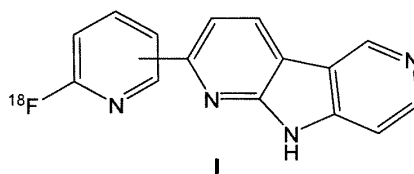


New PCT-application
based on EP 18 15 3326.6
AC Immune SA; Life Molecular Imaging SA
Vossius Ref.: AA3168 PCT

Vossius & Partner
Patentanwälte Rechtsanwälte mbB
Siebertstr. 4
81675 München

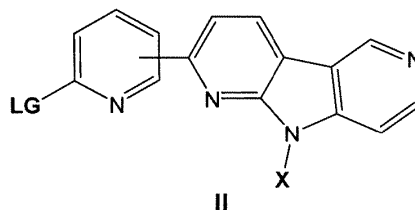
CLAIMS

1. A method of preparing a compound of the formula I



comprising the steps of

- A) reacting a compound of the formula II with a ^{18}F fluorinating agent



wherein **X** is H or **PG**,

LG is a leaving group, and

PG is an amine protecting group, and

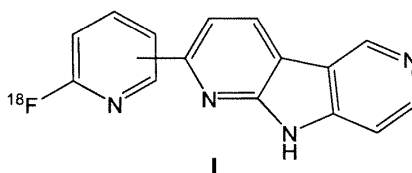
- B) optionally, if **X** is **PG**, cleaving the protecting group **PG**, and
- C) subjecting the resultant compound of the formula I to high-performance liquid chromatography (HPLC) using a mobile phase comprising ethanol and water.

2. The method according to claim 1, wherein **X** is **PG**, step B is absent and the protecting group **PG** is cleaved in step A.

3. The method according to claim 1, wherein **X** is **PG** and the protecting group **PG** is cleaved in step B.

4. The method according to any one of claims 1 to 3, wherein the ratio of ethanol to water in the mobile phase is from about 5/95 v/v to about 80/20 v/v.

5. The method according to any of claims 1 to 4, wherein the pH of the mobile phase is from about 0 to about 8, preferably about 1 to about 3.
6. The method according to any of claims 1 to 5, wherein the mobile phase further
5 comprises a buffer, which is preferably selected from alkali metal dihydrogen phosphates, di alkali metal hydrogen phosphates, tri alkali metal phosphates, alkali metal acetates, alkali metal formates, and mono/di/tri alkali metal citrates.
7. The method according to any one of claims 1 to 6, wherein the high-performance liquid
10 chromatography (HPLC) is conducted under a pressure of about 50 to about 400 bars, preferably about 50 to about 250 bar.
8. The method according to any one of claims 1 to 7, wherein the method is an automated
15 method, in which Step A, optional Step B, and Step C are performed on an automated synthesizer.
9. The method according to any one of claims 1 to 8, wherein the high-performance liquid
20 chromatography (HPLC) results in a fraction comprising the compound of the formula I and this fraction is subjected to a step D) sterile filtration.
10. The method according to any one of claims 1 to 9, wherein the method does not
25 comprise solid phase extraction of the compound of the formula I after step C, preferably wherein the method does not comprise solid phase extraction of the compound of the formula I before or after step C.
11. The method according to any one of claims 1 to 10, wherein the compound of the
30 formula I is not subjected to chromatography after the high-performance liquid chromatography (HPLC) of step C, preferably wherein the compound of the formula I is not subjected to chromatography other than the high-performance liquid chromatography (HPLC) of step C.
12. A diagnostic composition comprising a compound of the formula I



which is obtainable by the process according to any one of claims 1 to 12 and optionally a diagnostically acceptable carrier, diluent, adjuvant or excipient.

13. The composition according to claim 12 for use in diagnostics.
- 5
14. The composition according to claim 12 for use in the imaging of Tau aggregates, particularly for use in positron emission tomography imaging of Tau aggregates.
15. The composition for use according to claim 13 or 14, wherein the disorder is selected from Alzheimer's disease (AD), familial AD, Creutzfeldt-Jacob disease, dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury (TBI), amyotrophic lateral sclerosis, Parkinsonism-dementia complex of Guam, non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain disease, corticobasal degeneration (CBD), diffuse neurofibrillary tangles with calcification, frontotemporal dementia with Parkinsonism linked to chromosome 17, Hallervorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, pallido-ponto-nigral degeneration, Pick's disease (PiD), progressive subcortical gliosis, progressive supranuclear palsy (PSP), subacute sclerosing panencephalitis, tangle only dementia, postencephalitic Parkinsonism, myotonic dystrophy, Tau panencephalopathy, AD-like with astrocytes, certain prion diseases (GSS with Tau), mutations in LRRK2, chronic traumatic encephalopathy, familial British dementia, familial Danish dementia, frontotemporal lobar degeneration, Guadeloupean Parkinsonism, neurodegeneration with brain iron accumulation, SLC9A6-related mental retardation, white matter tauopathy with globular glial inclusions, traumatic stress syndrome, epilepsy, Lewy body dementia (LBD), hereditary cerebral hemorrhage with amyloidosis (Dutch type), mild cognitive impairment (MCI), multiple sclerosis, Parkinson's disease, atypical parkinsonism, HIV-related dementia, adult onset diabetes, senile cardiac amyloidosis, endocrine tumors, glaucoma, ocular amyloidosis, primary retinal degeneration, macular degeneration (such as age-related macular degeneration (AMD)), optic nerve drusen, optic neuropathy, optic neuritis, lattice dystrophy, Huntington's disease, ischemic stroke and psychosis in AD; preferably Alzheimer's disease.
- 10
- 15
- 20
- 25
- 30
- 35
16. The composition for use according to any one of claims 13 to 15, wherein the composition is to be administered by injection.

17. A composition as defined in claim 12 for use in the diagnosis of a disorder associated with Tau aggregates or for use in the diagnosis of a tauopathy, particularly wherein the diagnosis is conducted by positron emission tomography.
- 5 18. A composition for use according to claim 17, wherein the tauopathy is a 3R tauopathy.
19. A composition for use according to claim 17, wherein the tauopathy is a 4R tauopathy.
- 10 20. The composition for use according to claim 17, wherein the disorder is selected from from Alzheimer's disease (AD), familial AD, Creutzfeldt-Jacob disease, dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury (TBI), amyotrophic lateral sclerosis, Parkinsonism-dementia complex of Guam, non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain disease, corticobasal degeneration (CBD), diffuse neurofibrillary tangles with calcification, frontotemporal dementia with Parkinsonism linked to chromosome 17, Hallervorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, pallido-ponto-nigral degeneration, Pick's disease (PiD), progressive subcortical gliosis, progressive supranuclear palsy (PSP), subacute sclerosing panencephalitis, tangle only dementia, postencephalitic Parkinsonism, myotonic dystrophy, Tau panencephalopathy, AD-like with astrocytes, certain prion diseases (GSS with Tau), mutations in LRRK2, chronic traumatic encephalopathy, familial British dementia, familial Danish dementia, frontotemporal lobar degeneration, Guadeloupean Parkinsonism, neurodegeneration with brain iron accumulation, SLC9A6-related mental retardation, white matter tauopathy with globular glial inclusions, traumatic stress syndrome, epilepsy, Lewy body dementia (LBD), hereditary cerebral hemorrhage with amyloidosis (Dutch type), mild cognitive impairment (MCI), multiple sclerosis, Parkinson's disease, atypical parkinsonism, HIV-related dementia, adult onset diabetes, senile cardiac amyloidosis, endocrine tumors, glaucoma, ocular amyloidosis, primary retinal degeneration, macular degeneration (such as age-related macular degeneration (AMD)), optic nerve drusen, optic neuropathy, optic neuritis, lattice dystrophy, Huntington's disease, ischemic stroke and psychosis in AD; preferably Alzheimer's disease.
- 15 25
- 20 30
- 35 21. The composition for use according to claim 20, wherein the disorder is Alzheimer's disease (AD).

22. The composition for use according to claim 20, wherein the disorder is Parkinson's disease or atypical parkinsonism.
23. The composition for use according to claim 20, wherein the disorder is progressive supranuclear palsy (PSP).
24. The composition for use according to claim 20, wherein the disorder is Pick's disease (PiD).
25. The composition for use according to any one of claims 17 to 24, wherein the Tau aggregates are imaged in the brain or in the eye.
26. A method of imaging of Tau aggregates, particularly a method of positron emission tomography imaging of Tau aggregates, wherein an effective amount of a composition as defined in claim 12 is administered to a patient.
27. A method of diagnosing a disorder associated with Tau aggregates or a tauopathy, wherein an effective amount of a composition as defined in claim 12 is administered to a patient, particularly wherein the diagnosis is conducted by positron emission tomography.
28. A method according to claim 27, wherein the tauopathy is a 3R tauopathy.
29. A method according to claim 27, wherein the tauopathy is a 4R tauopathy.
30. The method according to claim 27, wherein the disorder is selected from from Alzheimer's disease (AD), familial AD, Creutzfeldt-Jacob disease, dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury (TBI), amyotrophic lateral sclerosis, Parkinsonism-dementia complex of Guam, non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain disease, corticobasal degeneration (CBD), diffuse neurofibrillary tangles with calcification, frontotemporal dementia with Parkinsonism linked to chromosome 17, Hallervorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, pallido-ponto-nigral degeneration, Pick's disease (PiD), progressive subcortical gliosis, progressive supranuclear palsy (PSP), subacute sclerosing panencephalitis, tangle only dementia, postencephalitic Parkinsonism, myotonic dystrophy, Tau panencephalopathy, AD-like

with astrocytes, certain prion diseases (GSS with Tau), mutations in LRRK2, chronic traumatic encephalopathy, familial British dementia, familial Danish dementia, frontotemporal lobar degeneration, Guadeloupean Parkinsonism, neurodegeneration with brain iron accumulation, SLC9A6-related mental retardation, white matter tauopathy with globular glial inclusions, traumatic stress syndrome, epilepsy, Lewy body dementia (LBD), hereditary cerebral hemorrhage with amyloidosis (Dutch type), mild cognitive impairment (MCI), multiple sclerosis, Parkinson's disease, atypical parkinsonism, HIV-related dementia, adult onset diabetes, senile cardiac amyloidosis, endocrine tumors, glaucoma, ocular amyloidosis, primary retinal degeneration, macular degeneration (such as age-related macular degeneration (AMD)), optic nerve drusen, optic neuropathy, optic neuritis, lattice dystrophy, Huntington's disease, ischemic stroke and psychosis in AD; preferably Alzheimer's disease.

31. The method according to claim 30, wherein the disorder is Alzheimer's disease (AD).
32. The method according to claim 30, wherein the disorder is Parkinson's disease or atypical parkinsonism.
33. The method according to claim 30, wherein the disorder is progressive supranuclear palsy (PSP).
34. The method according to claim 30, wherein the disorder is Pick's disease (PiD).
35. The method according to any one of claims 26 to 34, wherein the Tau aggregates are imaged in the brain or in the eye.
36. Use of a composition as defined in claim 12 for the manufacture of a diagnostic agent for imaging of Tau aggregates, particularly for positron emission tomography imaging of Tau aggregates.
37. Use of a composition as defined in claim 12 for the manufacture of a diagnostic agent for diagnosing a disorder associated with Tau aggregates or for diagnosing a tauopathy, particularly wherein the diagnosis is conducted by positron emission tomography.
38. The use according to claim 37, wherein the tauopathy is a 3R tauopathy.

39. The use according to claim 37, wherein the tauopathy is a 4R tauopathy.
40. The use according to claim 37, wherein the disorder is selected from from Alzheimer's disease (AD), familial AD, Creutzfeldt-Jacob disease, dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury (TBI), amyotrophic lateral sclerosis, Parkinsonism-dementia complex of Guam, non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain disease, corticobasal degeneration (CBD), diffuse neurofibrillary tangles with calcification, frontotemporal dementia with Parkinsonism linked to chromosome 17, Hallervorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, pallido-ponto-nigral degeneration, Pick's disease (PiD), progressive subcortical gliosis, progressive supranuclear palsy (PSP), subacute sclerosing panencephalitis, tangle only dementia, postencephalitic Parkinsonism, myotonic dystrophy, Tau panencephalopathy, AD-like with astrocytes, certain prion diseases (GSS with Tau), mutations in LRRK2, chronic traumatic encephalopathy, familial British dementia, familial Danish dementia, frontotemporal lobar degeneration, Guadeloupean Parkinsonism, neurodegeneration with brain iron accumulation, SLC9A6-related mental retardation, white matter tauopathy with globular glial inclusions, traumatic stress syndrome, epilepsy, Lewy body dementia (LBD), hereditary cerebral hemorrhage with amyloidosis (Dutch type), mild cognitive impairment (MCI), multiple sclerosis, Parkinson's disease, atypical parkinsonism, HIV-related dementia, adult onset diabetes, senile cardiac amyloidosis, endocrine tumors, glaucoma, ocular amyloidosis, primary retinal degeneration, macular degeneration (such as age-related macular degeneration (AMD)), optic nerve drusen, optic neuropathy, optic neuritis, lattice dystrophy, Huntington's disease, ischemic stroke and psychosis in AD; preferably Alzheimer's disease.
41. The use according to claim 40, wherein the disorder is Alzheimer's disease (AD).
42. The use according to claim 40, wherein the disorder is Parkinson's disease or atypical parkinsonism.
43. The use according to claim 40, wherein the disorder is progressive supranuclear palsy (PSP).
44. The use according to claim 40, wherein the disorder is Pick's disease (PiD).

45. The use according to any one of claims 36 to 44, wherein the Tau aggregates are imaged in the brain or in the eye.
46. Use of the composition according to claim 12 as an analytical reference.
- 5 47. Use of the composition according to claim 12 as an *in vitro* screening tool.
48. A method of collecting data for the diagnosis of a disorder associated with tau aggregates in a sample or a patient comprising:
- 10 (a) bringing a sample or a specific body part or body area suspected to contain a tau aggregate into contact with a composition as defined in claim 12 which contains the compound of formula I;
- (b) allowing the compound of formula I to bind to the tau aggregate;
- (c) detecting the compound of formula I bound to the tau aggregate; and
- 15 (d) optionally correlating the presence or absence of compound of formula I binding with the tau aggregate with the presence or absence of tau aggregate in the sample or specific body part or body area.
49. A method of determining the amount of tau aggregate in a tissue and/or a body fluid comprising:
- 20 (a) providing a sample representative of the tissue and/or body fluid under investigation;
- (b) testing the sample for the presence of tau aggregate with a composition as defined in claim 12 which contains the compound of formula I;
- 25 (c) determining the amount of compound of formula I bound to the tau aggregate; and
- (d) calculating the amount of tau aggregate in the tissue and/or body fluid.
50. A method of collecting data for determining a predisposition to a disorder associated with tau aggregates in a patient comprising detecting the specific binding of a composition as defined in claim 12, which contains the compound of formula I, to a tau aggregate in a sample or *in situ* which comprises the steps of:
- 30 (a) bringing the sample or a specific body part or body area suspected to contain the tau aggregate into contact with the composition as defined in claim 12, which contains compound of formula I that specifically binds to the tau aggregate;
- 35 (b) allowing the compound of formula I to bind to the tau aggregate to form a compound/tau aggregate complex;

- (c) detecting the formation of the compound/tau aggregate complex;
 - (d) optionally correlating the presence or absence of the compound/tau aggregate complex with the presence or absence of tau aggregate in the sample or specific body part or body area; and
 - 5 (e) optionally comparing the amount of the compound/tau aggregate to a normal control value.
51. A method of collecting data for monitoring residual disorder in a patient suffering from a disorder associated with tau aggregates who has been treated with a medicament,
- 10 wherein the method comprises:
- (a) bringing a sample or a specific body part or body area suspected to contain a tau aggregate into contact with a composition as defined in claim 12, which contains compound of formula I that specifically binds to the tau aggregate;
 - (b) allowing the compound of formula I to bind to the tau aggregate to form a
 - 15 compound/tau aggregate complex;
 - (c) detecting the formation of the compound/tau aggregate complex;
 - (d) optionally correlating the presence or absence of the compound/tau aggregate complex with the presence or absence of tau aggregate in the sample or specific body part or body area; and
 - 20 (e) optionally comparing the amount of the compound/tau aggregate to a normal control value.
52. A method of collecting data for predicting responsiveness of a patient suffering from a disorder associated with tau aggregates and being treated with a medicament
- 25 comprising:
- (a) bringing a sample or a specific body part or body area suspected to contain an tau aggregate into contact with a composition as defined in claim 12, which contains compound of formula I that specifically binds to the tau aggregate;
 - (b) allowing the compound of formula I to bind to the tau aggregate to form a
 - 30 compound/tau aggregate complex;
 - (c) detecting the formation of the compound/tau aggregate complex;
 - (d) optionally correlating the presence or absence of the compound/tau aggregate complex with the presence or absence of tau aggregate in the sample or specific body part or body area; and
 - 35 (e) optionally comparing the amount of the compound/tau aggregate to a normal control value.