

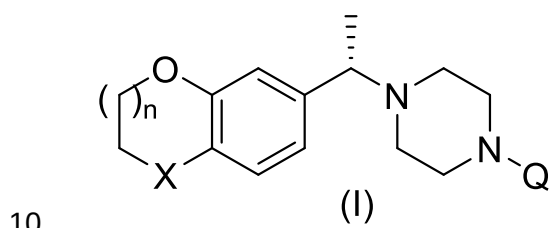
Acid addition salts of piperazine derivatives

Field of the invention

The invention relates to acid addition salts of hydrochloric acid, maleic acid or tartraic acid or other acids 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



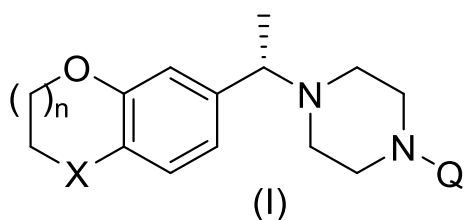
wherein X, n and Q are as defined further below, are as pharmaceutical ingredients and show high activity as glycosidase inhibitors. For example, PCT/EP2015/069598 describes e.g. N-(5-{4-[(1S)-1-(2,3-dihydro-1-benzofuran-6-yl)ethyl]piperazin-1-yl}-1,3,4-thiadiazol-2-yl)acetamide and N-(2-{4-[(1S)-1-(2H-1,3-benzodioxol-5-yl)ethyl]piperazin-1-yl}pyrimidin-5-yl)acetamide as active glycosidase inhibitors having high inhibitory activities.

Although the compounds of formula I have very useful pharmaceutical activities as free piperazine 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

In a first aspect, the present disclosure refers to an acid addition salt of hydrochloric acid, maleic acid, tartaric acid, sulfuric acid or p-toluolsulfonic acid with compounds of formula I



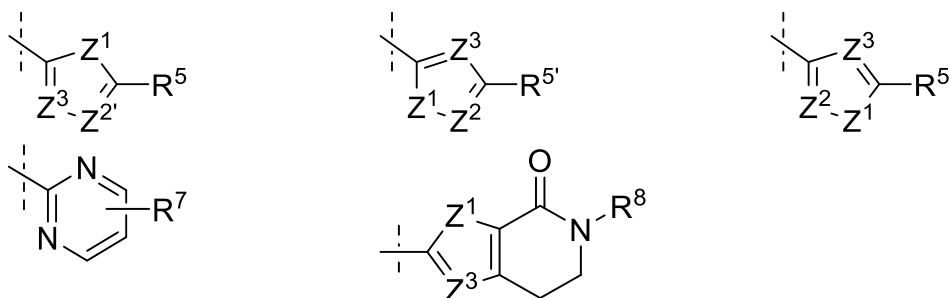
5 wherein

X denotes O or CH₂,

n denotes 0 or 1,

and

Q denotes one of the following groups:



10

Z¹ is S, O, NR³;

Z², Z^{2'}, Z³ independently denote CR⁵, CR⁶ or N;

15

R⁵, R^{5'}, R⁶, R⁷ independently denote H, Hal, NR³R⁴, NO₂, straight chain or branched alkyl having 1 to 12 carbon atoms, wherein 1 to 3 CH₂-groups may be replaced by a group selected from O, NR³, S, SO, SO₂, CO, COO, OCO, CONR³, NR³CO and wherein 1 to 5 hydrogen atoms may be replaced by Hal, NR³R⁴, NO₂, OR³, Het, Ar, Cyc, or denote Ar, Het or Cyc;

20

R⁸ denotes H, methyl or straight chain or branched alkyl having 2 to 12 carbon atoms, wherein 1 to 3 CH₂-groups may be replaced by a group selected from O, NR³, S, SO, SO₂, CO, COO, OCO, CONR³, NR³CO and wherein 1 to 5 hydrogen atoms may be replaced by Hal, NR³R⁴ or NO₂;

	R^3, R^4	denote each independently H or a straight chain or branched alkyl group having 1 to 12 carbon atoms;
	Hal	denotes F, Cl, Br or I;
5	Het	denotes a saturated, unsaturated or aromatic ring, being monocyclic or bicyclic or fused-bicyclic and having 3- to 8- members and containing 1 to 4 heteroatoms selected from N, O and S, which may be substituted by 1 to 3 substituents selected from NR_3R_4 , NH_2 , $N(CH_3)_2$, phenyl, 2-,3- or 4-hydroxy or methoxyphenyl, alkyl, CF_3 , alkoxy (Oalkyl), hydroxyalkylen, alkoxyalkylen, $COOH$, $COOalkyl$, $CONHalkyl$, $CONH_2$, $CON(CH_3)_2$, $NHCOalkyl$, $NHalkyl$, CO-N-morpholinyl, $CON(CH_3)CH_2CH_2N(CH_3)_2$, CO-1-piperidinyl, CO-4-hydroxy-1-piperidinyl, CO-1-piperazinyl, CO-4-methyl-1-piperazinyl, $CH_2-N-morpholinyl$, $CH_2N(H)COCH_3$, $CH_2N(CH_3)COCH_3$, Hal and OR^3 ;
10		
15	Ar	denotes a 6-membered carbocyclic aromatic ring or a fused or non fused bicyclic aromatic ring system, which is optionally substituted by 1 to 3 substituents independently selected from NR_3R_4 , NH_2 , $N(CH_3)_2$, phenyl, 2-,3- or 4-hydroxy or methoxyphenyl, alkyl, CF_3 , alkoxy (Oalkyl), hydroxyalkylen, alkoxyalkylen, $COOH$, $COOalkyl$, $CONHalkyl$, $CONH_2$, $CON(CH_3)_2$, $NHCOalkyl$, $NHalkyl$, CO-N-morpholinyl, $CON(CH_3)CH_2CH_2N(CH_3)_2$, CO-1-piperidinyl, CO-4-hydroxy-1-piperidinyl, CO-1-piperazinyl, CO-4-methyl-1-piperazinyl, $CH_2-N-morpholinyl$, $CH_2N(H)COCH_3$, $CH_2N(CH_3)COCH_3$, OR^3 and Hal;
20		
25	Cyc	denotes a saturated or an unsaturated carbocyclic ring having from 3 to 8 carbon atoms which is optionally substituted by 1 to 3 substituents independently selected from NR_3R_4 , NH_2 , $N(CH_3)_2$, phenyl, 2-,3- or 4-hydroxy or methoxyphenyl, alkyl, CF_3 , alkoxy (Oalkyl), hydroxyalkylen, alkoxyalkylen, $COOH$, $COOalkyl$, $CONHalkyl$, $CONH_2$, $CON(CH_3)_2$, $NHCOalkyl$, $NHalkyl$, CO-N-morpholinyl, $CON(CH_3)CH_2CH_2N(CH_3)_2$, CO-1-piperidinyl, CO-4-hydroxy-1-piperidinyl, CO-1-piperazinyl, CO-4-methyl-1-piperazinyl, $CH_2-N-morpholinyl$, $CH_2N(H)COCH_3$, $CH_2N(CH_3)COCH_3$, Hal and OH,
30		

as well as solid forms thereof.

In another aspect, the present disclosure refers to a method for the preparation of an acid additions salt of hydrochloric acid, maleic acid, tartaric acid sulfuric acid or p-

toluolsulfonic acid with compounds of formula I disclosed herein, comprising the following steps :

- a) suspending or dissolving the selected compound of formula I and the selected acid in a suitable solvent or solvent mixture;
- 5 b) heating the mixture obtained in step a) to a temperature of between 30 °C to 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.

- 10 In yet another aspect, the present disclosure refers to a solid oral dosage form comprising an acid addition salt disclosed herein.

In a further aspect, the present disclosure refers to an acid addition salt disclosed herein for use as a medicament.

- 15 In another aspect, the present disclosure refers to an acid addition salt disclosed herein for use in a treatment of a condition selected from neurodegenerative diseases, diabetes, cancer, cardiovascular diseases and stroke.

In yet another aspect, the present disclosure refers to an acid addition salt disclosed herein for use in a method for treating a tauopathy, wherein the acid addition salt is to be administered to a mammal in need of such treatment.

- 20 In a further aspect, the present disclosure refers to a method for inhibiting a glycosidase, wherein a system expressing the glycosidase is contacted with an acid addition salt of hydrochloric acid, maleic acid or tartaric acid with acid addition salt disclosed herein under in-vitro conditions such that the glycosidase is inhibited.

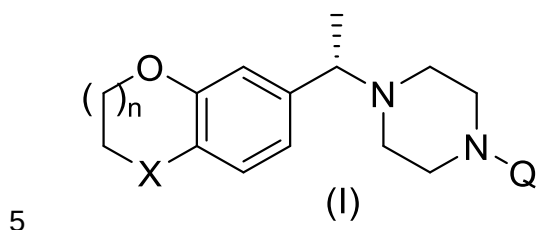
- 25 In another aspect, the present disclosure refers to a use of an acid addition salt disclosed herein, in the manufacture of a medicament for treating a tauopathy, wherein the acid addition salt is to be administered to a mammal in need of such treatment.

- 30 In yet another aspect, the present disclosure refers to a use of an acid addition salt disclosed herein, in the manufacture of a medicament for treating a condition selected from neurodegenerative diseases, diabetes, cancer, cardiovascular diseases and stroke.

It has now been found that compounds of formula I

Claims

1. An acid addition salt of hydrochloric acid, maleic acid, tartaric acid, sulfuric acid or p-toluolsulfonic acid with compounds of formula I



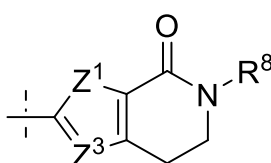
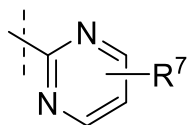
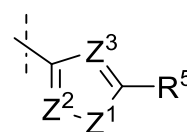
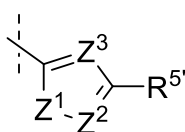
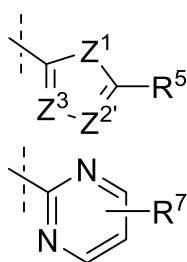
wherein

X denotes O or CH₂,

n denotes 0 or 1,

and

10 Q denotes one of the following groups:



Z¹ is S, O, NR³;

Z², Z^{2'}, Z³ independently denote CR⁵, CR⁶ or N;

15 R⁵, R^{5'}, R⁶, R⁷ independently denote H, Hal, NR³R⁴, NO₂, straight chain or branched alkyl having 1 to 12 carbon atoms, wherein 1 to 3 CH₂-groups may be replaced by a group selected from O, NR³, S, SO, SO₂, CO, COO, OCO, CONR³, NR³CO and wherein 1 to 5 hydrogen atoms may be replaced by Hal, NR³R⁴, NO₂, OR³, Het, Ar, Cyc, or denote Ar, Het or Cyc;

20 R⁸ denotes H, methyl or straight chain or branched alkyl having 2 to 12 carbon atoms, wherein 1 to 3 CH₂-groups may be replaced by a group selected

from O, NR³, S, SO, SO₂, CO, COO, OCO, CONR³, NR³CO and wherein 1 to 5 hydrogen atoms may be replaced by Hal, NR³R⁴ or NO₂;

R³, R⁴ denote each independently H or a straight chain or branched alkyl group having 1 to 12 carbon atoms;

5 Hal denotes F, Cl, Br or I;

10 Het denotes a saturated, unsaturated or aromatic ring, being monocyclic or bicyclic or fused-bicyclic and having 3- to 8- members and containing 1 to 4 heteroatoms selected from N, O and S, which may be substituted by 1 to 3 substituents selected from NR₃R₄, NH₂, N(CH₃)₂, phenyl, 2-,3- or 4-hydroxy or methoxyphenyl, alkyl, CF₃, alkoxy (Oalkyl), hydroxyalkylen, alkoxyalkylen, COOH, COOalkyl, CONHalkyl, CONH₂, CON(CH₃)₂, NHCOalkyl, NHalkyl, CO-N-morpholinyl, CON(CH₃)CH₂CH₂N(CH₃)₂, CO-1-piperidiny, CO-4-hydroxy-1-piperidiny, CO-1-piperazinyl, CO-4-methyl-1-piperazinyl, CH₂-N-morpholinyl, CH₂N(H)COCH₃, CH₂N(CH₃)COCH₃, Hal and OR³;

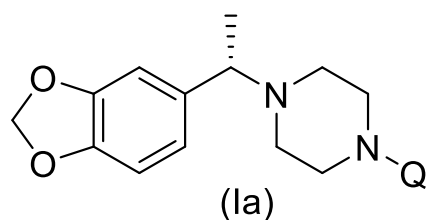
15 Ar denotes a 6-membered carbocyclic aromatic ring or a fused or non fused bicyclic aromatic ring system, which is optionally substituted by 1 to 3 substituents independently selected from NR₃R₄, NH₂, N(CH₃)₂, phenyl, 2-,3- or 4-hydroxy or methoxyphenyl, alkyl, CF₃, alkoxy (Oalkyl), hydroxyalkylen, alkoxyalkylen, COOH, COOalkyl, CONHalkyl, CONH₂, CON(CH₃)₂, NHCOalkyl, NHalkyl, CO-N-morpholinyl, CON(CH₃)CH₂CH₂N(CH₃)₂, CO-1-piperidiny, CO-4-hydroxy-1-piperidiny, CO-1-piperazinyl, CO-4-methyl-1-piperazinyl, CH₂-N-morpholinyl, CH₂N(H)COCH₃, CH₂N(CH₃)COCH₃, OR³ and Hal;

25 Cyc denotes a saturated or an unsaturated carbocyclic ring having from 3 to 8 carbon atoms which is optionally substituted by 1 to 3 substituents independently selected from NR₃R₄, NH₂, N(CH₃)₂, phenyl, 2-,3- or 4-hydroxy or methoxyphenyl, alkyl, CF₃, alkoxy (Oalkyl), hydroxyalkylen, alkoxyalkylen, COOH, COOalkyl, CONHalkyl, CONH₂, CON(CH₃)₂, NHCOalkyl, NHalkyl, CO-N-morpholinyl, CON(CH₃)CH₂CH₂N(CH₃)₂, CO-1-piperidiny, CO-4-hydroxy-1-piperidiny, CO-1-piperazinyl, CO-4-methyl-1-piperazinyl, CH₂-N-morpholinyl, CH₂N(H)COCH₃, CH₂N(CH₃)COCH₃, Hal and OH,

as well as solid forms thereof.

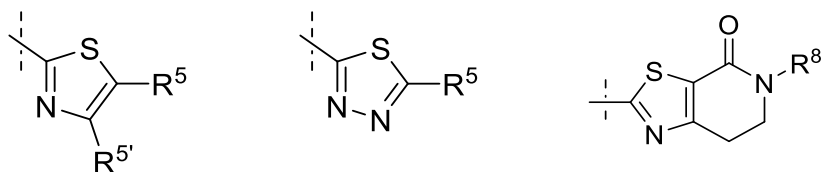
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2. An acid addition salt according to claim 1, wherein the acid addition salt is an acid addition salt of hydrochloric acid, maleic acid, tartaric acid, sulfuric acid or p-toluolsulfonic acid with compounds of formula Ia

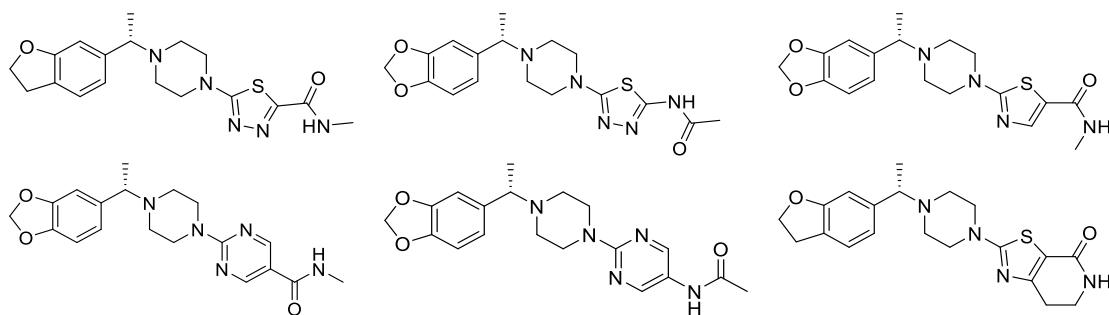


5 wherein Q has the meaning given in claim 1, and solid forms thereof.

3. The acid addition salt according to claim 1 or 2, wherein Q is selected from the group



10 4. An acid addition salt according to claim 1, wherein the acid addition salt is an acid addition salt of hydrochloric acid, maleic acid, tartaric acid, sulfuric acid or p-toluolsufonic acid with one of the following compounds:



15 5. The acid addition salt according to any one of claims 1 to 4 in a molar ratio of compounds of formula I to acid of 1 to 1.

6. An acid addition salt according to claim 5, selected from:

N-(5-{4-[(1S)-1-(2,3-dihydro-1-benzofuran-6-yl)ethyl]piperazin-1-yl}-1,3,4-thiadiazol-2-yl)acetamide, mono-hydrochloride,

- N-(5-{4-[(1S)-1-(2H-1,3-benzodioxol-5-yl)ethyl]piperazin-1-yl}-1,3,4-thiadiazol-2-yl)acetamide, mono-hydrochloride,
- 2-{4-[(1S)-1-(2H-1,3-benzodioxol-5-yl)ethyl]piperazin-1-yl}-N-methyl-1,3-thiazole-5-carboxamide, mono-hydrochloride,
- 5 2-{4-[(1S)-1-(2H-1,3-benzodioxol-5-yl)ethyl]piperazin-1-yl}-N-methylpyrimidine-5-carboxamide, mono-hydrochloride,
- N-(2-{4-[(1S)-1-(2H-1,3-benzodioxol-5-yl)ethyl]piperazin-1-yl}pyrimidin-5-yl)acetamide, mono-hydrochloride and
- 10 2-{4-[(1S)-1-(2,3-dihydro-1-benzofuran-6-yl)ethyl]piperazin-1-yl}-4H,5H,6H,7H-[1,3]thiazolo[5,4-c]pyridin-4-one, mono-hydrochloride.
7. An acid addition salt according to claim 1, wherein the acid addition salt is N-(5-{4-[(1S)-1-(2H-1,3-benzodioxol-5-yl)ethyl]piperazin-1-yl}-1,3,4-thiadiazol-2-yl)acetamide, mono-hydrochloride in a solid form having the characteristic X-ray powder diffraction pattern as shown on Figure 11.
- 15 7. A method for the preparation of an acid additions salt of hydrochloric acid, maleic acid, tartaric acid sulfuric acid or p-toluolsulfonic acid with compounds of formula I according to claim 1, comprising the following steps :
- 20 a) suspending or dissolving the selected compound of formula I and the selected acid in a suitable solvent or solvent mixture;
- b) heating the mixture obtained in step a) to a temperature of between 30 °C to the boiling point of the selected solvent or solvent mixture, and allowing the mixture to cool to room temperature;
- 25 c) optionally repeating step b) several times;
- d) separating and drying the solid thus obtained.
9. A solid oral dosage form comprising an acid addition salt according to any one of claims 1 to 7.

10. An acid addition salt according to any one of claims 1 to 7 for use as a medicament.
- 5 11. An acid addition salt according to any one of claims 1 to 7 for use in a treatment of a condition selected from neurodegenerative diseases, diabetes, cancer, cardiovascular diseases and stroke.
- 10 12. An acid addition salt according to any one of claims 1 to 7 for use in a treatment of a condition according to claim 11, 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 dmenetia (BvFTD), Bluit disease, Chronic traumatic encephalopathy, Corticobasal degeneration (CBP), Dementia pugilistica, Diffuse neurofibrillary
15 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
20 (neurodegeneration with brain iron accumulation type 1), Lead encephalopathy, Lipofuscinosis, Meningioangiomas, Multiple system atrophy, Myotonic dystrophy, Niemann-Pick disease (type C), Pallidoponto-nigral degeneration, Parkinsonism-dementia complex of Guam, Pick's disease (PiD), Parkinson's disease dementia, Postencephalitic parkinsonism (PEP), Primary progressive
25 aphasia, Prion diseases (including Creutzfeldt-Jakob Disease (GJD), Progressive nonfluent aphasia, Variant Creutzfeldt-Jakob Disease (vCJD), Fatal Familial Insomnia, Kuru, Progressive supracortical gliosis, Progressive supranuclear palsy (PSP), Semantic dementia, Steele-Richardson-Olszewski syndrome, Subacute sclerosing panencephalitis, Tangle-only dementia, Tuberous sclerosis,
30 Huntington's disease and Parkinson's disease.
13. An acid addition salt according to any one of claims 1 to 7 for use in a treatment of a condition according to claim 11, wherein the condition is selected from the group of one or more tauopathies and Alzheimer's disease.

14. An acid addition salt according to any one of claims 1 to 7 for use in a method for treating a tauopathy, wherein the acid addition salt is to be administered to a mammal in need of such treatment.
- 5 15. A method for inhibiting a glycosidase, wherein a system expressing the glycosidase is contacted with an acid addition salt of hydrochloric acid, maleic acid or tartaric acid with acid addition salt according to any one of claims 1 to 7 under in-vitro conditions such that the glycosidase is inhibited.
- 10 16. Use of an acid addition salt according to any one of claims 1 to 7, in the manufacture of a medicament for treating a tauopathy, wherein the acid addition salt is to be administered to a mammal in need of such treatment.
- 15 17. Use of an acid addition salt according to any one of claims 1 to 7, in the manufacture of a medicament for treating a condition selected from neurodegenerative diseases, diabetes, cancer, cardiovascular diseases and stroke.
- 20 18. Use of an acid addition salt according to any one of claims 1 to 7, in the manufacture of a medicament for treating a condition according to claim 17, 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), Argrophilic grain disease, Behavioural variant frontotemporal dmenetia (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), Pallidoponto-nigral degeneration, Parkinsonism-dementia complex of Guam, Pick's disease (PiD),
- 30

5 Parkinson's disease dementia, Postencephalitic parkinsonism (PEP), Primary progressive aphasia, Prion diseases (including Creutzfeldt-Jakob Disease (GJD), 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.

10 19. Use of an acid addition salt according to any one of claims 1 to 7, in the manufacture of a medicament for treating a condition according to claim 17, wherein the condition is selected from the group of one or more tauopathies and Alzheimer's disease.