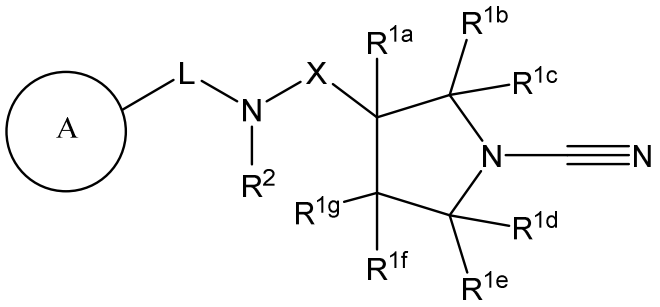
Claims

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;

R^{1a} and R^{1g} each independently represent hydrogen, fluorine, cyano, hydroxyl, amino, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

R^{1f} represents hydrogen, fluorine, cyano, hydroxyl, amino, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

R^2 represents hydrogen or C_1-C_6 alkyl;

X is $C(R^3)(R^4)$, wherein R^3 and R^4 each independently represent hydrogen, cyano or C_1-C_6 alkyl;

L represents a covalent bond, -C(O)-, or $CONR^5$;

R^5 represents hydrogen or C_1-C_6 alkyl;

A represents a 5 to 10-membered monocyclic or bicyclic heteroaryl ring, which comprises 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur;

wherein ring A is substituted with one $-Q^1-(R^6)_n$ wherein n is 1; and is optionally substituted with one, two or three $-Q^1-(R^6)_n$, wherein n is 0;

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;

R^6 is a 3 to 10-membered heterocyclyl, cycloalkyl, heteroaryl, or phenyl ring; wherein said heterocyclyl and heteroaryl rings each comprise 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur;

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

wherein R^6 is optionally substituted with one to four substituents, each independently selected from 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.

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 any one of claims 1 to 6, wherein the ring of A is a 5 or 6-membered heteroaryl ring.

8. The compound according to claim 7, wherein the ring of A is selected from oxazolyl, isoxazolyl, pyrazolyl, thiazolyl, pyridinyl, pyrimidinyl, imidazolyl, and oxadiazolyl.

9. The compound according to any one of claims 1 to 6, wherein the ring of A is a 9 or 10-membered bicyclic heteroaryl ring.

10. The compound according to claim 9, wherein the ring of A is selected from quinolinyl, benzothiazolyl, isoquinolinyl, benzomorpholinyl, indazolyl, imidazopyridinyl, quinazolinyl, pyrazolopyridinyl, and benzimidazolyl.

11. 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.

12. A compound according to claim 1 selected from the group consisting of:
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;
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)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide;
3-(1-((6-(1H-pyrazol-4-yl)benzo[d]thiazol-2-yl)amino)ethyl)pyrrolidine-1-carbonitrile;
(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.

13. 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;
(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.

14. 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.

15. 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.

16. Use of a compound according to any one of claims 1 to 15, 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 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.

17. Use of a compound according to claim 16, 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.

18. Use of a compound according to any one of claims 1 to 15, a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, in the manufacture of a medicament for the treatment of cancer.

19. Use of a compound according to claim 18, 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.

20. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 15, a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, together with one or more pharmaceutically acceptable excipients.