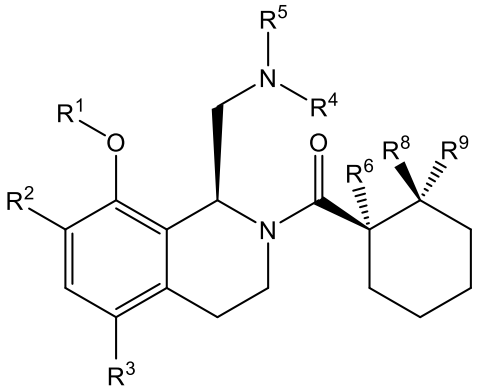
vision preservation in early AMD patients (Bellezza, Front Pharmacol. 2018; 9: 1280). In addition, Nrf2 activators may also be useful in other eye conditions such as Fuchs Endothelial Corneal Dystrophy and uveitis.

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

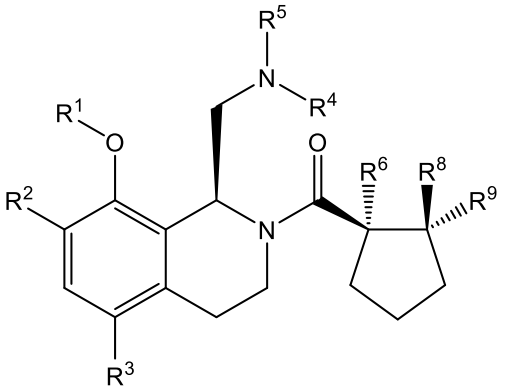
[0015] Therefore, there is an ongoing need for agents capable of Nrf2 activation, given the role of Nrf2 in multiple indications.

SUMMARY ~~OF THE INVENTION~~

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



(IC)



(IF)

wherein:

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

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

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

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

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

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

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

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

optionally is fused to an aryl or heteroaryl ring;

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

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

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

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

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

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

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

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

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

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

R^9 is methyl;

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

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

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

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

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

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

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

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

R^{29} is selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-3}haloalkyl, aryl and heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more

substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{46} halo, OH, C_{1-3}alkoxy and cyano;

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

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

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

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

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

R^{14}, R^{15}, R^{16}, R^{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;

provided that the compound is not (1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide.

[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 ~~aspect~~example, the present ~~invention~~disclosure provides a compound, or a pharmaceutically acceptable salt thereof as defined herein.

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

[0018] In another ~~aspect~~example, the present ~~invention~~disclosure relates to a compound of the ~~invention~~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 ~~aspect~~example, the present ~~invention~~disclosure relates to a compound of the ~~invention~~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 ~~aspect~~example, the present ~~invention~~disclosure relates to the use of a compound of the ~~invention~~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 ~~aspect~~example, the present ~~invention~~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 ~~invention~~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 ~~aspect~~example, the present ~~invention~~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 ~~aspect~~example, the present ~~invention~~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 ~~aspect~~example, the present ~~invention~~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 ~~invention~~disclosure further provides a method of synthesising a compound, or a pharmaceutically acceptable salt thereof, as defined herein.

[0027] In another ~~aspect~~example, the present ~~invention~~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 ~~aspect~~example, the present ~~invention~~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 ~~aspect~~example of the present ~~invention~~disclosure are also preferred, suitable, and optional features of any other ~~aspect~~example.

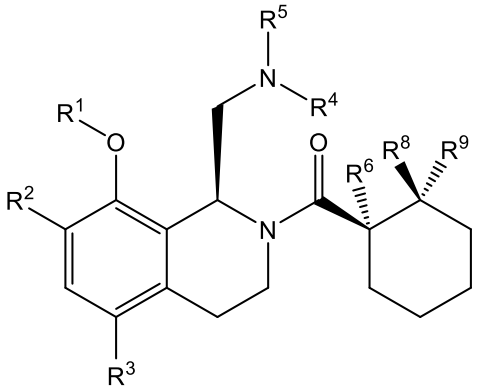
DETAILED DESCRIPTION OF THE INVENTION

Definitions

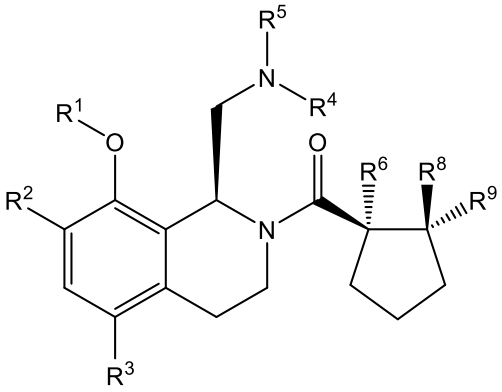
[0030] Unless otherwise stated, the following terms used in the specification and claims

CLAIMS

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



(IC)



(IF)

wherein:

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

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

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

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

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

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

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

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

optionally is fused to an aryl or heteroaryl ring;

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

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

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

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

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

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

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

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

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

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

R^9 is methyl;

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

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

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

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

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

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

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

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

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

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

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

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

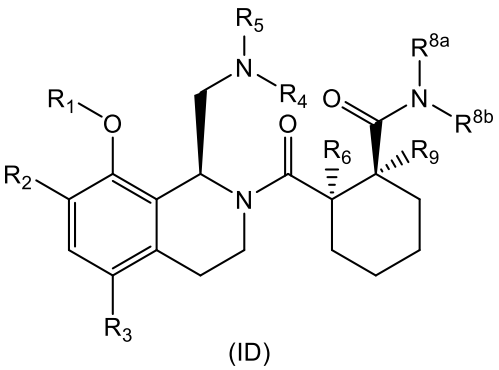
R^{40} and R^{41}, taken together with the nitrogen atom to which they are attached, form a 4-, 5-, or 6-membered heteroaryl or heterocyclyl ring, wherein said heteroaryl and heterocyclyl rings are optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH,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

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

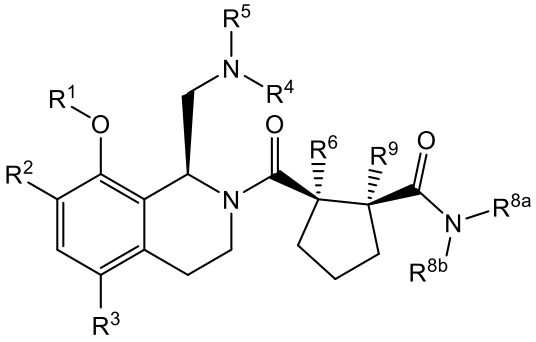
R^{14}, R^{15}, R^{16}, R^{26}, R^{28}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{42}, R^{43}, R^{44}, R^{47} and R^{48} are independently selected from hydrogen, C_{1-4}alkyl and C_{3-7}cycloalkyl;

provided that the compound is not (1*S*,2*R*)-2-((*S*)-5-chloro-8-((5-(difluoromethyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-((2-oxopyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1-methylcyclohexane-1-carboxamide.

2. A compound according to claim 1, wherein said compound has the structural formulae ID or IG shown below:



(ID)



(IG)

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

3. A compound according to claim 1 or 2, wherein R^1 is C_{1-4}alkylene-R^{11}, such as CH_2-R^{11}.

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

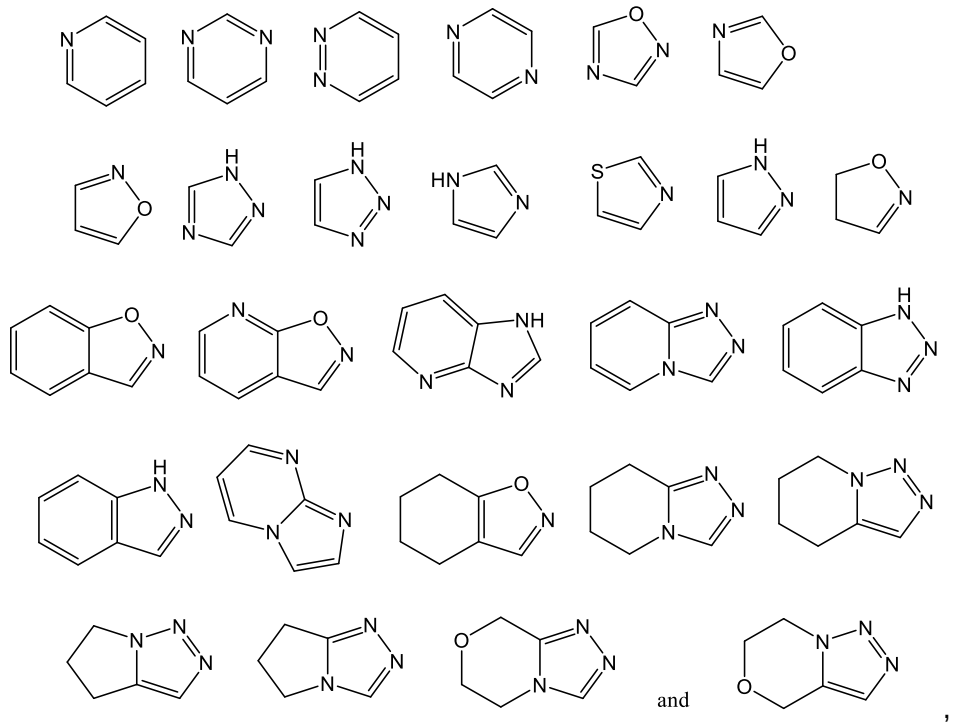
~~5. A compound according to any one of claims 1 to 4, wherein R^{11} is~~ (b) heteroaryl optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocyclyl and cyano;

~~6. A compound according to any one of claims 1 to 5, wherein R^{11} is~~ (c) heteroaryl optionally substituted with one or more substituents independently selected from methyl, ethyl, isopropyl, difluoromethyl, trifluoromethyl, chloro, fluoro, cyclopropyl, methoxy, CH_2-R^{30} and CH_2CH_2-R^{30};

~~7. A compound according to any one of claims 1 to 5, wherein R^{11} is~~ (d) pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, oxazolyl, isoxazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, indazolyl, benzotriazolyl, benzisoxazolyl,

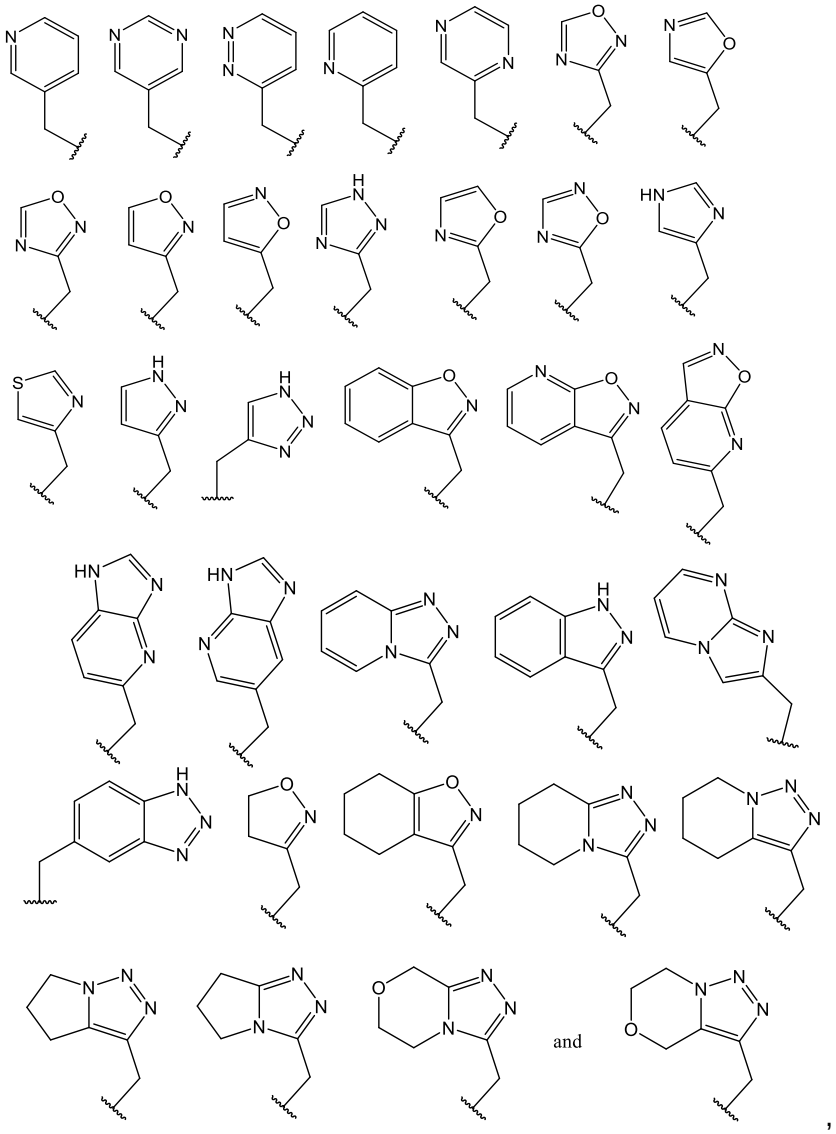
isoxazolopyridinyl, imidazopyridinyl or triazolopyridinyl, each optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, C_{1-4}alkylene-R^{30}, halo, OH, C_{1-3}alkoxy, heterocyclyl and cyano; or.

8. A compound according to any one of claims 1 to 5, wherein R^{11} is (e) heteroaryl selected from:



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

9.5. A compound according to claim 1 or 2, wherein R^1 is: (a) selected from one of the following groups:



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

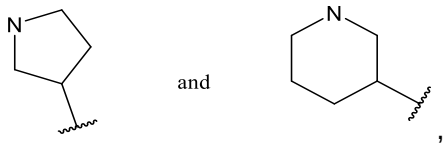
10. A compound according to claim 1 or 2, wherein R^1 is (b) heterocyclyl optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, -C(O)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy and cyano;

11. A compound according to claim 1 or 2, wherein R^1 is (c) piperidinyl or pyrrolidinyl, each optionally substituted with one or more substituents independently selected from -C(O)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl

is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, halo, OH, C_{1-3}alkoxy and cyano;~~.~~

~~12. A compound according to claim 11, wherein R^1 is~~ (d) pyrrolidinyl optionally substituted with one or more substituents independently selected from -C(O)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl is optionally substituted with C_{1-4}alkyl or C_{3-7}cycloalkyl; or~~.~~

~~13. A compound according to claim 1 or 2, wherein R^1 is~~ (e) 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)-R^{12}, SO_2-R^{13}, heteroaryl and C_{1-3}alkylene-OR^{14}, wherein said heteroaryl is optionally substituted with C_{1-4}alkyl or C_{3-7}cycloalkyl.

~~14.~~6. A compound according to any one of claims 1 to ~~5~~13, wherein R^2 is hydrogen or fluoro.

~~15.~~7. A compound according to any one of claims 1 to ~~6~~14, wherein R^3 is hydrogen or chloro, such as chloro.

~~16. A compound according to any one of claims 1 to 14, wherein R^3 is chloro.~~

~~17.~~8. A compound according to any one of claims 1 to ~~7~~16, wherein R^4 is hydrogen and R^5 is -C(O)-C_{1-4}alkyl, -C(O)-C_{3-7}cycloalkyl, or -C(O)-aryl, wherein said aryl is optionally substituted with one or more substituents selected from C_{1-4}alkyl, halo, hydroxy, C_{1-3}alkoxy, CO_2R^{15} and cyano.

~~18.~~9. A compound according to any one of claims 1 to ~~7~~16, wherein R^4 and R^5, taken together with the nitrogen atom to which they are attached;~~,~~ (a) form a 5-, or 6-membered heterocyclyl ring, wherein said heterocyclyl ring:

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

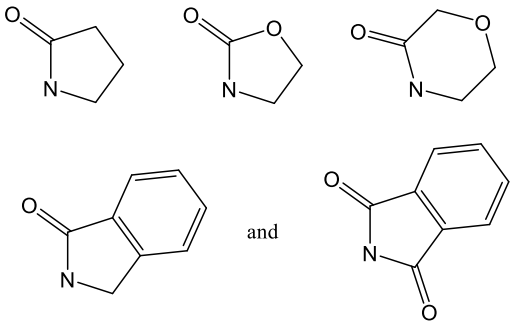
optionally contains one or more additional heteroatoms selected from oxygen, nitrogen and sulfur;

optionally is fused to an aryl ring;

optionally is spiro-attached to a C_{3-7}cycloalkyl group or a 3- to 5-membered heterocyclyl ring; and

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

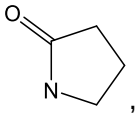
~~19. A compound according to any one of claims 1 to 16, wherein R^4 and R^5, taken together with the nitrogen atom to which they are attached,~~ (b) form a heterocyclic moiety selected from one of the following:



,

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

~~20. A compound according to any one of claims 1 to 16, wherein R^4 and R^5, taken together with the nitrogen atom to which they are attached,~~ (c) form the following heterocyclic moiety:



,

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

~~21.~~10. A compound according to any one of claims 1 to ~~9~~20, wherein R^6 is hydrogen.

~~22.~~11. A compound according to any one of claims 1 to 10~~21~~, wherein R^8 is $C(=O)NR^{8a}R^{8b}$.

~~23.~~12. A compound according to claim 11~~22~~, wherein R^{8a} is hydrogen.

~~24.~~13. A compound according to claim ~~22 or 23~~11 or 12, wherein R^{8b} is:

(a) hydrogen, C_{1-4}alkyl or C_{3-5}cycloalkyl, wherein the C_{1-4}alkyl group is optionally

substituted with one or more substituents independently selected from halo, OH, C_{1-3}alkoxy, C_{3-7}cycloalkyl and cyano;~~.~~

~~25. A compound according to claim 22 or 23, wherein R^{8b} is~~ (b) C_{1-4}alkyl or C_{3-5}cycloalkyl, wherein the C_{1-4}alkyl group is optionally substituted with one or more substituents independently selected from fluoro, OH, C_{1-3}alkoxy, C_{3-7}cycloalkyl and cyano; or~~.~~

~~26. A compound according to claim 25, wherein R^{8b} is~~ (c) methyl.

~~27.~~14. A compound according to claim 11~~22~~, wherein R^{8a} and R^{8b}, taken together with the nitrogen atom to which they are attached, form a 4-, or 5-membered heterocyclyl ring, wherein the heterocyclyl ring is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, halo, OH, C_{1-3}alkoxy, C_{1-3}haloalkyl, C_{3-7}cycloalkyl, cyano, $NR^{16}R^{17}$, $C(O)R^{18}$, $S(O)R^{19}$ and SO_2R^{20}.

~~28.~~15. A compound according to claim 1 or claims 3 to 10~~21~~, wherein R^{8c} is C_{1-3}fluoroalkyl.

~~29.~~16. A compound according to claim 1, which is selected from any one of the following:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

or a pharmaceutically acceptable salt thereof.

~~30.~~17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16~~29~~, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

~~31.~~18. A compound according to any one of claims 1 to 16~~29~~, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 17~~30~~, for use in: (a) therapy;~~.~~

~~32. A compound according to any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 30, for use in~~ (b) the treatment of diseases or disorders mediated by Nrf2 activation; or ~~.~~

~~33. A compound according to any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 30, for use in~~ (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.

~~34.~~19. Use of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 17, in the manufacture of a medicament for: (a) the treatment of diseases or disorders mediated by Nrf2 activation; or (b) the treatment of ~~A method of treating a disease or disorder selected from~~ 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~~and~~ preeclampsia~~, said method comprising administering to a subject in need of such a treatment a therapeutically effective amount of a compound according to any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof~~.