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

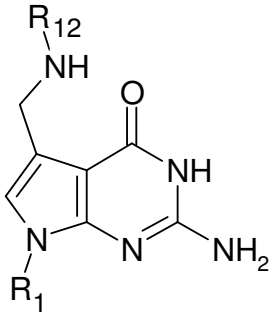
Summary

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.

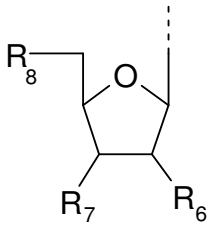
The present disclosure relates to a compound of the following formula (A):



(A)

wherein:

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



wherein:

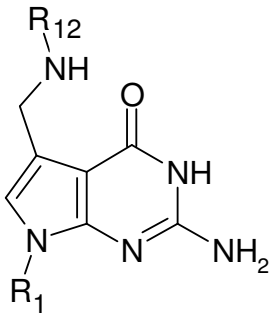
- R_6 represents –H; -O-R_9 or -O-CO-R_9 wherein R_9 is H, an alkyl group having from 1 to 6 carbon atoms or an aryl group having from 3 to 12 carbon atoms;
- R_7 represents –H; -O-R_{10} or –O-CO-R_{10} wherein R_{10} is H, an alkyl group having from 1 to 6 carbon atoms or an aryl group having from 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.

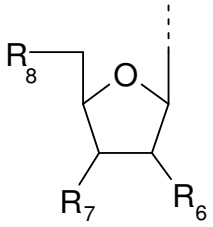
In one aspect, the present disclosure relates to use of a compound of the following formula (A):



(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,

in the manufacture of a medicament for the prevention or treatment of Parkinson's disease 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 example 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.

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 another aspect, the present disclosure relates to use of a composition comprising as active substance a compound of formula (A) or a pharmaceutically acceptable salt or hydrate thereof as defined herein, optionally in association with at least one pharmaceutically acceptable excipient or vehicle, in the manufacture of a medicament for the prevention or treatment of Parkinson's disease in an individual.

In an example 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.

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 relates to use of a composition comprising as active substance a compound of formula (A) or a pharmaceutically acceptable salt or hydrate thereof as defined herein, optionally in association with at least one pharmaceutically acceptable excipient or vehicle, in the manufacture of a medicament for the prevention or treatment of Parkinson's disease in an individual, wherein the medicament further comprises at least one additional compound useful for the prevention or treatment of Parkinson's disease.

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 relates to use of products comprising:

- a compound of formula (A) as defined herein,
- at least one additional compound useful for the prevention or treatment of Parkinson's disease,

in the manufacture of a medicament as a combined preparation for simultaneous, separated or sequential use in the prevention or treatment of Parkinson's disease in an individual.

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 another aspect, the present disclosure relates to use of a compound of formula (A) as defined herein in the manufacture of a dietary supplement, for reducing the risk of Parkinson's disease in an individual.

In an example 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 example 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 example 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

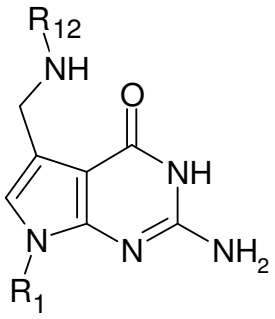
Compound of formula (A)

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 Lett*ers **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,

Claims

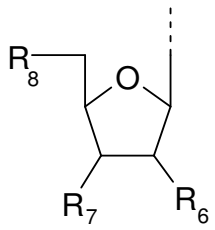
1. Use of a compound of the following formula (A):



(A)

wherein:

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



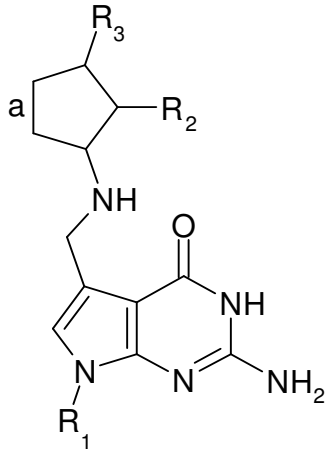
wherein:

- 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,
in the manufacture of a medicament for the prevention or treatment of Parkinson's disease in an individual.

2. The use of a compound or pharmaceutically acceptable salt or hydrate thereof according to claim 1, wherein the compound of formula (A) is of the following formula (I):

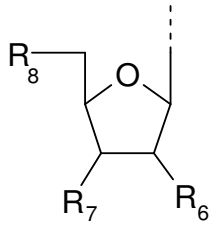


(I)

wherein:

- a represents a double bond or an epoxy group, and

- 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_2 and R_3, which are identical or different, represent -O-R_4 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; or –O-CO-R_5 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.

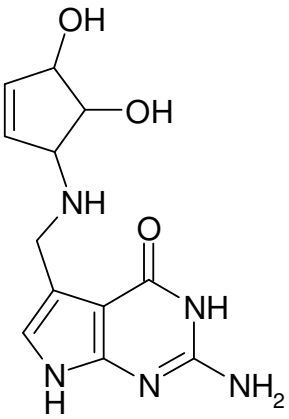
3. The use of a compound or pharmaceutically acceptable salt or hydrate thereof according to claim 1 or 2, wherein:

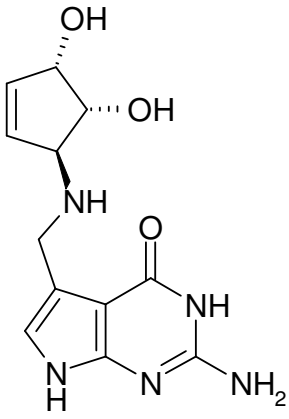
- R_2 and R_3, which are identical or different, represent -OH, a -O-mannosyl group, a -O-galactosyl group or a -O-glutamyl group;
- R_6 represents -OH;
- R_7 and R_8, which are identical or different, represent –OH or a ribonucleic acid group.

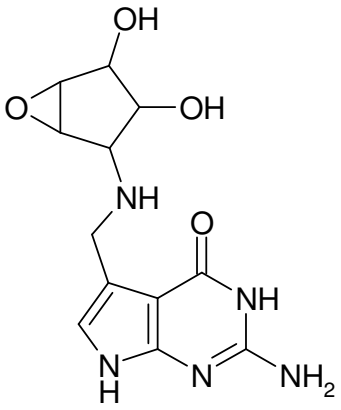
4. The use of a compound or pharmaceutically acceptable salt or hydrate thereof according to any one of claims 1 to 3, wherein the compound is selected form the group consisting of queuine, ent-queuine, queuosine, epoxyqueuine,

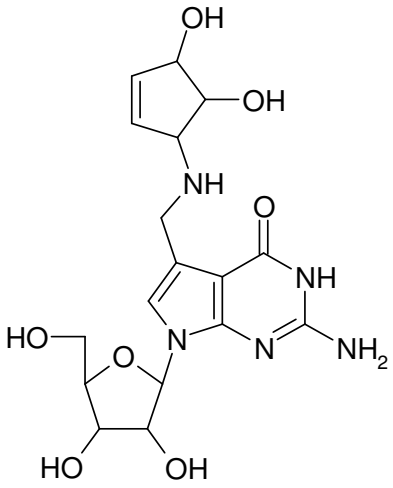
epoxyqueuosine, mannosyl-queuine, galactosyl-queuine, glutamyl-queuine, galactosyl-queuosine, mannosyl-queuosine, glutamyl-queuosine, queuine-tRNA and epoxyqueuine-tRNA.

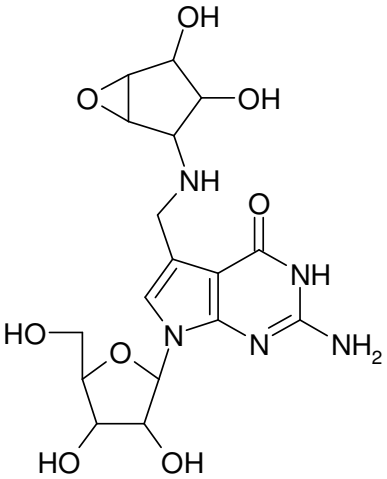
5. The use of a compound or pharmaceutically acceptable salt or hydrate thereof according to any one of claims 1 to 4, wherein the compound is selected from the group consisting of the compounds of the following formulae:

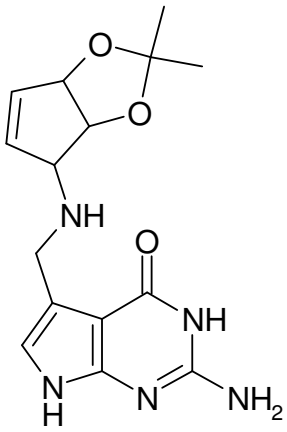


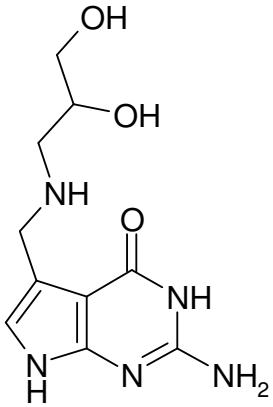


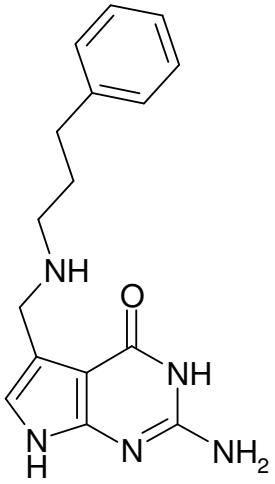


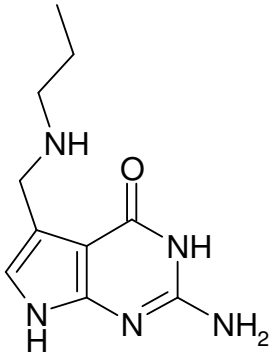


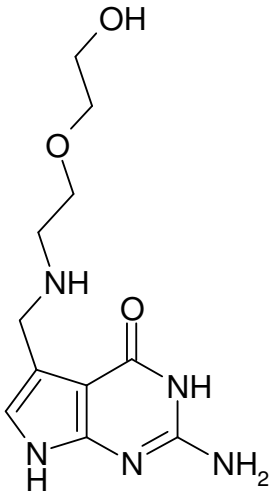


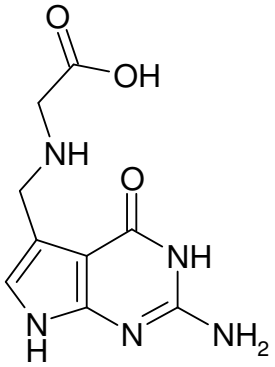


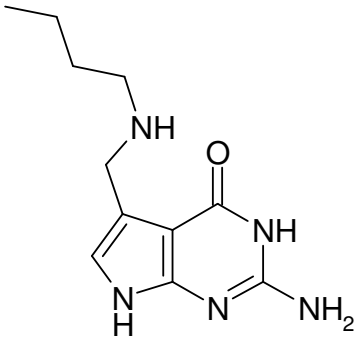


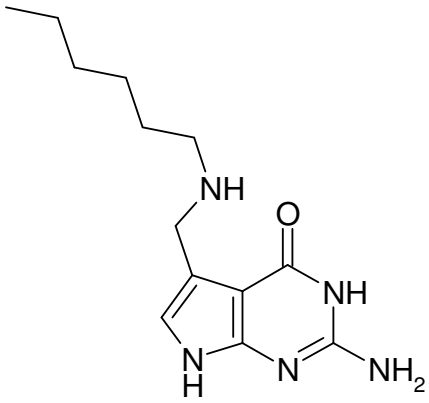












6. The use of a compound or pharmaceutically acceptable salt or hydrate thereof according to any one of claims 1 to 5, for an administration with a dosage regimen of from 0.01 to 40 mg/kg/d.

7. The use of a compound or pharmaceutically acceptable salt or hydrate thereof according to any one of claims 1 to 6, in a form suitable for an administration by the oral route, the intradermal route, the intravenous route, the intramuscular route or the subcutaneous route.

8. The use of a compound or pharmaceutically acceptable salt or hydrate thereof according to any one of claims 1 to 7, in combination with at least one additional compound useful for the prevention or treatment of Parkinson's disease.

9. Use of a composition comprising as active substance a compound of formula (A) or a pharmaceutically acceptable salt or hydrate thereof as defined in any one of

claims 1 to 5, optionally in association with at least one pharmaceutically acceptable excipient or vehicle, in the manufacture of a medicament for the prevention or treatment of Parkinson's disease in an individual.

10. Use of a composition comprising as active substance a compound of formula (A) or a pharmaceutically acceptable salt or hydrate thereof as defined in any one of claims 1 to 5, optionally in association with at least one pharmaceutically acceptable excipient or vehicle, in the manufacture of a medicament for the prevention or treatment of Parkinson's disease in an individual, wherein the medicament further comprises at least one additional compound useful for the prevention or treatment of Parkinson's disease.

11. Use of products comprising:
- a compound of formula (A) as defined in any one of claims 1 to 5,
- at least one additional compound useful for the prevention or treatment of Parkinson's disease,

in the manufacture of a medicament as a combined preparation for simultaneous, separated or sequential use in the prevention or treatment of Parkinson's disease in an individual.

12. Use of a compound of formula (A) as defined in any one of claims 1 to 5 in the manufacture of a dietary supplement, for reducing the risk of Parkinson's disease in an individual.

13. The use of a compound according to claim 12, wherein the dietary supplement further comprises additional compounds selected from the group consisting of vitamins, minerals, fatty acids, amino acids and antioxidants.