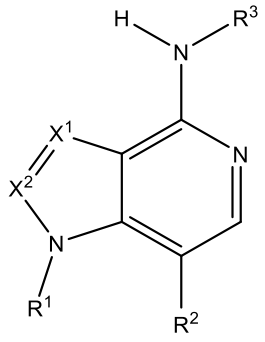
SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~ disclosure is directed to compounds of Formula (I)



(I),

and the tautomers and the stereoisomeric forms thereof, and the deuterated forms thereof, wherein

X^1 and X^2 are each independently selected from CR^4 and N, with the proviso that one of X^1 or X^2 is N;

R^1 is selected from the group consisting of C_{1-6}alkyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, -C(=O)NR^xR^y, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents, wherein the 5-or 6-membered heteroaryl is optionally substituted with one or two independently selected C_{1-4}alkyl substituents; C_{1-6}alkyl substituted with oxetanyl, C_{1-6}alkyl wherein two geminal hydrogens are replaced by oxetanylidene; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein

R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl;

R^2 and R^4 when present, are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of

(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

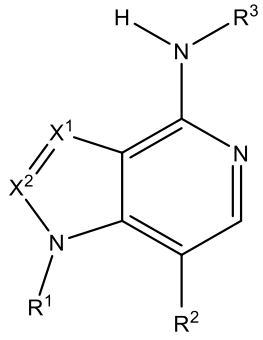
(b) a 9- to 10-membered bicyclic heteroaryl radical selected from the group consisting of 1H-indazolyl, 1H-benzo[d]imidazolyl, 1,8-naphthyridinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-b]pyridazinyl, indolizinyl, 1H-indolyl, quinolinyl, isoquinolinyl, and thiazolo[4,5-b]pyridinyl; optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, C_{1-4}alkyloxy;

and the pharmaceutically acceptable salts and the solvates thereof,

for use as a medicament; in particular for use as a medicament for the prevention or treatment of a tauopathy, in particular a tauopathy selected from the group consisting of Alzheimer's disease, progressive supranuclear palsy, Down's syndrome, frontotemporal lobe dementia, frontotemporal dementia with Parkinsonism-17, Pick's disease, corticobasal degeneration, and agryophilic grain disease; or a neurodegenerative disease accompanied by a tau pathology, in particular a neurodegenerative disease selected from amyotrophic lateral sclerosis or frontotemporal lobe dementia caused by C9ORF72 mutations or for use in preventing or treating a disorder selected from an alpha synucleinopathy, in particular Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, or alpha synucleinopathy caused by Gaucher's disease, in a subject in need thereof.

In one aspect, there is provided a compound of Formula (I)



(I),

or a tautomer or a stereoisomeric form thereof, or a deuterated form thereof, wherein

X^1 and X^2 are each independently selected from CR^4 and N, with the proviso that one of X^1 or X^2 is N;

R^1 is selected from the group consisting of C_{1-6}alkyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, $-C(=O)NR^xR^y$, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents, wherein the 5-or 6-membered heteroaryl is optionally substituted with one or two independently selected C_{1-4}alkyl substituents; C_{1-6}alkyl substituted with oxetanyl, C_{1-6}alkyl wherein two geminal hydrogens are replaced by oxetanylidene; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein

R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl;

R^2 and R^4 when present, are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of

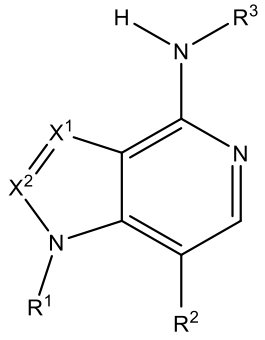
(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

(b) a 9- to 10-membered bicyclic heteroaryl radical selected from the group consisting of 1H-indazolyl, 1H-benzo[d]imidazolyl, 1,8-naphthyridinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-b]pyridazinyl, indolizinyl, 1H-indolyl, quinolinyl, isoquinolinyl, and thiazolo[4,5-b]pyridinyl; optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, C_{1-4}alkyloxy;

or a pharmaceutically acceptable salt, or a solvate thereof; for use as a medicament.

The present ~~invention~~ disclosure also relates to compounds of Formula (I)



(I),

and the tautomers and the stereoisomeric forms thereof, and the deuterated forms thereof, wherein

X^1 and X^2 are each independently selected from CR^4 and N, with the proviso that one of X^1 or X^2 is N;

R^1 is selected from the group consisting of unsubstituted C_{2-6}alkyl; C_{1-6}alkyl substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, -C(=O)NR^xR^y, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents, wherein the 5-or 6-membered heteroaryl is optionally substituted with one or two independently selected C_{1-4}alkyl substituents; C_{1-6}alkyl substituted with oxetanyl, C_{1-6}alkyl wherein two geminal hydrogens are replaced by oxetanylidene; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein

R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl;

R^2 and R^4 when present, are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of

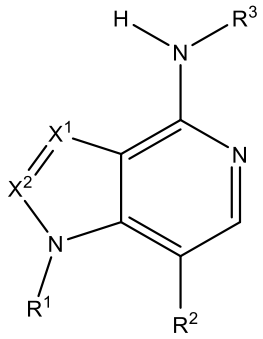
(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

(b) a 9- to 10-membered bicyclic heteroaryl radical selected from the group consisting of 1H-indazolyl, 1H-benzo[d]imidazolyl, 1,8-naphthyridinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-b]pyridazinyl, indolizinyl, 1H-indolyl, quinolinyl, isoquinolinyl, and thiazolo[4,5-b]pyridinyl; optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, C_{1-4}alkyloxy;

and the pharmaceutically acceptable salts and the solvates thereof,

In another aspect, there is provided a compound of Formula (I)



(I),

or a tautomer or a stereoisomeric form thereof, or a deuterated form thereof, wherein

X^1 and X^2 are each independently selected from CR^4 and N, with the proviso that one of X^1 or X^2 is N;

R^1 is selected from the group consisting of unsubstituted C_{2-6}alkyl; C_{1-6}alkyl substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, -C(=O)NR^xR^y, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl,

triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents, wherein the 5-or 6-membered heteroaryl is optionally substituted with one or two independently selected C_{1-4}alkyl substituents; C_{1-6}alkyl substituted with oxetanyl, C_{1-6}alkyl wherein two geminal hydrogens are replaced by oxetanylidene; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein

R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl;

R^2 and R^4 when present, are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of

(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

(b) a 9- to 10-membered bicyclic heteroaryl radical selected from the group consisting of 1H-indazolyl, 1H-benzo[d]imidazolyl, 1,8-naphthyridinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-b]pyridazinyl, indolizinyl, 1H-indolyl, quinolinyl, isoquinolinyl, and thiazolo[4,5-b]pyridinyl; optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, C_{1-4}alkyloxy;

or a pharmaceutically acceptable salt, or a solvate thereof.

Illustrative of the ~~invention~~ disclosure is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. In another aspect, there is provided a pharmaceutical composition comprising a prophylactically or a therapeutically effective amount of a compound as defined herein and a pharmaceutically acceptable carrier. An illustration of the disclosure ~~invention~~ is a pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. Illustrating the disclosure ~~invention~~ is a process for making a pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier. In another aspect, there is provided a process for preparing the pharmaceutical composition as defined herein, comprising mixing a pharmaceutically acceptable carrier with a prophylactically or a therapeutically effective amount of a compound as defined herein.

Exemplifying the disclosure ~~invention~~ are methods of preventing or treating a disorder mediated by the inhibition of O-GlcNAc hydrolase (OGA), comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

Further exemplifying the disclosure ~~invention~~ are methods of inhibiting OGA, comprising administering to a subject in need thereof a prophylactically or a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

An example of the disclosure ~~invention~~ is a method of preventing or treating a disorder selected from a tauopathy, in particular a tauopathy selected from the group consisting of Alzheimer's disease, progressive supranuclear palsy, Down's syndrome, frontotemporal lobe dementia, frontotemporal dementia with Parkinsonism-17, Pick's disease, corticobasal degeneration, and agryophilic grain disease; or a neurodegenerative disease accompanied by a tau pathology, in particular a neurodegenerative disease selected from amyotrophic lateral sclerosis or frontotemporal lobe dementia caused by C9ORF72 mutations, or preventing or treating a disorder selected from an alpha synucleinopathy, in particular Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, or alpha synucleinopathy caused by Gaucher's disease, comprising administering to a subject in need thereof, a prophylactically or a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

In another aspect, there is provided the compound as defined herein, or the pharmaceutical composition as defined herein, for use as a medicament.

In another aspect, there is provided the compound as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment or prevention of a tauopathy, or an alpha synucleinopathy.

In another aspect, there is provided the compound as defined herein, or the pharmaceutical composition as defined herein, for use in the control or reduction of the risk of preclinical Alzheimer's disease, prodromal Alzheimer's disease, or tau-related neurodegeneration as observed in different forms of tauopathies.

In another aspect, there is provided the compound as defined herein, or the pharmaceutical composition as defined herein, for use in the control or reduction of the risk of prodromal Parkinson's disease.

Another example of the disclosure ~~invention~~ is any of the compounds described above for use in preventing or treating a tauopathy, in particular a tauopathy selected from the group consisting of Alzheimer's disease, progressive supranuclear palsy, Down's syndrome, frontotemporal lobe dementia, frontotemporal dementia with Parkinsonism-17, Pick's disease, corticobasal degeneration, and agryophilic grain disease; or a neurodegenerative disease accompanied by a tau pathology, in particular a neurodegenerative disease selected from amyotrophic lateral sclerosis or frontotemporal lobe dementia caused by C9ORF72 mutations or for use in preventing or treating a disorder selected from an alpha synucleinopathy, in particular Parkinson's

disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, or alpha synucleinopathy caused by Gaucher's disease, in a subject in need thereof.

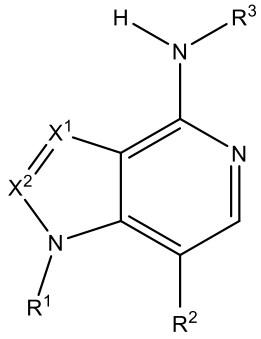
In another aspect, there is provided use of the compound as defined herein, or the pharmaceutical composition as defined herein, in the manufacture of a medicament to prevent or treat a disorder selected from the group consisting of tauopathy or an alpha synucleinopathy, in particular a tauopathy selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis and parkinsonism-dementia complex, argyrophilic grain disease, chronic traumatic encephalopathy, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by MAPT mutations), Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations), Gerstmann-Sträussler-Scheinker disease, Parkinson's disease, Guadeloupean parkinsonism, myotonic dystrophy, neurodegeneration with brain iron accumulation, Niemann-Pick disease, type C, non-Guamanian motor neuron disease with neurofibrillary tangles, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, progressive supranuclear palsy, SLC9A6-related mental retardation, subacute sclerosing panencephalitis, tangle-only dementia, and white matter tauopathy with globular glial inclusions, or in particular an alpha synucleinopathy selected from the group consisting of Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, and alpha synucleinopathy caused by Gaucher's disease.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of Formula (I), as defined herein before, and pharmaceutically acceptable addition salts and solvates thereof. The compounds of Formula (I) are inhibitors of O-GlcNAc hydrolase (OGA) and may be useful in the prevention or treatment of tauopathies, in particular a tauopathy selected from the group consisting of Alzheimer's disease, progressive supranuclear palsy, Down's syndrome, frontotemporal lobe dementia, frontotemporal dementia with Parkinsonism-17, Pick's disease, corticobasal degeneration, and agryophilic grain

CLAIMS

1. A compound of Formula (I)



(I),

or a tautomer or a stereoisomeric form thereof, or a deuterated form thereof, wherein

X^1 and X^2 are each independently selected from CR^4 and N, with the proviso that one of X^1 or X^2 is N;

R^1 is selected from the group consisting of $C_{1\text{-}6}$alkyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -O$C_{1\text{-}4}$alkyl, OH, -C(=O)NR^xR^y, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and $C_{3\text{-}6}$cycloalkyl optionally substituted with one or more independently selected halo substituents, wherein the 5-or 6-membered heteroaryl is optionally substituted with one or two independently selected $C_{1\text{-}4}$alkyl substituents; $C_{1\text{-}6}$alkyl substituted with oxetanyl, $C_{1\text{-}6}$alkyl wherein two geminal hydrogens are replaced by oxetanylidene; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and $C_{1\text{-}4}$alkyl;

with the proviso that a -O$C_{1\text{-}4}$alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein

R^x and R^y are each independently selected from the group consisting of hydrogen, $C_{1\text{-}4}$alkyl, monohalo$C_{1\text{-}4}$alkyl, polyhalo$C_{1\text{-}4}$alkyl, and $C_{3\text{-}6}$cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl;

R^2 and R^4 when present, are each independently selected from the group consisting of hydrogen, halo, $C_{1\text{-}4}$alkyl and $C_{3\text{-}6}$cycloalkyl;

R^3 is selected from the group consisting of

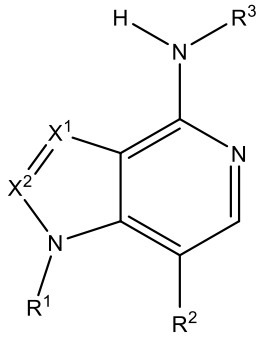
(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

(b) a 9- to 10-membered bicyclic heteroaryl radical selected from the group consisting of 1H-indazolyl, 1H-benzo[d]imidazolyl, 1,8-naphthyridinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-b]pyridazinyl, indolizinyl, 1H-indolyl, quinolinyl, isoquinolinyl, and thiazolo[4,5-b]pyridinyl; optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, C_{1-4}alkyloxy;

or a pharmaceutically acceptable salt, or a solvate thereof; for use as a medicament.

2. A compound of Formula (I)



(I),

or a tautomer or a stereoisomeric form thereof, or a deuterated form thereof, wherein

X^1 and X^2 are each independently selected from CR^4 and N, with the proviso that one of X^1 or X^2 is N;

R^1 is selected from the group consisting of unsubstituted C_{2-6}alkyl; C_{1-6}alkyl substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, -C(=O)NR^xR^y, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents, wherein the 5-or 6-membered heteroaryl

is optionally substituted with one or two independently selected C_{1-4}alkyl substituents; C_{1-6}alkyl substituted with oxetanyl, C_{1-6}alkyl wherein two geminal hydrogens are replaced by oxetanylidene; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein

R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl;

R^2 and R^4 when present, are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of

(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

(b) a 9- to 10-membered bicyclic heteroaryl radical selected from the group consisting of 1H-indazolyl, 1H-benzo[d]imidazolyl, 1,8-naphthyridinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-b]pyridazinyl, indolizinyl, 1H-indolyl, quinolinyl, isoquinolinyl, and thiazolo[4,5-b]pyridinyl; optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, C_{1-4}alkyloxy;

or a pharmaceutically acceptable salt, or a solvate thereof.

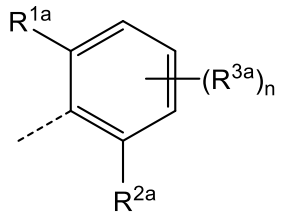
3. The compound according to claim 2, wherein R^3 is selected from the group consisting of

(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

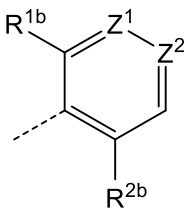
(b) 1H-indazolyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, and C_{1-4}alkyloxy.

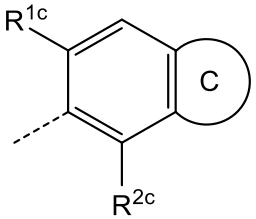
4. The compound according to claim 2 or 3, wherein R^3 is selected from the group consisting of (a), (b), and (c):



(a)



(b)



(c)

wherein R^{1a}, R^{2a}, R^{1b} and R^{2b} are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; with the proviso that at least one of R^{1a} or R^{2a}, and at least one of R^{1b} or R^{2b} is not hydrogen;

Z^1 and Z^2 are each independently selected from N, CH or CR^{3b}, with the proviso that at least one of Z^1 or Z^2 is N;

R^{3a} and R^{3b} when present, are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; wherein

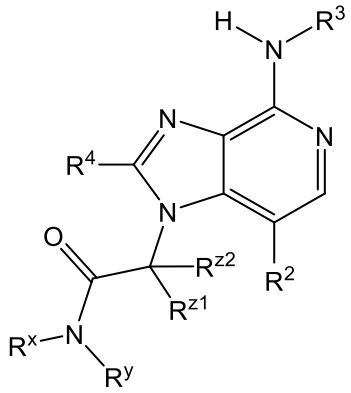
n represents 0, 1 or 2;

Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, and C_{1-4}alkyloxy;

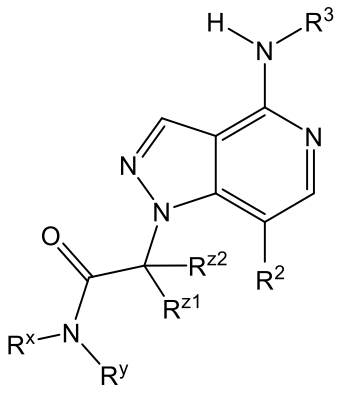
R^{1c} and R^{2c} are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, and -(C=O)C_{1-4}alkyl; and

C forms a fused 5-membered heteroaromatic ring selected from the group consisting of pyrazolyl, and imidazolyl, each being optionally substituted with one or more independently selected C_{1-4}alkyl substituents.

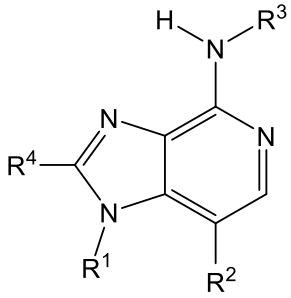
5. The compound according to any one of claims 2 to 4, wherein the compound of Formula (I) has the Formula (I-A), (I-B), (I-C) or (I-D)



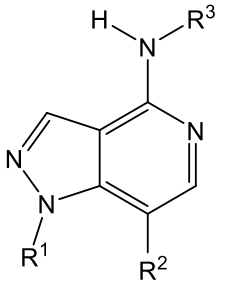
(I-A)



(I-B)



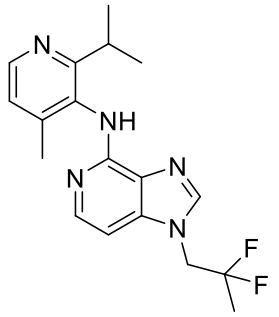
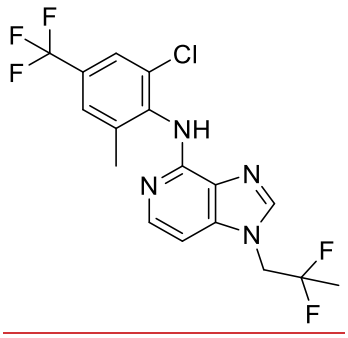
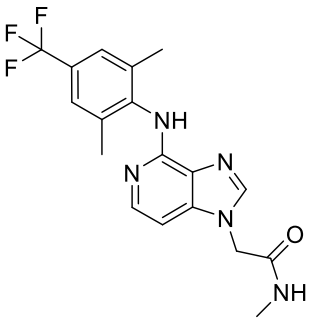
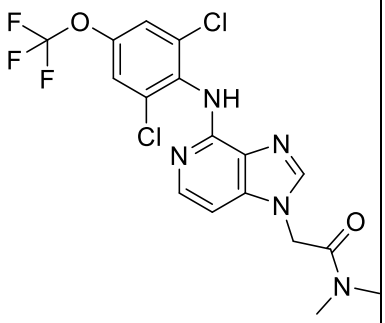
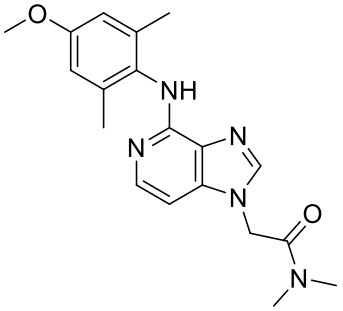
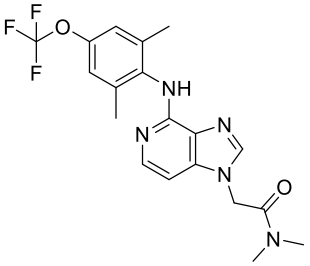
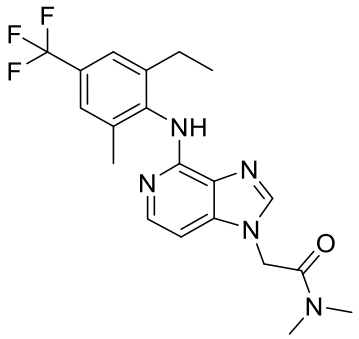
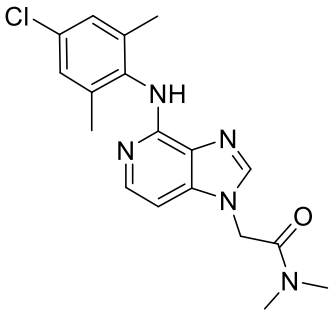
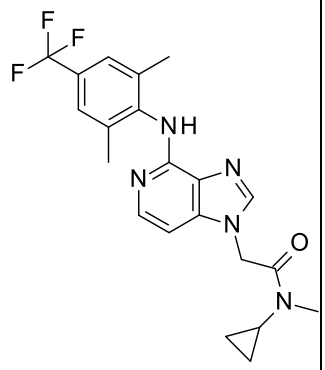
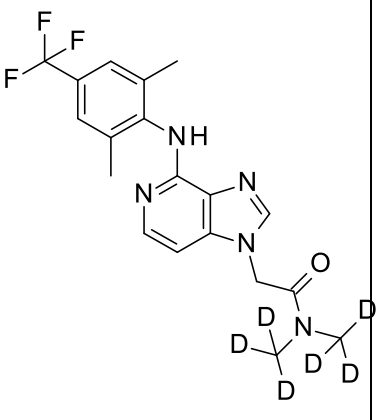
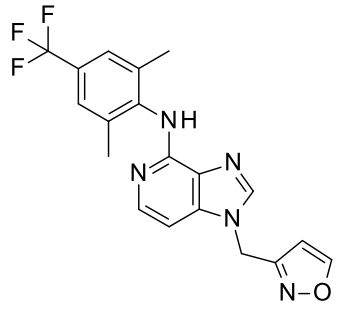
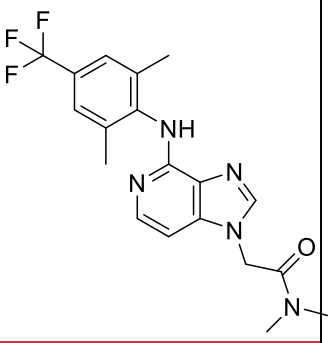
(I-C)

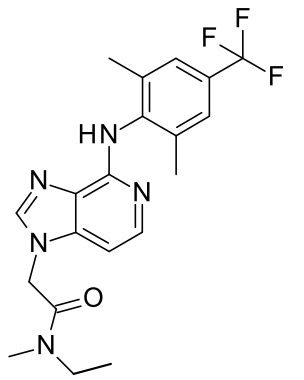
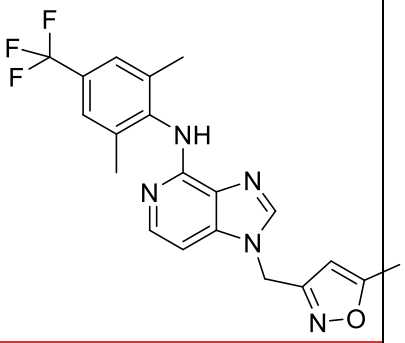


(I-D)

wherein z1 and z2 are each independently selected from hydrogen, deuterium and halogen and the rest of the variables are as defined in any one of claims 2 to 4.

6. The compound according to claim 2, wherein the compound is

 Co. No. 1,	 Co. No. 2,	 Co. No. 4,
 Co. No. 7,	 Co. No. 8,	 Co. No. 9,
 Co. No. 10,	 Co. No. 11,	 Co. No. 52,
 Co. No. 53,	 Co. No. 59,	 Co. No. 61,

		
Co. No. 63, or	Co. No. 80,	

or a pharmaceutically acceptable salt thereof.

~~6~~**7.** A pharmaceutical composition comprising a prophylactically or a therapeutically effective amount of a compound according to any one of claims 2 to ~~5~~ 6 and a pharmaceutically acceptable carrier.

~~7~~**8.** A process for preparing the pharmaceutical composition according to claim ~~6~~7, comprising mixing a pharmaceutically acceptable carrier with a prophylactically or a therapeutically effective amount of a compound according to any one of claims 2 to ~~5~~6.

~~8~~**9.** The compound as defined in any one of claims 2 to ~~5~~6, or the pharmaceutical composition as defined in claim ~~6~~7, for use as a medicament.

~~9~~**10.** The compound for use according to claim 1, in the treatment or prevention of a tauopathy, or an alpha synucleinopathy.

~~10~~**11.** The compound as defined in any one of claims 2 to ~~5~~6, or the pharmaceutical composition as defined in claim ~~6~~7, for use in the treatment or prevention of a tauopathy, or an alpha synucleinopathy.

~~11~~**12.** The compound or the pharmaceutical composition for use according to claim ~~9~~ 10 or ~~10~~11, wherein the tauopathy is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis and parkinsonism-dementia complex, argyrophilic grain disease, chronic traumatic encephalopathy, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia and parkinsonism linked to

chromosome 17 (caused by MAPT mutations), Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations), Gerstmann-Sträussler-Scheinker disease, Parkinson's disease, Guadeloupean parkinsonism, myotonic dystrophy, neurodegeneration with brain iron accumulation, Niemann-Pick disease, type C, non-Guamanian motor neuron disease with neurofibrillary tangles, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, progressive supranuclear palsy, SLC9A6-related mental retardation, subacute sclerosing panencephalitis, tangle-only dementia, and white matter tauopathy with globular glial inclusions; and the alpha synucleinopathy is selected from the group consisting of Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, and alpha synucleinopathy caused by Gaucher's disease.

~~12~~13. The compound for use according to claim 1, in the control or reduction of the risk of preclinical Alzheimer's disease, prodromal Alzheimer's disease, or tau-related neurodegeneration as observed in different forms of tauopathies.

~~13~~14. The compound as defined in any one of claims 2 to ~~5~~6, or the pharmaceutical composition as defined in claim ~~6~~7, for use in the control or reduction of the risk of preclinical Alzheimer's disease, prodromal Alzheimer's disease, or tau-related neurodegeneration as observed in different forms of tauopathies.

~~14~~15. The compound for use as defined in claim 1, in the control or reduction of the risk of prodromal Parkinson's disease.

~~15~~16. The compound as defined in any one of claims 2 to ~~5~~6, or the pharmaceutical composition as defined in claim ~~6~~7, for use in the control or reduction of the risk of prodromal Parkinson's disease.

~~16~~17. A ~~U~~use of ~~a~~ the compound as defined in claim 1 in the manufacture of a medicament ~~for~~ to prevent~~ing~~ or treat~~ing~~ a disorder selected from the group consisting of tauopathy or an alpha synucleinopathy, in particular a tauopathy selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis and parkinsonism-dementia complex, argyrophilic grain disease, chronic traumatic encephalopathy, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by

MAPT mutations), Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations), Gerstmann-Sträussler-Scheinker disease, Parkinson's disease, Guadeloupean parkinsonism, myotonic dystrophy, neurodegeneration with brain iron accumulation, Niemann-Pick disease, type C, non-Guamanian motor neuron disease with neurofibrillary tangles, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, progressive supranuclear palsy, SLC9A6-related mental retardation, subacute sclerosing panencephalitis, tangle-only dementia, and white matter tauopathy with globular glial inclusions, or in particular an alpha synucleinopathy selected from the group consisting of Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, and alpha synucleinopathy caused by Gaucher's disease.

~~17~~**18.** A ~~U~~use of ~~a~~ the compound as defined in any one of claims 2 to ~~5~~6, or the pharmaceutical composition as defined in claim ~~6~~7, in the manufacture of a medicament ~~for~~ to prevent~~ing~~ or treat~~ing~~ a disorder selected from the group consisting of tauopathy or an alpha synucleinopathy, in particular a tauopathy selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis and parkinsonism-dementia complex, argyrophilic grain disease, chronic traumatic encephalopathy, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by MAPT mutations), Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations), Gerstmann-Sträussler-Scheinker disease, Parkinson's disease, Guadeloupean parkinsonism, myotonic dystrophy, neurodegeneration with brain iron accumulation, Niemann-Pick disease, type C, non-Guamanian motor neuron disease with neurofibrillary tangles, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, progressive supranuclear palsy, SLC9A6-related mental retardation, subacute sclerosing panencephalitis, tangle-only dementia, and white matter tauopathy with globular glial inclusions, or in particular an alpha synucleinopathy selected from the group consisting of Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, and alpha synucleinopathy caused by Gaucher's disease.