Accordingly, there is a need for alternative treatments to L-DOPA administration in Parkinson's disease.

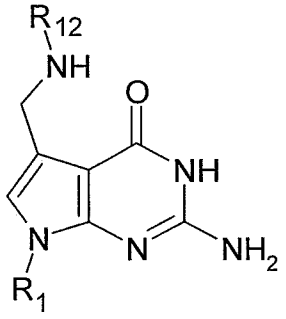
Summary

Recent research on the function and dysfunction of PD-associated genes has provided fundamental new insights into biochemical pathways which are associated with the disease process. These findings have established that mitochondrial dysfunction is a common denominator of sporadic and familial PD, moving mitochondria to the forefront of PD research (Winklhofer & Haass (2010) *Biochimica et Biophysica Acta* **1802**:29-44).

The present disclosure arises from the unexpected finding, by the present inventors, that queuine has a neuroprotective effect in an *in vitro* model of Parkinson's disease involving mitochondrial dysfunction.

Thus, the present disclosure relates to queuine, a precursor of queuine, a derivative of queuine, an analogue of queuine, or a stereoisomer of queuine, or a pharmaceutically acceptable salt or hydrate thereof, for use in the prevention or treatment of a disease associated with a mitochondrial dysfunction.

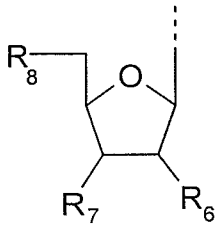
In an aspect, the present disclosure relates to a compound of the following formula (A):



(A)

wherein:

- R_1 represents –H or a ribosyl group of the following formula:



wherein:

- R_6 represents –H; -O-R_9 or -O-CO-R_9 wherein R_9 is H, an alkyl group having from 1 to 6 carbon atoms or an aryl group having from 3 to 12 carbon atoms;
- R_7 represents –H; -O-R_{10} or –O-CO-R_{10} wherein R_{10} is H, an alkyl group having from 1 to 6 carbon atoms or an aryl group having from 3 to 12 carbon atoms; a deoxyribonucleic acid group; or a ribonucleic acid group;
- R_8 represents –H; -O-R_{11} or –O-CO-R_{11} wherein R_{11} is H, an alkyl group having from 1 to 20 carbon atoms or an aryl group having from 3 to 20 carbon atoms; a phosphate group; a diphosphate group; a triphosphate group; a deoxyribonucleic acid group; or a ribonucleic acid group;

- R_{12} represents a saturated or unsaturated alkyl, cycloalkyl, heterocycloalkyl or ether group having from 1 to 20 carbon atoms, optionally substituted by at least one group selected from the group consisting of:
  - an alkyl group having from 1 to 20 carbon atoms,
  - an aryl or heteroaryl group having from 3 to 20 carbon atoms,
  - a cycloalkyl or heterocycloalkyl group having from 3 to 20 carbon atoms,
  - a hydroxyl group,
  - a carbonyl or carboxyl group having from 1 to 20 carbon atoms,
  - an epoxy group,
  - an -O-R_4 group wherein R_4 is H, an alkyl group having from 1 to 6 carbon atoms, an aryl group having from 3 to 12 carbon atoms, a glycosyl group or an aminoacyl group,
  - an –O-CO-R_5 group wherein R_5 is an alkyl group having from 1 to 6 carbon atoms, an aryl group having from 3 to 12 carbon atoms or a glycosyl group;

or a pharmaceutically acceptable salt or hydrate thereof,

for use in the prevention or treatment of a disease associated with a mitochondrial dysfunction in an individual.

The present disclosure also relates to a compound of formula (A) of the following formula (I):

R_5 is an alkyl group having from 1 to 6 carbon atoms, an aryl group having from 3 to 12 carbon atoms or a glycosyl group;

or a pharmaceutically acceptable salt or hydrate thereof,

for use in the prevention or treatment of a disease associated with a mitochondrial dysfunction.

In an embodiment of the disclosure, the compound of formula (A), in particular the compound of formula (I), or the pharmaceutically acceptable salt or hydrate thereof, for use as defined above, is in combination with at least one additional compound useful for the prevention or treatment of a disease associated with a mitochondrial dysfunction.

In another aspect, the present disclosure also relates to a pharmaceutical composition comprising as active substance a compound of formula (A), in particular a compound of formula (I), or a pharmaceutically acceptable salt or hydrate thereof, as defined above, optionally in association with at least one pharmaceutically acceptable excipient or vehicle, for use in the prevention or treatment of a disease associated with a mitochondrial dysfunction.

In an embodiment of the disclosure, the above defined pharmaceutical composition further comprises at least one additional compound useful for the prevention or treatment of a disease associated with a mitochondrial dysfunction.

In another aspect, the present disclosure also relates to a pharmaceutical composition comprising as active substance a compound of formula (A), in particular a compound of formula (I), or a pharmaceutically acceptable salt or hydrate thereof, as defined above, further comprising at least one additional compound useful for the prevention or treatment of a disease associated with a mitochondrial dysfunction, optionally in association with at least one pharmaceutically acceptable excipient or vehicle.

In another aspect, the present disclosure also relates to products comprising:

- a compound of formula (A), in particular a compound of formula (I), or a pharmaceutically acceptable salt or hydrate thereof, as defined above,
- at least one additional compound useful for the prevention or treatment of a disease associated with a mitochondrial dysfunction,

as a combined preparation for simultaneous, separated or sequential use in the prevention or treatment of a disease associated with a mitochondrial dysfunction in an individual.

In another aspect, the present disclosure also relates to a dietary supplement comprising a compound of formula (A), in particular a compound of formula (I), or a pharmaceutically acceptable salt or hydrate thereof, as defined above, for use for reducing the risk of a disease associated with a mitochondrial dysfunction.

In an embodiment of the disclosure, the dietary supplement as defined above, optionally comprises additional compounds, preferably selected from the group consisting of vitamins, minerals, fatty acids, amino acids and antioxidants.

The present disclosure also relates to a method for the prevention or treatment of a disease associated with a mitochondrial dysfunction in an individual, comprising administering to the individual an effective amount of a compound of formula (A), in particular a compound of formula (I), or of a pharmaceutically acceptable salt or hydrate thereof, as defined above.

In an embodiment of the disclosure, the method as defined above further comprises the administration of at least one compound useful for the prevention or treatment of a disease associated with a mitochondrial dysfunction.

The present disclosure also relates to the use of a compound of formula (A), in particular a compound of formula (I), as defined above for the manufacture of a medicament intended for the prevention or treatment of a disease associated with a mitochondrial dysfunction in an individual.

In an embodiment of the disclosure, the medicament as defined above further comprises at least one compound useful for the prevention or treatment of a disease associated with a mitochondrial dysfunction.

Detailed description of the invention

Compound of formula (A)

Compounds of formula (A), in particular compounds of formula (I), as defined above can be readily chemically synthesized by one of skill in the art, as is in particular described in Barnett & *Grubb* (2000), *Tetrahedron* **56:** 9221-9225, Oxenford *et al.* (2004) *Tetrahedron Letters* **45**:9053-9055, Brooks *et al.* (2010) *Tetrahedron Letters* **51:** 4163-4165, Gerber *et al.* (2012) *Org. Biomol. Chem.* **10**: 8660-8668, the thesis by Allen Brook entitled "*Synthesis of Tritium Labeled Queuine, PreQ*$_1$ *and Related Azide Probes Toward Examining the Prevalence of Queuine*" (2012, University of Michigan), Akimoto *et al.* (1986) *J. Med. Chem.*, **29**: 1749-1753, Kelly *et al.* (2016) *Nucleic Acids Research*, 1-11,