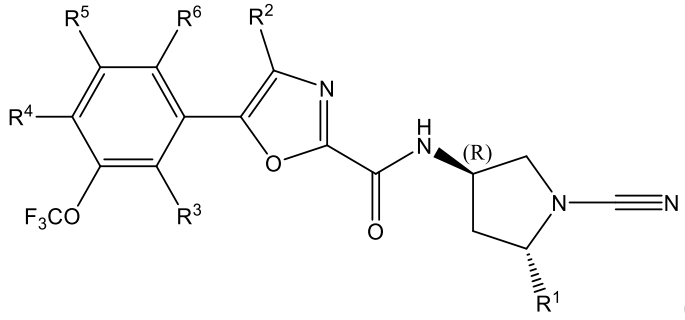
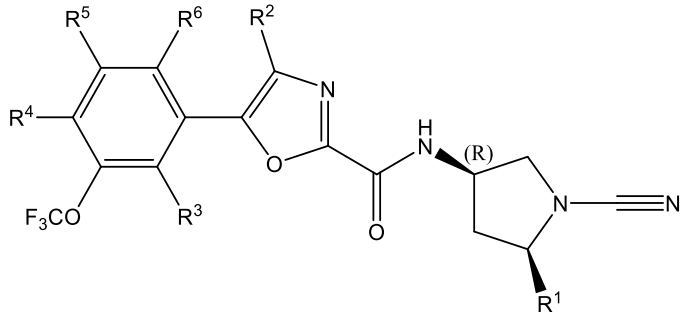
Claims

1. A compound of formula (I), which is selected from formula (I-A) and formula (I-B):



(I-A)



(I-B)

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

R^1 is selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$fluoroalkyl, CH_2OCH_3, $CH_2N(CH_3)_2$, $CH_2O(CH_2)_2N(CH_3)_2$ and $CH_2SO_2CH_3$;

R^2 is selected from hydrogen and methyl; and

R^3, R^4, R^5 and R^6 are each independently selected from hydrogen, deuterium and fluorine.

2. The compound according to claim 1, wherein R^1 is selected from methyl, CH_2F, CHF_2, CF_3, CH_2OCH_3, $CH_2N(CH_3)_2$, $CH_2O(CH_2)_2N(CH_3)_2$ and $CH_2SO_2CH_3$.

3. The compound according to claim 2, wherein R^1 is selected from methyl and CH_2OCH_3.

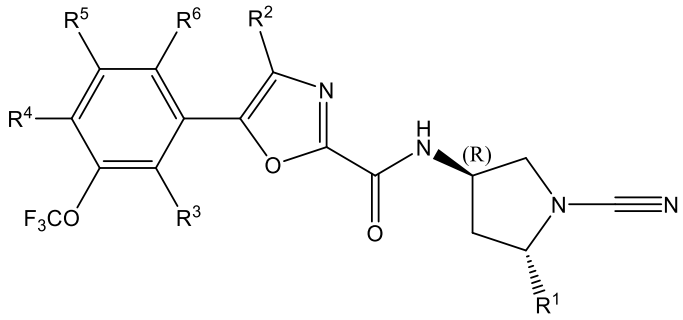
4. The compound according to any one of claims 1 to 3, wherein R^2 is hydrogen.

5. The compound according to any one of claims 1 to 4, wherein R^3, R^4 and R^6 are each hydrogen.

6. The compound according to any one of claims 1 to 5, wherein R^5 is selected from hydrogen and fluorine.

7. The compound according to claim 6, wherein R^5 is hydrogen.

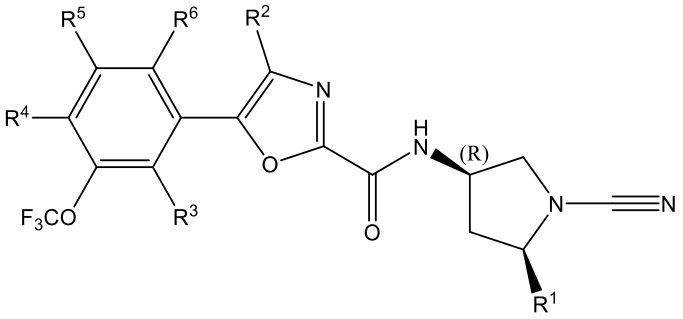
8. The compound according to any one of claims 1 to 7, having the formula (I-A):



(I-A).

9. The compound according to claim 8, which is selected from:
N-((3*R*,5*S*)-1-cyano-5-(methoxymethyl)pyrrolidin-3-yl)-5-(3-(trifluoromethoxy)phenyl)oxazole-2-carboxamide; and
N-((3*R*,5*R*)-1-cyano-5-methylpyrrolidin-3-yl)-5-(3-(trifluoromethoxy)phenyl)oxazole-2-carboxamide;
a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer.

10. The compound according to any one of claims 1 to 7, having the formula (I-B):



(I-B).

11. The compound according to claim 10, which is selected from:
N-((3*R*,5*R*)-1-cyano-5-(methoxymethyl)pyrrolidin-3-yl)-5-(3-(trifluoromethoxy)phenyl)oxazole-2-carboxamide; and
N-((3*R*,5*S*)-1-cyano-5-methylpyrrolidin-3-yl)-5-(3-(trifluoromethoxy)phenyl)oxazole-2-carboxamide;
a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer.

12. A compound according to any one of claims 1 to 11, a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, for use as a medicament.

13. Use of a compound according to any one of claims 1 to 11, a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, in the manufacture of a medicament for the treatment or prevention of a condition involving mitochondrial dysfunction, cancer, or fibrosis.

14. Use according to claim 13, wherein the condition involving mitochondrial dysfunction is selected from a CNS disorder; neurodegenerative disease; Parkinson's disease; Alzheimer's disease; amyotrophic lateral sclerosis; Huntington's disease; ischemia; stroke; dementia with Lewy bodies;

frontotemporal dementia; multiple sclerosis; mitochondrial encephalopathy, lactic acidosis and stroke-like episodes syndrome; materially-inherited diabetes and deafness; Leber's hereditary optic neuropathy; 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; Leigh Syndrome French Canadian variant; lethal infantile cardiomyopathy; Luft disease; 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; and very long-chain acyl-CoA dehydrogenase deficiency; peroxisomal disorders; methylmalonic acidemia; and age-dependent decline in cognitive function and muscle strength.

15. Use according to claim 14, 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, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, frontotemporal dementia; and Parkinson’s disease related to mutations in α-synuclein, parkin, PINK1, GBA, and LRRK2, and autosomal recessive juvenile Parkinson’s disease where parkin is mutated.

16. Use according to claim 14, wherein the neurodegenerative disease is Leigh syndrome or disease, X-linked Leigh's disease, Leigh Syndrome French Canadian Variant, and/or the symptoms associated with Leigh’s disease.

17. Use according to claim 13, wherein the cancer is selected from breast, ovarian, prostate, lung, kidney, gastric, colon, testicular, head and neck, pancreas, brain, melanoma, bone, liver, soft tissue, cancers of tissue organs, cancers of the blood cells, CML, AML, mantle cell lymphoma, neuroblastoma, melanoma, soft tissue sarcoma, liposarcoma, fibroblastic sarcoma, leiomyosarcoma, hepatocellular carcinoma, osteosarcoma, oesophageal cancer, leukaemia, lymphoma, multiple myeloma, metastatic carcinoma, osteosarcoma, chondosarcoma, Ewing’s sarcoma, nasopharyngeal carcinoma, colorectal

cancer, 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.

18. Use according to claim 13, wherein the fibrosis is selected from fibrosis or a fibrotic disorder associated with the accumulation of extracellular matrix constituents that occurs following trauma, inflammation, tissue repair, immunological reactions, cellular hyperplasia, and neoplasia.

19. Use according to claim 18, wherein the fibrosis is selected from fibrosis or a fibrotic disorder associated with major organ diseases, fibroproliferative disorders, and scarring associated with trauma.

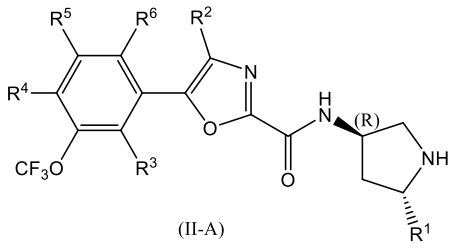
20. Use according to claim 19, wherein the fibrosis is selected from fibrosis or a fibrotic disorder associated with interstitial lung disease, liver cirrhosis, non-alcoholic fatty liver disease, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis, kidney disease, acute kidney injury, chronic kidney disease, delayed kidney graft function, heart or vascular disease, diseases of the eye, systemic and local scleroderma, keloids, hypertrophic scars, atherosclerosis, restenosis, Dupuytren's contracture, surgical complications, chemotherapeutics drug-induced fibrosis, radiation-induced fibrosis, accidental injury and burns, retroperitoneal fibrosis, and peritoneal fibrosis/peritoneal scarring.

21. Use according to claim 20, wherein the fibrosis associated with interstitial lung disease is selected from sarcoidosis, silicosis, drug reactions, infections, collagen vascular diseases, rheumatoid arthritis, systemic sclerosis, scleroderma, pulmonary fibrosis, idiopathic pulmonary fibrosis, usual interstitial pneumonitis, interstitial lung disease, cryptogenic fibrosing alveolitis, bronchiolitis obliterans, and bronchiectasis.

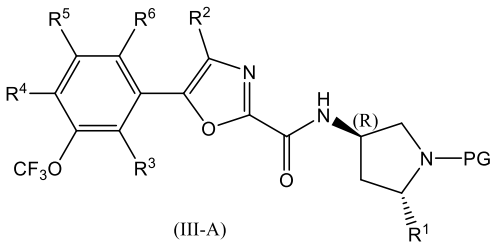
22. Use according to claim 20, wherein the kidney disease is acute kidney injury or chronic kidney disease.

23. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 11, a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, together with one or more pharmaceutically acceptable excipients.

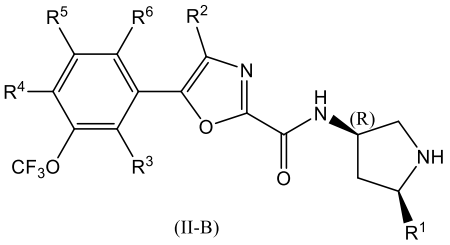
24. A compound, which is selected from formulae (II-A), (III-A), (II-B) and (III-B):



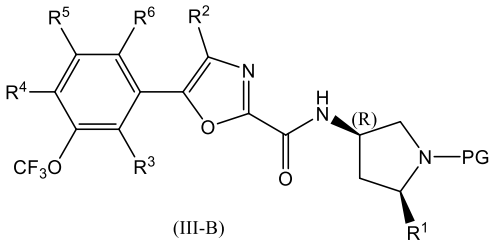
(II-A)



(III-A)



(II-B)



(III-B)

a tautomer thereof, or a salt of said compound or tautomer;

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined for the compound of formula (I) in any one of claims 1 to 11; and PG is a protecting group, which is preferably selected from from tert-butyloxycarbonyl, benzyloxycarbonyl, p-methoxybenzyl carbonyl, 9-fluorenylmethyloxycarbonyl, acetyl, benzoyl, benzyl, carbamate, p-methoxybenzyl, 3,4-dimethoxybenzyl, p-methoxyphenyl, tosyl, trichloroethoxycarbonyl, 4-nitrobenzenesulfonyl and 2-nitrophenylsulfenyl.