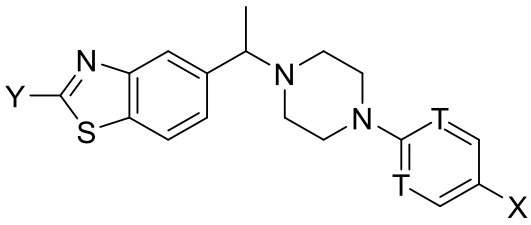
Succinate and fumarate acid addition salts of piperazine derivatives

Field of the invention

The invention relates to acid addition salts of succinic acid or fumaric acid with piperazine derivatives, as well as solid forms, such as polymorphic forms, thereof, which are useful as pharmaceutical ingredients and in particular as glycosidase inhibitors.

Background of the invention

Piperazine derivatives of formula I



(I)

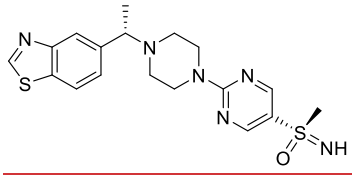
wherein X, Y and T are defined further below, are useful as pharmaceutical ingredients and show high activity as glycosidase inhibitors. Similar compounds are e.g. disclosed in PCT/EP2015/069598.

Although the compounds of formula I have very useful pharmaceutical activities as free bases, they are not ideal for pharmaceutical manufacturing and as such may not be suitable for certain dosage forms, especially oral dosage forms, due to their unfavorable dissolution behaviour and stability or reactivity and other properties in the solid state.

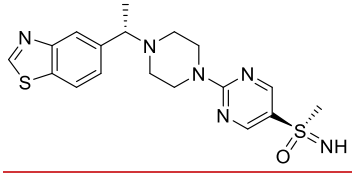
Thus, there is a need to provide improved solid forms comprising the compounds of formula I, which exhibit improved properties, can be easily manufactured into solid dosage forms or other pharmaceutical dosage forms, and show an improved dissolution behaviour and stability and/or are less reactive in the solid state.

Summary ~~of the invention~~

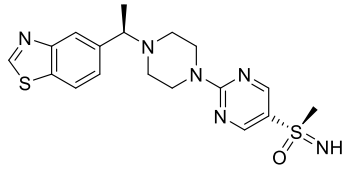
In a first aspect, the present disclosure refers to a mono-succinic acid salt of one of the compounds Ia, Ib, Ic, and Id in a solid form having the characteristic X-ray powder diffraction pattern as shown in Figure 1:



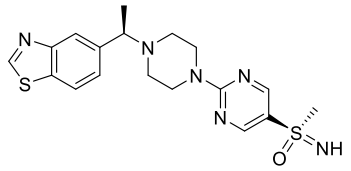
(Ia)



(Ib)

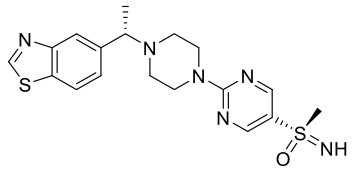


(Ic)

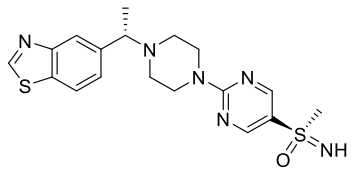


(Id)

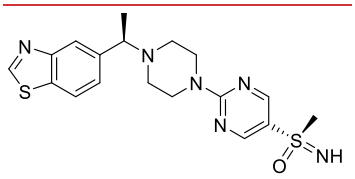
In another aspect, the present disclosure refers to a mono-fumaric acid salt of one of the compounds Ia, Ib, Ic, and Id in a solid form having the characteristic X-ray powder diffraction pattern as shown in Figure 4:



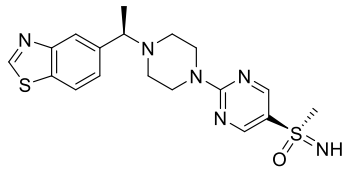
(Ia)



(Ib)



(Ic)



(Id)

In yet another aspect, the present disclosure refers to a method for the preparation of a mono-succinic acid salt as disclosed herein or a mono-fumaric acid salt as disclosed herein comprising the following steps:

a) suspending or dissolving the selected compound of formula I and the respective acid in a suitable solvent or solvent mixture;

b) heating the mixture obtained in step a) to a temperature of between about 30 °C to about the boiling point of the selected solvent or solvent mixture, and allowing the mixture to cool to room temperature;

c) optionally repeating step b) several times;

d) separating and drying the solid thus obtained.

In a further aspect, the present disclosure refers to a solid oral dosage form comprising a mono-succinic acid salt as disclosed herein or a mono-fumaric acid salt as disclosed herein.

In another aspect, the present disclosure refers to a mono-succinic acid salt as disclosed herein or a mono-fumaric acid salt as disclosed herein for use as a medicament.

In yet another aspect, the present disclosure refers to a mono-succinic acid salt as disclosed herein or a mono-fumaric acid salt as disclosed herein for use in a method of treating a condition selected from the group consisting of neurodegenerative diseases, diabetes, cancer, cardiovascular diseases and stroke.

In a further aspect, the present disclosure refers to a method for inhibiting a glycosidase, wherein a system expressing the glycosidase is contacted with a mono-succinic acid salt as disclosed herein or a mono-fumaric acid salt as disclosed herein under *in vitro* conditions such that the glycosidase is inhibited.

In another aspect, the present disclosure refers to a use of a mono-succinic acid salt as disclosed herein or a mono-fumaric acid salt as disclosed herein, in the manufacture of a medicament for treating a condition selected from the group consisting of neurodegenerative diseases, diabetes, cancer, cardiovascular diseases and stroke.

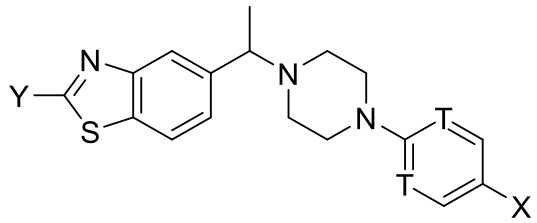
It has now been found that compounds of formula I show improved solid state properties, after they have been transformed in acid addition salts of succinic acid or fumaric acid. In particular, the acid addition salts can be easily manufactured into solid

dosage forms or other pharmaceutical dosage forms, and show an improved dissolution behavior and stability and/or are less reactive in the solid state. The acid addition salts of the present ~~invention~~ disclosure also exhibit low hygroscopicity.

It has also been found that certain polymorphic forms of the acid addition salts show even further improved properties, making them ideal for pharmaceutical manufacturing, in particular for solid oral dosage forms. Moreover, acid addition salts of the present ~~invention~~ disclosure that have a molar ratio of the compounds of formula I to the respective acid of 1 to 1 are especially stable, soluble and/or show other improved properties.

Detailed description of the invention

The invention relates to the acid addition salt of succinic acid or fumaric acid with compounds of formula I



(I)

wherein

Y denotes H or CH_3,

T denotes N or CH,

X denotes one of the following sulfoximine groups:

$S(O)(NR^{3'})CH_3$, $S(O)(NR^{3'})CH_2CH_3$, $S(O)(NR^{3'})CH_2CH_2OH$, $S(O)(NR^{3'})CH_2CH_2OCH_3$, $NS(O)(R^{3'})CH_3$, $NS(O)(R^{3'})CH_2CH_3$, $NS(O)(R^{3'})CH_2CH_2OH$ or $NS(O)(R^{3'})CH_2CH_2OCH_3$

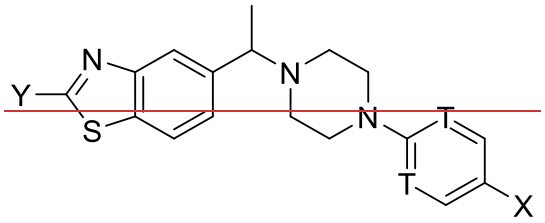
and

$R^{3'}$ denotes H or a straight chain or branched alkyl group having 1 to 12 carbon atoms, wherein 1 to 3 CH_2-groups may be replaced by a group selected from SO_2, CO, O and wherein 1 to 5 hydrogen atoms may be replaced by F, Cl, Br or I.

as well as stereoisomers, solid forms, such as solvates and polymorphic forms thereof.

Claims

~~1. An acid addition salt of succinic acid or fumaric acid with a compound of formula I~~



~~(I)~~

~~wherein~~

~~Y denotes H or CH_3,~~

~~T denotes N or CH,~~

~~X denotes one of the following sulfoximine groups:~~

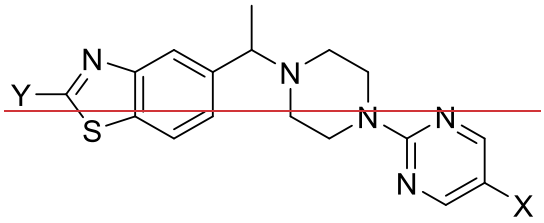
~~$S(O)(NR^{3'})CH_3$, $S(O)(NR^{3'})CH_2CH_3$, $S(O)(NR^{3'})CH_2CH_2OH$ or $S(O)(NR^{3'})CH_2CH_2OCH_3$, $NS(O)(R^{3'})CH_3$, $NS(O)(R^{3'})CH_2CH_3$, $NS(O)(R^{3'})CH_2CH_2OH$ or $NS(O)(R^{3'})CH_2CH_2OCH_3$~~

~~and~~

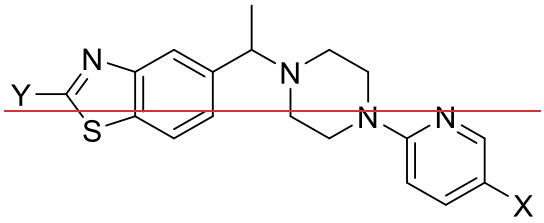
~~$R^{3'}$ denotes H or a straight chain or branched alkyl group having 1 to 12 carbon atoms, wherein 1 to 3 CH_2-groups may be replaced by a group selected from SO_2, CO, and O, and wherein 1 to 5 hydrogen atoms may be replaced by F, Cl, Br or I,~~

~~as well as stereoisomers and solid forms thereof.~~

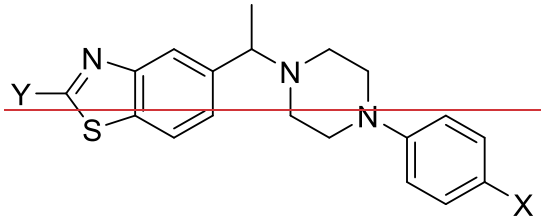
~~2. An acid addition salt of succinic acid or fumaric acid with compounds of formula I1, I2 or I3:~~



(I1)



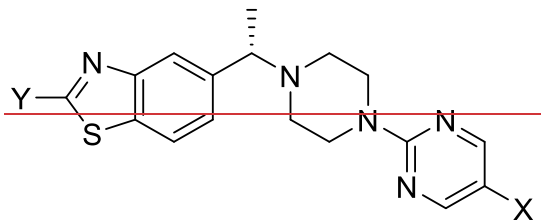
(I2)



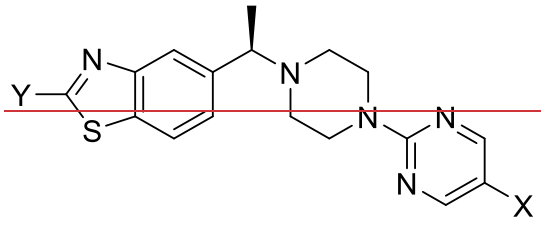
(I3)

wherein X, Y and T have the meaning given in claim 1, and solid forms thereof.

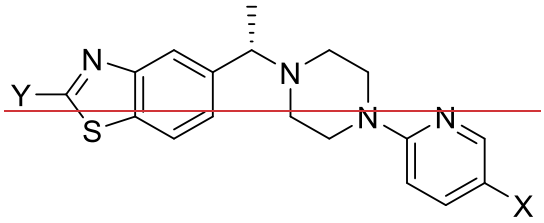
3. An acid addition salt of succinic acid or fumaric acid with compounds of formula I1a, I1b, I2a, I2b, I3a or I3b:



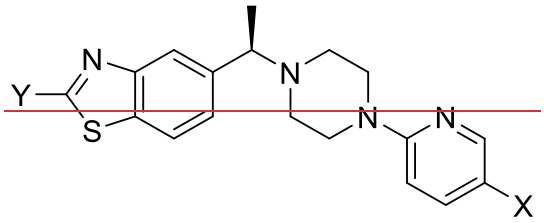
(I1a)



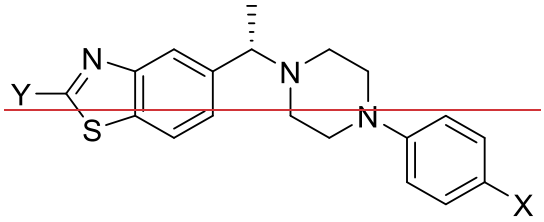
(I1b)



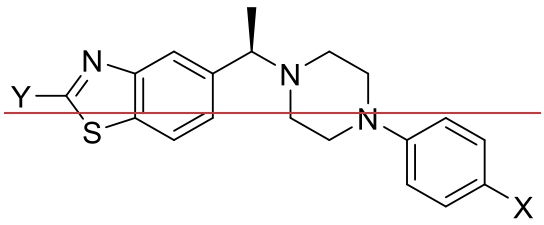
(I2a)



(I2b)



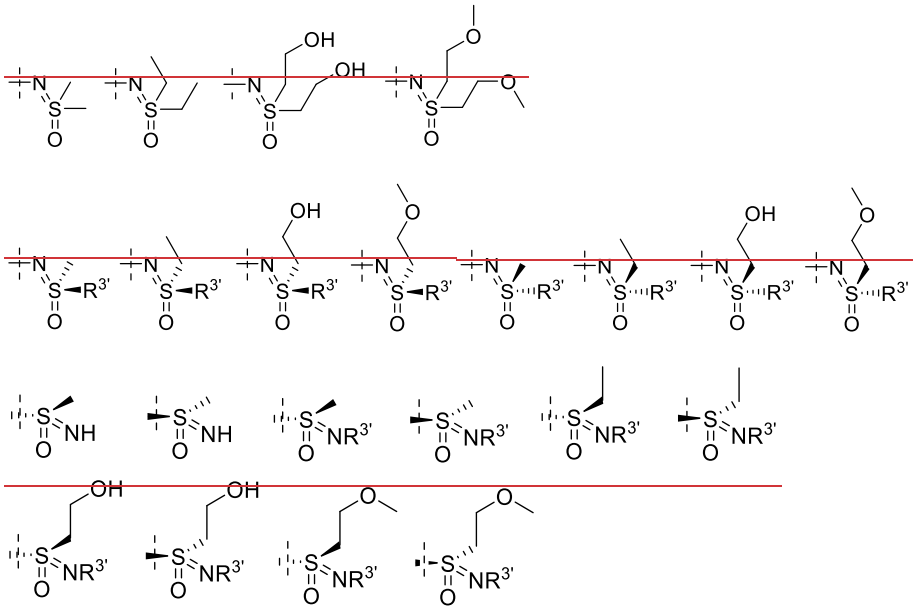
(I3a)



(I3b)

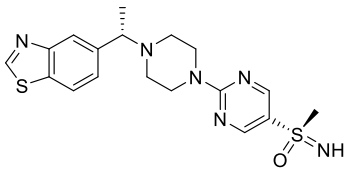
wherein X and Y have the meaning given in claim 1, and solid forms thereof.

~~4. The acid addition salt according to claim 1 to 3, wherein X is selected from the group~~

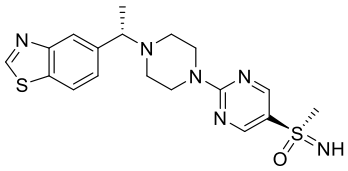


~~and wherein $R^{3'}$ has the meaning given in claim 1.~~

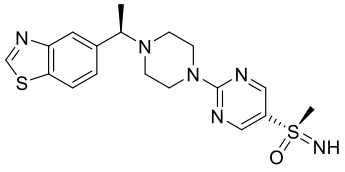
15. An acid addition salt of mono-succinic acid or fumaric acid with a salt of one of the compounds of formula Ia, Ib, Ic, and Id, Ie, If, Ig, Ih, Ii, Ij, Ik or IL in a solid form having the characteristic X-ray powder diffraction pattern as shown in Figure 1:



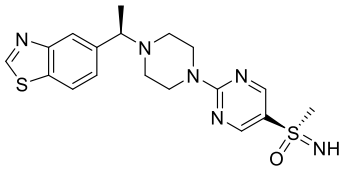
(Ia)



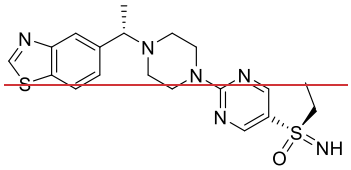
(Ib)



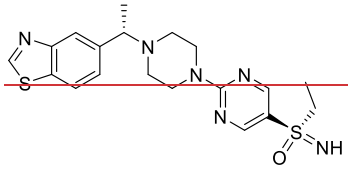
(Ic)



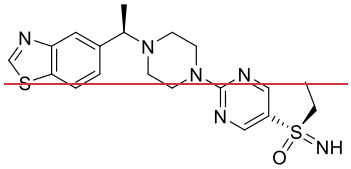
(Id)



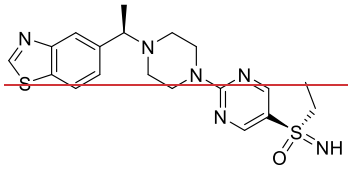
(Ie)



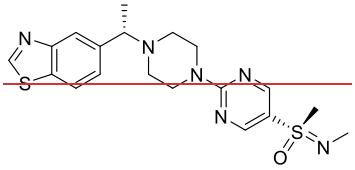
(If)



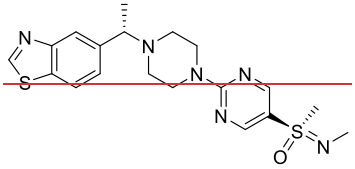
(Ig)



(Ih)



(Ii)



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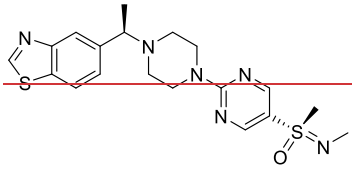
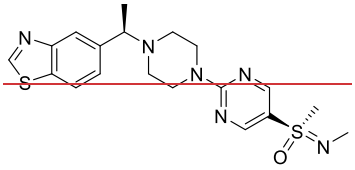


(Ik)



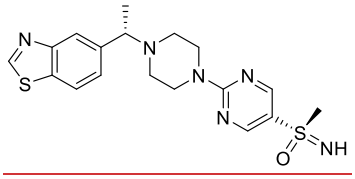
(IL)

and solid forms thereof.

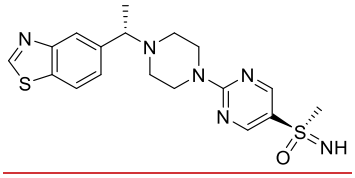
6. The succinic acid or fumaric acid addition salt according to any one of claims 1 to 5 in a molar ratio of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, IL, I1a, I1b, I2a, I2b, I3a, I3b, I1, I2 or I3 to acid of 1 to1.

~~7. The mono-succinic acid salt of one of the compounds Ia, Ib, Ic, Id according to claim 5 in a solid form having the characteristic X-ray powder diffraction pattern as shown on Figure 1.~~

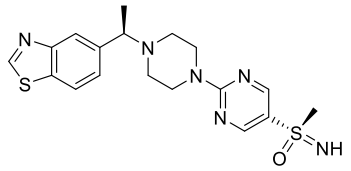
28. ~~The~~ A mono-fumaric acid salt of one of the compounds Ia, Ib, Ic, and Id ~~according to claim 5~~ in a solid form having the characteristic X-ray powder diffraction pattern as shown ~~i~~on Figure 4~~.~~:



(Ia)



(Ib)



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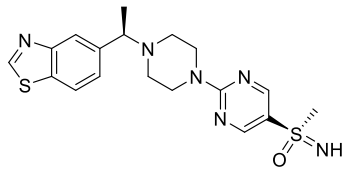

(Id)

39. A method for the preparation of ~~an acid addition salt of~~a mono-succinic acid salt of claim 1 or a mono-fumaric acid salt of claim 2 ~~with compounds of formula I and their stereoisomers~~ comprising the following steps:

a) suspending or dissolving the selected compound of formula I and the respective acid in a suitable solvent or solvent mixture;

b) heating the mixture obtained in step a) to a temperature of between about 30 °C to about the boiling point of the selected solvent or solvent mixture, and allowing the mixture to cool to room temperature;

c) optionally repeating step b) several times;

d) separating and drying the solid thus obtained.

410. A solid oral dosage form comprising a mono-succinic acid addition salt according to claim 1 or a mono-fumaric acid addition salt according to any one of claims 1 to 8claim 2.

511. A mono-succinic acid addition salt according to claim 1 or a mono-fumaric acid addition salt according to any one of claims 1 to 8 claim 2 for use as a medicament.

612. A mono-succinic acid addition salt according to claim 1 or a mono-fumaric acid addition salt according to any one of claims 21 to 8 for use in a method of treating a condition selected from the group consisting of neurodegenerative diseases, diabetes, cancer, cardiovascular diseases and stroke.

713. A mono-succcinic acid addition salt according to claim 1 or a mono-fumaric acid addition salt according to any one of claims 21 to 8 for use in a method of treating treatment of a condition according to claim 612, wherein the condition is selected from the group of one or more tauopathies and Alzheimer's disease, Dementia, Amyotrophic lateral sclerosis (ALS), Amyotrophic lateral sclerosis with cognitive impairment (ALSci), Argyrophilic grain disease, Behavioural variant frontotemporal dementia (BvFTD), Bluit disease, Chronic traumatic encephalopathy, Corticobasal degeneration (CBP), Dementia pugilistica, Diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Frontotemporal lobar degeneration (FTLD), Ganglioglioma, Gangliocytoma, Gerstmann-Straussler-Scheinker disease, Globular glia tauopathy, Guadeloupean parkinsonism, Hallevorden-Spatz disease (neurodegeneration with brain iron accumulation type 1), Lead encephalopathy, Lipofuscinosis, Meningioangiomatosis, Multiple system atrophy, Myotonic dystrophy, Niemann-Pick disease (type C), Pallido-ponto-nigral degeneration, Parkinsonism-dementia complex of Guam, Pick's disease (PiD), Parkinson's disease dementia, Postencephalitic parkinsonism (PEP), Primary progressive aphasia, Prion diseases (including Creutzfeldt-Jakob Disease (CJD), Progressive nonfluent aphasia, Variant Creutzfeldt-Jakob Disease (vCJD)), Fatal Familial Insomnia, Kuru, Progressive supercortical gliosis, Progressive supranuclear palsy (PSP), Semantic dementia, Steele-Richardson-Olszewski syndrome, Subacute sclerosing panencephalitis, Tangle-only dementia, Tuberous sclerosis, Huntington's disease

and Parkinson's disease, preferably one or more tauopathies and Alzheimer's disease.

~~14. A method for treating a tauopathy, wherein an acid addition salt according to any one of claims 1 to 8 is administered to a mammal in need of such treatment.~~

8~~15~~. A method for inhibiting a glycosidase, wherein a system expressing the glycosidase is contacted with a~~n~~ mono-succinic acid ~~addition~~ salt according to ~~any one of~~ claim~~s~~ 1 ~~to 8~~ or a mono-fumaric acid salt according to claim 2 under *in vitro* conditions such that the glycosidase is inhibited.

9. Use of a mono-succinic acid salt according to claim 1 or a mono-fumaric acid salt according to claim 2, in the manufacture of a medicament for treating a condition selected from the group consisting of neurodegenerative diseases, diabetes, cancer, cardiovascular diseases and stroke.

10. The use according to claim 9, wherein the condition is selected from the group of one or more tauopathies and Alzheimer's disease, Dementia, Amyotrophic lateral sclerosis (ALS), Amyotrophic lateral sclerosis with cognitive impairment (ALSci), Argyrophilic grain disease, Behavioural variant frontotemporal dementia (BvFTD), Bluit disease, Chronic traumatic encephalopathy, Corticobasal degeneration (CBP), Dementia pugilistica, Diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Frontotemporal lobar degeneration (FTLD), Ganglioglioma, Gangliocytoma, Gerstmann-Straussler-Scheinker disease, Globular glia tauopathy, Guadeloupean parkinsonism, Hallevorden-Spatz disease (neurodegeneration with brain iron accumulation type 1), Lead encephalopathy, Lipofuscinosis, Meningioangiomatosis, Multiple system atrophy, Myotonic dystrophy, Niemann-Pick disease (type C), Pallido-ponto-nigral degeneration, Parkinsonism-dementia complex of Guam, Pick's disease (PiD), Parkinson's disease dementia, Postencephalitic parkinsonism (PEP), Primary progressive aphasia, Prion diseases (including Creutzfeldt-Jakob Disease (CJD), Progressive nonfluent aphasia, Variant Creutzfeldt-Jakob Disease (vCJD)), Fatal Familial Insomnia, Kuru, Progressive supercortical gliosis, Progressive supranuclear palsy (PSP), Semantic dementia, Steele-Richardson-Olszewski syndrome, Subacute sclerosing panencephalitis, Tangle-only dementia, Tuberous sclerosis, Huntington's disease and Parkinson's disease, preferably one or more tauopathies and Alzheimer's disease.