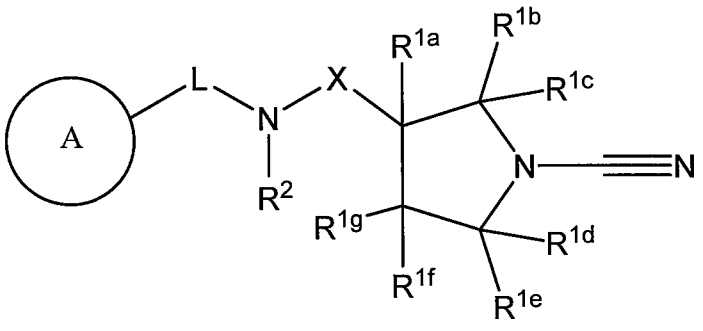
Claims

1. A compound of formula (I):



(I)

a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein:

R^{1b}, R^{1c}, R^{1d}, R^{1e} each independently represent hydrogen or C_1-C_6 alkyl, or R^{1b} is linked to R^{1a} or R^{1c} to form a 3 to 6-membered cycloalkyl ring, or R^{1e} is linked to R^{1d} or R^{1f} to form a 3 to 6-membered cycloalkyl ring;

R^{1a} and R^{1g} each independently represent hydrogen, fluorine, cyano, hydroxyl, amino, C_1-C_6 alkyl, or C_1-C_6 alkoxy, or R^{1a} and R^{1g} together form a 3 to 6-membered cycloalkyl ring, or R^{1a} is linked to R^{1b} to form a 3 to 6-membered cycloalkyl ring, or R^{1g} is linked to R^{1f} to form a 3 to 6-membered cycloalkyl ring;

R^{1f} represents hydrogen, fluorine, cyano, hydroxyl, amino, C_1-C_6 alkyl, or C_1-C_6 alkoxy, or R^{1f} is linked to R^{1g} or R^{1e} to form a 3 to 6-membered cycloalkyl ring, or R^{1f} together with R^2 forms a 5 to 7-membered heterocyclic ring;

R^2 represents hydrogen or C_1-C_6 alkyl, or R^2 together with R^{1f} forms a 5 to 7-membered heterocyclic ring;

X is $C(R^3)(R^4)$, wherein R^3 and R^4 each independently represent hydrogen, cyano, C_1-C_6 alkyl, a 5 or 6-membered heteroaryl or aryl ring, or R^3 and R^4 together form a 3 to 6-membered heterocyclyl or cycloalkyl ring;

L represents a covalent bond, -SO-, -SO_2-, -C(O)-, -C(O)O-, -$CONR^5$-, -SO_2NR^5-, -C(O)-C_1-C_6 alkylene, -C(O)-C_2-C_6 alkenylene, C_1-C_6 alkylene-C(O)-, C_2-C_6 alkenylene-C(O)-, -C_1-C_6 alkylene-NR^5CO-, -C_1-C_6 alkylene-$CONR^5$-, C_1-C_6 alkylene, or -C_2-C_6 alkenylene;

A represents a substituted 5 to 10-membered monocyclic, heteroaryl or aryl ring, or an optionally substituted 5 to 10-membered bicyclic, heteroaryl or aryl ring;

R^5 represents hydrogen or C_1-C_6 alkyl;

wherein ring A, when substituted, is substituted with one to four $-Q^1-(R^6)_n$, wherein each occurrence of $-Q^1-(R^6)_n$ is the same or different;

n is 0 or 1;

Q^1 represents halogen, cyano, oxo, nitro, $-OR^7$, $-SR^7$, $-NR^7R^8$, $-CONR^7R^8$, $-NR^7COR^8$, $-NR^7CONR^8R^9$, $-COR^7$, $-C(O)OR^7$, $-SO_2R^7$, $-SO_2NR^7R^8$, $-NR^7SO_2R^8$, $NR^7SO_2NR^8R^9$, $-NR^7C(O)OR^8$, $-C_1$-C_6 alkyl, $-C_1$-C_6 alkoxy,$-C_2$-C_6 alkenyl,$-C_2$-C_6 alkynyl, a covalent bond, an oxygen atom, a sulphur atom, -SO-, $-SO_2$-, -C(O)-, -C(O)O-, $-CONR^7$-, $-NR^7$-, $-NR^7CO$-, $-NR^7CONR^8$-, $-SO_2NR^7$-, $-NR^7SO_2$-, $-NR^7SO_2NR^8$-, $-NR^7C(O)O$-, $-NR^7C(O)OR^8$-, C_1-C_6 alkylene, or $-C_2$-C_6 alkenylene;

R^6 is a 3 to 10-membered heterocyclyl, cycloalkyl, heteroaryl, or aryl ring;

R^7, R^8 and R^9 each independently represent hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkylene;

wherein R^6 is optionally substituted with one to four substituents, each independently selected from halogen, cyano, oxo, nitro, $-OR^{10}$, $-SR^{10}$, $-NR^{10}R^{11}$, $-CONR^{10}R^{11}$, $-NR^{10}COR^{11}$, $-NR^{10}CONR^{11}R^{12}$, $-COR^{10}$, $-C(O)OR^{10}$, $-SO_2R^{10}$, $-SO_2NR^{10}R^{11}$, $-NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{11}R^{12}$, $-NR^{10}C(O)OR^{11}$, $-C_1$-C_6 alkyl, $-C_1$-C_6 alkoxy,$-C_2$-C_6 alkenyl, $-C_2$-C_6 alkynyl, $-Q^2-R^{10}$, $-Q^2-NR^{10}CONR^{11}R^{12}$, $-Q^2-NR^{10}R^{11}$, $-Q^2-COR^{10}$, $-Q^2-NR^{10}COR^{11}$, $-Q^2-NR^{10}C(O)OR^{11}$, $-Q^2-SO_2R^{10}$, $Q^2-CONR^{10}R^{11}$, $-Q^2-CO_2R^{10}$, $-Q^2-SO_2NR^{10}R^{11}$, $-Q^2-NR^{10}SO_2R^{11}$, and $-Q^2-NR^{10}SO_2NR^{11}R^{12}$;

Q^2 represents a covalent bond, an oxygen atom, a sulphur atom, -SO-, $-SO_2$-, -CO-, C_1-C_6 alkylene, or C_2-C_6 alkenylene;

R^{10}, R^{11} and R^{12} each independently represent hydrogen or C_1-C_6 alkyl;

wherein each cycloalkyl ring formed by two of R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f} and R^{1g}, together, is independently, optionally further substituted with one to four substituents, each independently selected from fluorine, chlorine, oxo, cyano, C_1-C_3 alkyl, and C_1-C_3 alkoxy;

wherein the heterocyclic ring formed by R^{1f} together with R^2 is optionally further substituted with one to four substituents, each independently selected from fluorine, oxo, cyano, hydroxyl, amino, C_1-C_6 alkyl, and C_1-C_6 alkoxy; and

wherein said C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkylene and C_2-C_6 alkenylene, are each independently optionally substituted with one to four substituents, each independently selected from halogen, hydroxyl, thiol, cyano, amino, nitro, and SF_5.

2. The compound according to claim 1, wherein R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently hydrogen or C_1-C_3 alkyl.

3. The compound according to claim 1, wherein R^{1a} and R^{1g} are each independently hydrogen, fluorine, or C_1-C_6 alkyl.

4. The compound according to any one of claims 1 to 3, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f}, and R^{1g} are each hydrogen.

5. The compound according to any one of claims 1 to 4, wherein R^2 is hydrogen or methyl.

6. The compound according to claim 1, wherein X is CH_2, CHCN, or CHMe.

7. The compound according to claim 1, wherein L is a covalent bond, -SO_2-, -C(O)-, -C(O)-C_1-C_6 alkylene, -C(O)-C_2-C_6 alkenylene, or –$CONR^5$-, wherein R^5 is hydrogen or methyl.

8. The compound according to any one of claims 1 to 7, wherein the ring of A is a 5 or 6-membered heteroaryl or aryl ring.

9. The compound according to claim 8, wherein the ring of A is selected from oxazolyl, isoxazolyl, pyrazolyl, thiazolyl, pyridinyl, pyrimidinyl, phenyl, imidazolyl, and oxadiazolyl.

10. The compound according to any one of claims 1 to 7, wherein the ring of A is a 9 or 10-membered bicyclic heteroaryl or aryl ring.

11. The compound according to claim 10, wherein the ring of A is selected from quinolinyl, benzothiazolyl, isoquinolinyl, benzomorpholinyl, indazolyl, imidazopyridinyl, quinazolinyl, pyrazolopyridinyl, and benzimidazolyl.

12. The compound according to claim 1, wherein when n is 0, Q^1 is selected from halogen, cyano, oxo, -$CONR^7R^8$, -NR^7COR^8, -C_1-C_6 alkyl, and -C_1-C_6 alkoxy, wherein said alkyl and alkoxy may be optionally substituted with one to four halogen; and

when n is 1, Q^1 is selected from a covalent bond, an oxygen atom, and methylene.

13. The compound according to claim 1, wherein the ring of R^6 is a selected from phenyl, thiazolyl, pyridinyl, pyrrolidinyl pyrazolyl, isoindolyl, isoxazolyl, and cyclopropyl.

14. The compound according to claim 1, wherein R^6 is substituted with halogen, cyano, C_1-C_4 alkyl, or C_1-C_4 alkoxy, wherein the alkyl and alkoxy is optionally substituted with one or more fluorine.

15. A compound according to claim 1 selected from the group consisting of:
3-((quinolin-2-ylamino)methyl)pyrrolidine-1-carbonitrile;
3-(((6-fluorobenzo[d]thiazol-2-yl)amino)methyl)pyrrolidine-1-carbonitrile;
3-((isoquinolin-1-ylamino)methyl)pyrrolidine-1-carbonitrile;
3-(((6-(1H-pyrazol-4-yl)benzo[d]thiazol-2-yl)amino)methyl)pyrrolidine-1-carbonitrile;
(R)-3-(((7-(1H-pyrazol-4-yl)quinazolin-2-yl)amino)methyl)pyrrolidine-1-carbonitrile;
3-(((3-(1,3-dimethyl-1H-pyrazol-4-yl)phenyl)amino)methyl)pyrrolidine-1-carbonitrile;
3-(((4-(1,3-dimethyl-1H-pyrazol-4-yl)phenyl)amino)methyl)pyrrolidine-1-carbonitrile;
3-(((4-(1,3-dimethyl-1H-pyrazol-4-yl)-2-fluorophenyl)amino)methyl)pyrrolidine-1-carbonitrile;
3-(((1-cyanopyrrolidin-3-yl)methyl)amino)isoquinoline-6-carbonitrile;
3-(((1-cyanopyrrolidin-3-yl)methyl)amino)-N-methylisoquinoline-6-carboxamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-4-(pyridin-4-yl)benzamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-1-(2,4-dichlorobenzyl)-1H-indazole-3-carboxamide;
1-benzyl-N-((1-cyanopyrrolidin-3-yl)methyl)-1H-indazole-3-carboxamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-4-(N-phenylsulfamoyl)benzamide;
(E)-N-((1-cyanopyrrolidin-3-yl)methyl)-3-(2-fluoro-4-methoxyphenyl)acrylamide;
(S)-N-((1-cyanopyrrolidin-3-yl)methyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide;
(R)-6-chloro-N-((1-cyanopyrrolidin-3-yl)methyl)imidazo[1,2-a]pyridine-2-carboxamide;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)pyrazolo[1,5-a]pyridine-2-carboxamide;
2-([1,1'-biphenyl]-4-yl)-N-((1-cyanopyrrolidin-3-yl)methyl)-N-methylacetamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide;
1-(3-chlorophenyl)-3-((1-cyanopyrrolidin-3-yl)methyl)urea;
1-((1-cyanopyrrolidin-3-yl)methyl)-3-(2-fluoro-5-methylphenyl)urea;
1-(3-benzylphenyl)-3-((1-cyanopyrrolidin-3-yl)methyl)urea;
1-((1-cyanopyrrolidin-3-yl)methyl)-3-(2,4-dichlorophenyl)urea;
1-((1-cyanopyrrolidin-3-yl)methyl)-3-(4-(trifluoromethyl)phenyl)urea;
N-((1-cyanopyrrolidin-3-yl)methyl)-N-methyl-3-(2-methylthiazol-4-yl)benzenesulfonamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-N-methyl-4-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzenesulfonamide;
3-(1-((6-(1H-pyrazol-4-yl)benzo[d]thiazol-2-yl)amino)ethyl)pyrrolidine-1-carbonitrile;
3-(1-(isoquinolin-3-ylamino)ethyl)pyrrolidine-1-carbonitrile;

3-((1-(1-cyanopyrrolidin-3-yl)ethyl)amino)isoquinoline-6-carbonitrile;
3-((benzo[d]thiazol-2-ylamino)(cyano)methyl)pyrrolidine-1-carbonitrile;
2-((1-(1-cyanopyrrolidin-3-yl)ethyl)amino)benzo[d]thiazole-6-carbonitrile;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-1H-benzo[d]imidazole-2-carboxamide;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)isoquinoline-3-carboxamide;
(R)-7-chloro-N-((1-cyanopyrrolidin-3-yl)methyl)imidazo[1,2-a]pyridine-2-carboxamide;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-6-(1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide;
and
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-7-cyclopropylimidazo[1,2-a]pyridine-2-carboxamide;
a tautomer thereof, or pharmaceutically acceptable salt of said compound or tautomer.

16. A compound according to claim 1 selected from the group consisting of:
(R)-3-(((5-phenylthiazol-2-yl)amino)methyl)pyrrolidine-1-carbonitrile;
(S)-3-(((5-phenylthiazol-2-yl)amino)methyl)pyrrolidine-1-carbonitrile;
N-((1-cyanopyrrolidin-3-yl)methyl)-2-phenyloxazole-5-carboxamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-3-phenylisoxazole-5-carboxamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-5-phenyl-1H-pyrazole-3-carboxamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-3-(o-tolyl)-1H-pyrazole-5-carboxamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-2-phenylthiazole-4-carboxamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-3-(2-fluorophenyl)-1H-pyrazole-5-carboxamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-5-phenyloxazole-2-carboxamide;
1-benzyl-N-((1-cyanopyrrolidin-3-yl)methyl)-5-methyl-1H-pyrazole-3-carboxamide;
3-(1-((6-(5-methylisoxazol-4-yl)benzo[d]thiazol-2-yl)amino)ethyl)pyrrolidine-1-carbonitrile;
(3aR,6aS)-4-oxo-5-(5-phenylthiazol-2-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carbonitrile;
(R)-3-(3-chlorophenyl)-N-((1-cyanopyrrolidin-3-yl)methyl)isoxazole-5-carboxamide;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-5-phenylisoxazole-3-carboxamide;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-5-phenylthiazole-2-carboxamide;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-4-phenylthiazole-2-carboxamide;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-1-phenyl-1H-pyrazole-3-carboxamide;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-2-phenyl-1H-imidazole-5-carboxamide;
(R)-3-(2-chlorophenyl)-N-((1-cyanopyrrolidin-3-yl)methyl)isoxazole-5-carboxamide;
(R)-3-(4-chlorophenyl)-N-((1-cyanopyrrolidin-3-yl)methyl)isoxazole-5-carboxamide;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-1-phenyl-1H-imidazole-4-carboxamide;
(R)-1-(3-cyanophenyl)-N-((1-cyanopyrrolidin-3-yl)methyl)-1H-imidazole-4-carboxamide;
(R)-1-(4-cyanophenyl)-N-((1-cyanopyrrolidin-3-yl)methyl)-1H-imidazole-4-carboxamide;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-1-(2-methoxyphenyl)-1H-imidazole-4-carboxamide;

(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-1-(3-methoxyphenyl)-1H-imidazole-4-carboxamide;
(R)-1-benzyl-N-((1-cyanopyrrolidin-3-yl)methyl)-1H-imidazole-4-carboxamide; and
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-1-(cyclopropylmethyl)-1H-imidazole-4-carboxamide;
a tautomer thereof, or pharmaceutically acceptable salt of said compound or tautomer.

17. A compound according to claim 1 selected from the group consisting of:
(R)-5-(3-cyanophenyl)-N-((1-cyanopyrrolidin-3-yl)methyl)-1,3,4-oxadiazole-2-carboxamide; and
(S)-5-(3-cyanophenyl)-N-((1-cyanopyrrolidin-3-yl)methyl)-1,3,4-oxadiazole-2-carboxamide;
a tautomer thereof, or pharmaceutically acceptable salt of said compound or tautomer.

18. A compound according to claim 1 selected from the group consisting of:
3-(((3-phenylpyridin-2-yl)amino)methyl)pyrrolidine-1-carbonitrile;
3-(((4-phenylpyridin-2-yl)amino)methyl)pyrrolidine-1-carbonitrile;
3-(((5-phenylpyridin-2-yl)amino)methyl)pyrrolidine-1-carbonitrile;
3-(((6-phenylpyridin-2-yl)amino)methyl)pyrrolidine-1-carbonitrile;
3-(((4-phenylpyrimidin-2-yl)amino)methyl)pyrrolidine-1-carbonitrile;
3-(((2-(isoindolin-2-yl)pyridin-4-yl)amino)methyl)pyrrolidine-1-carbonitrile;
(S)-3-(((4-phenylpyrimidin-2-yl)amino)methyl)pyrrolidine-1-carbonitrile;
N-((1-cyanopyrrolidin-3-yl)methyl)-4-(pyrrolidin-1-yl)picolinamide;
N-((1-cyanopyrrolidin-3-yl)methyl)-5-(4-fluorophenyl)nicotinamide;
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-4-phenylpicolinamide; and
(R)-N-((1-cyanopyrrolidin-3-yl)methyl)-5-phenylpicolinamide;
a tautomer thereof, or pharmaceutically acceptable salt of said compound or tautomer.

19. Use of a compound according to any one of claims 1 to 18, a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, in the manufacture of a medicament.

20. Use of a compound according to any one of claims 1 to 18, a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, in the manufacture of a medicament for the treatment of a condition involving mitochondrial dysfunction selected from a neurodegenerative disease; multiple sclerosis, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes syndrome; Leber's hereditary optic neuropathy; cancer; neuropathy, ataxia, retinitis pigmentosa-maternally inherited Leigh syndrome; Danon disease; diabetes; diabetic nephropathy; metabolic disorders; heart failure; ischemic heart disease leading to myocardial infarction; psychiatric diseases, schizophrenia; multiple sulfatase deficiency; mucolipidosis II; mucolipidosis III; mucolipidosis IV; GMl-gangliosidosis; neuronal ceroid-lipofuscinoses; Alpers disease; Barth syndrome; Beta-oxidation defects; carnitine-acyl-carnitine deficiency; carnitine deficiency; creatine deficiency syndromes; co-enzyme Q10 deficiency; complex I deficiency;

complex II deficiency; complex III deficiency; complex IV deficiency; complex V deficiency; COX deficiency; chronic progressive external ophthalmoplegia syndrome; CPT I deficiency; CPT II deficiency; glutaric aciduria type II; Kearns-Sayre syndrome; lactic acidosis; long-chain acyl-CoA dehydrogenase deficiency; Leigh disease or syndrome; lethal infantile cardiomyopathy; Luft disease; glutaric aciduria type II; medium-chain acyl-CoA dehydrogenase deficiency; myoclonic epilepsy and ragged-red fiber syndrome; mitochondrial cytopathy; mitochondrial recessive ataxia syndrome; mitochondrial DNA depletion syndrome; myoneurogastrointestinal disorder and encephalopathy; Pearson syndrome; pyruvate dehydrogenase deficiency; pyruvate carboxylase deficiency; POLG mutations; medium/short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; very long-chain acyl-CoA dehydrogenase deficiency; and age-dependent decline in cognitive function and muscle strength.

21. Use of a compound according to claim 20, wherein the neurodegenerative disease is selected from Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, ischemia, stroke, dementia with Lewy bodies, and frontotemporal dementia; and Parkinson's disease related to mutations in α-synuclein, parkin, and PINK1, and autosomal recessive juvenile Parkinson's disease, where parkin is mutated.

22. Use of a compound according to any one of claims 1 to 18, a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, in the manufacture of a medicament for the treatment of cancer.

23. Use of a compound according to claim 22, wherein the cancer is selected from breast, ovarian, prostate, lung, kidney, gastric, colon, testicular, head and neck, pancreas, brain, melanoma, bone, cancers of tissue organs, cancers of the blood cells, leukaemia, lymphoma, multiple myeloma, colorectal cancer, non-small cell lung carcinoma, cancer where apoptotic pathways are dysregulated, and cancer where proteins of the BCL-2 family are mutated, or over or under expressed.

24. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 18, a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, together with one or more pharmaceutically acceptable excipients.