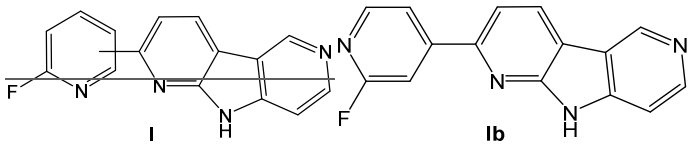
Summary

In one aspect, the present disclosure refers to a diagnostic composition comprising:

a. a compound of Formula **Ib**,



I **Ib**

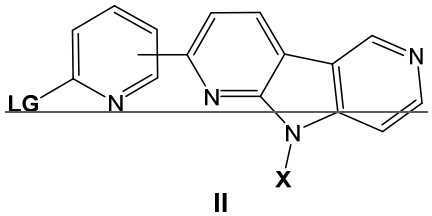
b. ethanol,

c. water, and

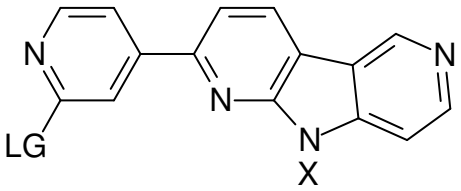
d. a hydroxycarboxylic acid, a salt of a hydroxycarboxylic acid or a mixture thereof.

In another aspect, the present disclosure refers to a method for manufacturing a diagnostic composition as defined herein comprising the steps of:

a. reacting a compound of Formula **IIb** with a ^{18}F fluorinating agent,



II



(IIb),

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

LG is a leaving group, and

PG is an amine protecting group,

b. optionally, if X is PG, cleaving the protecting group PG,

c. purification of the compound of Formula **Ib**,

d. optionally, mixing the compound of Formula **Ib** obtained in step c) with one or more selected from the group consisting of ethanol, water, the hydroxycarboxylic acid and the salt of the hydroxycarboxylic acid to provide the diagnostic composition, and

e. optionally sterile filtration before or after step d).

In another aspect, the present disclosure refers to the composition as described herein for use in the imaging of Tau aggregates, particularly for use in positron emission tomography

imaging of Tau aggregates. In yet another aspect, the present disclosure refers to use of a composition as defined herein in 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. In yet another aspect, the present disclosure refers to use of the composition as described herein as an analytical reference or as an *in vitro* screening tool.

In a further aspect, the present disclosure refers to an *in vitro* method of collecting data for the diagnosis of a disorder associated with tau aggregates in a sample comprising:

(a) bringing a sample suspected to contain a tau aggregate into contact with a composition as defined herein which contains the compound of Formula **Ib**;

(b) allowing the compound of Formula **Ib** to bind to the tau aggregate;

(c) detecting the compound of Formula **Ib** bound to the tau aggregate; and

(d) optionally correlating the presence or absence of compound of Formula **Ib** binding with the tau aggregate with the presence or absence of tau aggregate in the sample.

In a further aspect, the present disclosure refers to an *in vitro* method of determining the amount of tau aggregate in a tissue and/or a body fluid comprising:

(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 herein which contains the compound of Formula **Ib**;

(c) determining the amount of compound of Formula **Ib** bound to the tau aggregate; and

(d) calculating the amount of tau aggregate in the tissue and/or body fluid.

In a further aspect, the present disclosure refers to an *in vitro* method which comprises the steps of:

(a) bringing the sample suspected to contain the tau aggregate into contact with the composition as defined herein, which contains compound of Formula **Ib** that specifically binds to the tau aggregate;

(b) allowing the compound of Formula **Ib** 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; and

(e) optionally comparing the amount of the compound/tau aggregate to a normal control value,

wherein the *in vitro* method is

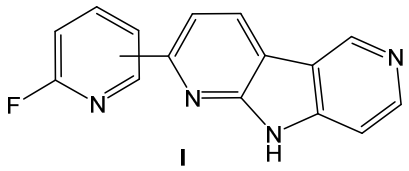
(i) a method of collecting data for determining a predisposition to a disorder associated with tau aggregates in a patient comprising detecting the specific binding of a composition as defined herein, which contains the compound of Formula **Ib**, to a tau aggregate in a sample,

(ii) 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, or

(iii) 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.

The present disclosure relates to the following items:

1. A diagnostic composition comprising:
   a. a compound of Formula **I**,

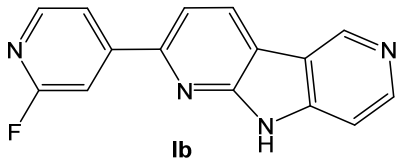


I

   b. ethanol,
   c. water, and
   d. a hydroxycarboxylic acid, a salt of a hydroxycarboxylic acid or a mixture thereof.

2. A diagnostic composition according to item 1, wherein F in Formula **I** is ^{18}F or ^{19}F, preferably ^{18}F or a mixture of ^{18}F and ^{19}F.

3. A diagnostic composition according to item 1 or 2, wherein the compound of Formula **I** is a compound of Formula **Ib**



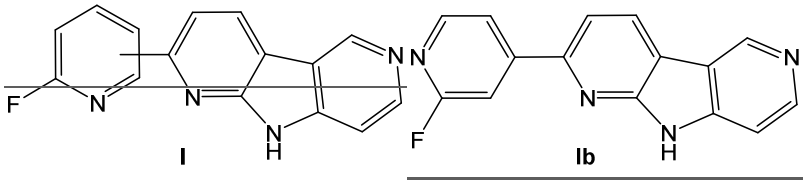
Ib

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4. A diagnostic composition according to any one of items 1 to 3 comprising about 0.03 GBq/mL to about 10 GBq/mL of the compound of Formula **I**, preferably about 0.03 GBq/mL to about 5 GBq/mL of the compound of Formula **I**.

CLAIMS

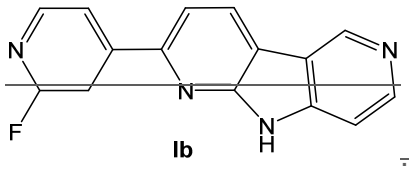
1. A diagnostic composition comprising:
   a. a compound of Formula **Ib**,



   b. ethanol,
   c. water, and
   d. a hydroxycarboxylic acid, a salt of a hydroxycarboxylic acid or a mixture thereof.

2. A diagnostic composition according to claim 1, wherein F in Formula **Ib** is ^{18}F or ^{19}F, preferably ^{18}F or a mixture of ^{18}F and ^{19}F.

~~3. A diagnostic composition according to claim 1 or 2, wherein the compound of Formula **I** is a compound of Formula **Ib**~~



43. A diagnostic composition according ~~to any one of~~ claim~~s~~ 1 ~~to 3~~or 2, wherein the hydroxycarboxylic acid, the salt of the hydroxycarboxylic acid or the mixture thereof are selected from the group consisting of ascorbic acid and salts of ascorbic acid, hydroxybenzoic acids and salts of hydroxybenzoic acids, hydroxybenzoic acid derivatives and salts of hydroxybenzoic acid derivatives, citric acid and salts of citric acid and a mixture thereof, preferably wherein the hydroxybenzoic acid derivative is selected from the group consisting of hydroxybenzoic acid, dihydroxybenzoic acid and trihydroxybenzoic acid, more preferably wherein the dihydroxybenzoic acid is gentisic acid.

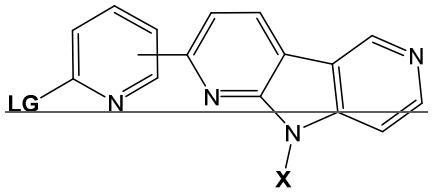
54. A diagnostic composition according to any one of claims 1 to ~~4~~ 3 comprising ~~about~~ 2.5 to ~~about~~ 500 µmol/mL of the hydroxycarboxylic acid, the salt of the hydroxycarboxylic acid or the mixture thereof, preferably ~~about~~ 10 to ~~about~~ 300 µmol/mL of the hydroxycarboxylic acid, the salt of the hydroxycarboxylic acid or the mixture thereof,

more preferably ~~about~~ 25 to ~~about~~ 300 µmol/mL of the hydroxycarboxylic acid, the salt of the hydroxycarboxylic acid or the mixture thereof.

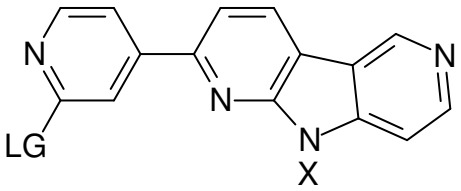
~~6~~5. A diagnostic composition according to any one of claims 1 to ~~5~~ 4 further comprising one or more of an inorganic acid, an organic acid, a base, or a salt, wherein the organic acid, the salt or the mixture thereof is/are different from the hydroxycarboxylic acid, the salt of the hydroxycarboxylic acid or the mixture thereof, preferably wherein the inorganic acid, the organic acid, the base, the salt or the mixture thereof is/are selected from the group consisting of sodium chloride, potassium chloride, monosodium phosphate, disodium phosphate, trisodium phosphate, monopotassium phosphate, dipotassium phosphate, tripotassium phosphate, hydrochloric acid, phosphoric acid, sodium hydroxide and potassium hydroxide.

~~7~~6. A method for manufacturing a diagnostic composition as defined in any one of claims 1 to ~~6~~ 5 comprising the steps of:

a. reacting a compound of Formula **II**b with a ^{18}F fluorinating agent,



II



(IIb),

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

LG is a leaving group, and

PG is an amine protecting group,

b. optionally, if X is PG, cleaving the protecting group PG,

c. purification of the compound of Formula **I**b,

d. optionally, mixing the compound of Formula **I**b obtained in step c) with one or more selected from the group consisting of ethanol, water, the hydroxycarboxylic acid and the salt of the hydroxycarboxylic acid to provide the diagnostic composition, and

e. optionally sterile filtration before or after step d).

87. A method according to claim 76, wherein **LG** in Formula **IIb** is a leaving group, which can be substituted by a nucleophilic [^{18}F]fluoride ion or an electrophilic [^{18}F]fluorine atom, preferably **LG** is selected from the group consisting of nitro, bromo, iodo, chloro, trialkyl ammonium, hydroxyl, boronic acid, iodonium, sulfonic ester, more preferably **LG** is nitro or trimethyl ammonium, wherein the compounds containing trialkyl ammonium or iodonium may further comprise an anion.

98. A method according to claim 7 6 or 87, wherein **PG** in Formula **IIb** is a protecting group, preferably **PG** is selected from the group consisting of carbobenzyloxy (Cbz), (p-methoxybenzyl)oxycarbonyl (Moz or MeOZ), tert-butyloxycarbonyl (BOC), 9-fluorenylmethyloxycarbonyl (FMOC), benzyl (Bn), p-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP), triphenylmethyl (Trityl), methoxyphenyl diphenylmethyl (MMT), or dimethoxytrityl (DMT), more preferably **PG** is selected from tert-butyloxycarbonyl (BOC), dimethoxytrityl (DMT) and triphenylmethyl (Trityl), even more preferably **PG** is tert-butyloxycarbonyl (BOC) or triphenylmethyl (Trityl).

109. The composition according to any one of claims 1 to 6 5 for use in the imaging of Tau aggregates, particularly for use in positron emission tomography imaging of Tau aggregates.

1110. Use of a composition as defined in any one of claims 1 to 6 5 in 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.

1211. The use according to claim 1110, 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.

~~13~~12. The use according to claim ~~12~~11, wherein the disorder is Alzheimer's disease (AD), Parkinson's disease, atypical parkinsonism, progressive supranuclear palsy (PSP) or Pick's disease (PiD).

~~14~~13. Use of the composition according to any one of claims 1 to ~~6~~ 5 as an analytical reference or as an *in vitro* screening tool.

~~15~~14. An *in vitro* method of collecting data for the diagnosis of a disorder associated with tau aggregates in a sample comprising:

(a) bringing a sample suspected to contain a tau aggregate into contact with a composition as defined in any one of claims 1 to ~~6~~ 5 which contains the compound of Formula **Ib**;

(b) allowing the compound of Formula **Ib** to bind to the tau aggregate;

(c) detecting the compound of Formula **Ib** bound to the tau aggregate; and

(d) optionally correlating the presence or absence of compound of Formula **Ib** binding with the tau aggregate with the presence or absence of tau aggregate in the sample.

~~16~~15. An *in vitro* method of determining the amount of tau aggregate in a tissue and/or a body fluid comprising:

(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 any one of claims 1 to ~~6~~ 5 which contains the compound of Formula **Ib**;

(c) determining the amount of compound of Formula **Ib** bound to the tau aggregate; and

(d) calculating the amount of tau aggregate in the tissue and/or body fluid.

~~17~~16. An *in vitro* method which comprises the steps of:

(a) bringing the sample suspected to contain the tau aggregate into contact with the composition as defined in any one of claims 1 to ~~6~~5, which contains compound of Formula **Ib** that specifically binds to the tau aggregate;

(b) allowing the compound of Formula **Ib** 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; and

(e) optionally comparing the amount of the compound/tau aggregate to a normal control value,

wherein the *in vitro* method is

(i) 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 any one of claims 1 to ~~6~~5, which contains the compound of Formula **Ib**, to a tau aggregate in a sample,

(ii) 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, or

(iii) 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.