising a compound according to any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.
30. A compound according to any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 29, for use in therapy.
- 25 31. Use of a compound according to any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 29 in the manufacture of a medicament for the treatment of diseases or disorders mediated by Nrf2 activation.
- 30 32. Use of a compound according to any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 29 in the manufacture of a medicament for 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,
- 35 pulmonary fibrosis including idiopathic pulmonary fibrosis, cystic fibrosis, diabetes, atherosclerosis, hypertension, heart failure, myocardial infarction and repair, cardiac remodelling, cardiac arrhythmias, cardiac hypertrophy, heart failure with preserved ejection fraction, diabetic cardiomyopathy, 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, lung cancer, breast cancer, colon cancer, age related macular degeneration (AMD), Fuchs Endothelial Corneal Dystrophy or uveitis.