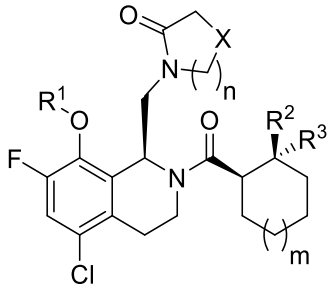
vision preservation in early AMD patients (Bellezza, Front Pharmacol. 2018; 9: 1280). In addition, Nrf2 activators may also be useful in other eye conditions such as Fuchs Endothelial Corneal Dystrophy and uveitis.

[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

[0015a] In a first aspect of the present disclosure, there is provided a compound according to Formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is C_{1-4}alkylene-R^4;

R^2 is selected from CO_2H and tetrazolyl;

R^3 is selected from hydrogen and methyl;

X is CR^5R^6 or O;

R^4 is 1,2,3-triazolyl, 1,2,4-triazolyl or pyrimidinyl, wherein said triazolyl or pyrimidinyl 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-C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy, and cyano; and

optionally fused to a cycloalkyl or heterocyclyl ring;

R^5 is selected from hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl and C_{1-3}haloalkyl; and

R^6 is selected from hydrogen and C_{1-4}alkyl; or

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

m is 0 or 1; and

n is 1 or 2;

provided that the compound of formula I is not one of the following compounds:

(1*S*,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-carboxylic acid;

(1*S*,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-carboxylic acid;

(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5,6-dihydro-4*H*-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;

(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)-1-methylcyclohexane-1-carboxylic acid; or

(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-carboxylic acid.

[0015b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0015c] In yet another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, for use in:

(a) therapy;

(b) the treatment of diseases or disorders mediated by Nrf2 activation; or

(c) 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.

[0015d] In a further aspect of the present disclosure, there is provided 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:

(a) the treatment of diseases or disorders mediated by Nrf2 activation; or

(b) 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.

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

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

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

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

[0020] In another example, the present disclosure relates to the use of a compound of the present 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.

[0021] 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 present disclosure 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 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, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Friedreich's ataxia, sickle cell disease or non-alcoholic steatohepatitis.

[0024] 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, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Friedreich's ataxia, sickle cell disease or non-alcoholic steatohepatitis.

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

[0027] In another example, the present disclosure 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 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.

[0029] 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.

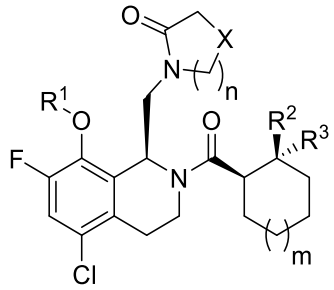
DETAILED DESCRIPTION OF THE INVENTION

Definitions

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

CLAIMS

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



(I)

wherein:

R^1 is C_{1-4}alkylene-R^4;

R^2 is selected from CO_2H and tetrazolyl;

R^3 is selected from hydrogen and methyl;

X is CR^5R^6 or O;

R^4 is 1,2,3-triazolyl, 1,2,4-triazolyl or pyrimidinyl, wherein said triazolyl or pyrimidinyl 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-C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy, and cyano; and

optionally fused to a cycloalkyl or heterocyclyl ring;

R^5 is selected from hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl and C_{1-3}haloalkyl; and

R^6 is selected from hydrogen and C_{1-4}alkyl; or

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

m is 0 or 1; and

n is 1 or 2;

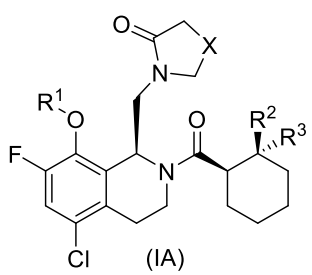
provided that the compound of formula I is not one of the following compounds:

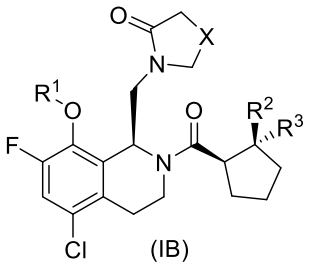
(1*S*,2*R*)-2-((*S*)-5-chloro-8-((1,5-dimethyl-1*H*-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;

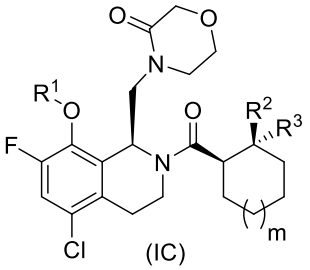
(1*S*,2*R*)-2-((*S*)-5-chloro-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-8-((4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyridin-3-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;

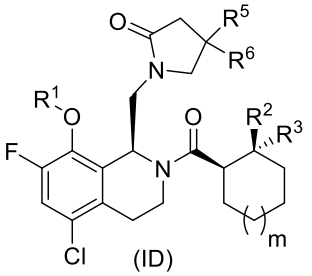
(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazol-3-yl)methoxy)-7-fluoro-1-((6-oxo-5-azaspiro[2.4]heptan-5-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid;
(1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-7-fluoro-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxylic acid; or
(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-carboxylic acid.

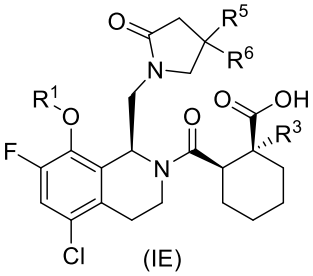
2. A compound according to claim 1, wherein said compound has one of the structural formulae IA to IK shown below:

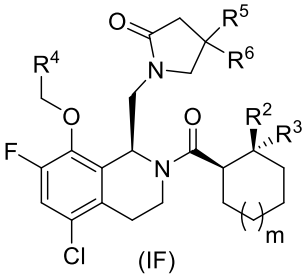

(IA)

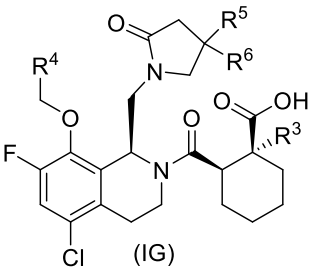

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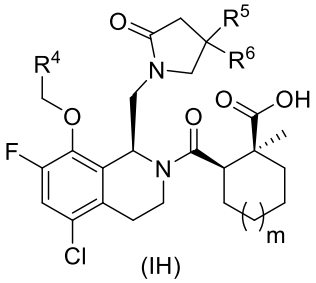

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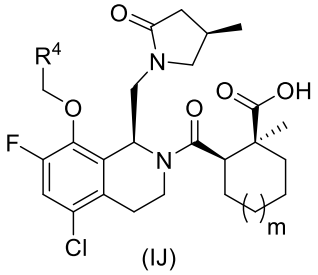

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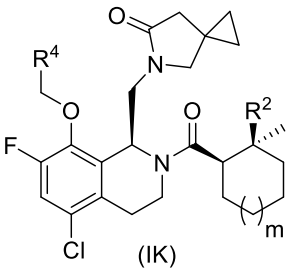

(IE)


(IF)


(IG)


(IH)


(IJ)


(IK)

,

wherein R^1 to R^6, X and m are as defined in claim 1.

3. A compound according to claim 1 or claim 2, wherein R^1 is CH_2-R^4.

4. A compound according to any one of claims 1 to 3, wherein R^2 is CO_2H.

5. A compound according to any one of claims 1 to 4, wherein R^3 is methyl.

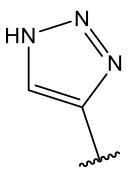
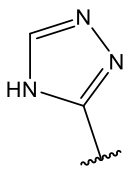
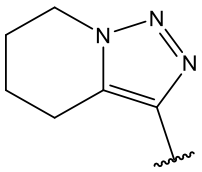
6. A compound according to any one of claims 1 to 5, wherein R^4 is:

(a) 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 and C_{1-4}alkylene-C_{3-7}cycloalkyl;

(b) 1,2,4-triazolyl 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-C_{3-7}cycloalkyl;

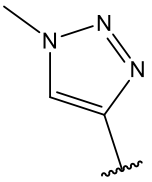
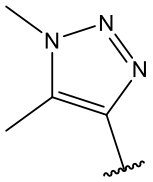
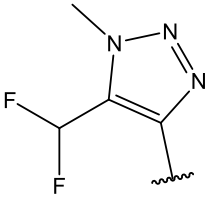
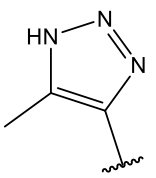
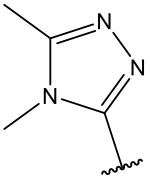
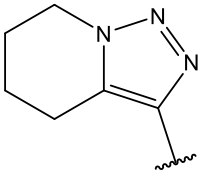
(c) pyrimidinyl optionally substituted with one or more substituents independently selected from C_{1-4}alkyl and C_{1-3}haloalkyl;

(d) selected from one of the following groups:



and

,

wherein said group is optionally substituted with C_{1-4}alkyl and C_{1-3}fluoroalkyl; or

(e) selected from one of the following groups:






and

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7. A compound according to any one of claims 1 to 6, wherein X is CR^5R^6.

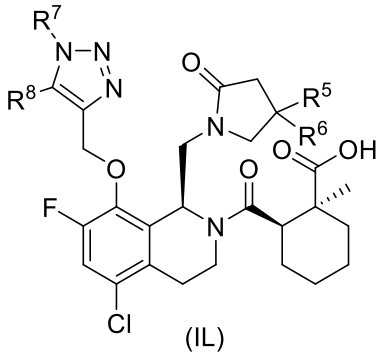
8. A compound according to any one of claims 1 to 7, wherein:

(a) R^5 is methyl and R^6 is hydrogen; or

(b) R^5 and R^6, together with the carbon atom to which they are attached, form a cyclopropyl ring.

9. A compound according to any one of claims 1 to 8, wherein m is 1.

10. A compound according to claim 1, wherein said compound has the structural formula IL shown below, or a pharmaceutically acceptable salt thereof:



(IL)

wherein R^5 and R^6 are as defined in claim 1 and R^7 and R^8 are independently selected from hydrogen, C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy and cyano; or R^7 and R^8, taken together with the atoms to which they are attached, form a 5- or 6-membered heterocyclyl ring.

11. A compound according to claim 10, wherein:

(a) R^5 is methyl and R^6 is hydrogen; or

(b) R^5 and R^6, together with the carbon atom to which they are attached, form a cyclopropyl ring.

12. A compound according to claim 10 or claim 11, wherein R^7 is methyl and R^8 is hydrogen, methyl, or difluoromethyl.

13. A compound according to claim 1, which is selected from:

5-(((S)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-7-fluoro-2-((1R,2S)-2-methyl-2-(1H-tetrazol-5-yl)cyclohexane-1-carbonyl)-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-((3-oxomorpholino)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)-7-fluoro-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-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-methylcyclopentane-1-carboxylic acid;

(1S,2R)-2-((S)-5-chloro-8-((4,5-dimethyl-4H-1,2,4-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;

(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)-1-methylcyclohexane-1-carboxylic acid; and

(1*S*,2*R*)-2-((S)-5-chloro-7-fluoro-8-((5-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;

or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

15. A compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 14, for use in:

(a) therapy;

(b) the treatment of diseases or disorders mediated by Nrf2 activation; or

(c) 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.

16. Use of a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 14, in the manufacture of a medicament for:

(a) the treatment of diseases or disorders mediated by Nrf2 activation; or

(b) 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.