Summary

It was an object of the present disclosure to provide compounds that can be employed in the diagnosis, monitoring of disease progression, monitoring of drug activity, of a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, such as Parkinson's disease. In particular, the compounds should be suitable for determining a predisposition to such a disorder, monitoring residual disorder, or predicting the responsiveness of a patient who is suffering from such a disorder to the treatment with a certain medicament.

Furthermore, there exists a need in the art for compounds which can be used as imaging agents for alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites. In particular, it was an object of the present disclosure to provide compounds that are suitable as a diagnostic composition for positron emission tomography imaging of synucleinopathies, e.g., wherein the compounds are detectably labeled with ^{18}F. The present inventors have surprisingly found that these objects can be achieved by the compounds of formulae (I) and (II) as described hereinafter.

I~~n another aspect, i~~t was also an object of the present disclosure to provide compounds that can be employed to treat, alleviate or prevent a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, such as Parkinson's disease.

The compounds of formulae (I) and (II) display high binding affinity to different alpha-synuclein aggregates in human tissues. Moreover, the compounds of formulae (I) and (II) display high selectivity for aSyn over Aβ and tau pathological deposits enabling the differentiation of PD from other proteinopathies that share common clinical and pathological features. Due to their unique design features, these compounds display properties such as appropriate lipophilicity and molecular weight, brain uptake and pharmacokinetics, cell permeability, solubility, and autofluorescence in order to be successful imaging probes for detection and quantification of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites load *in vivo*, *ex vivo* and *in vitro*.

The present disclosure discloses novel compounds of formulae (I) and (II) having enhanced binding properties to alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites. The compounds of this disclosure may be labeled (e.g., radiolabeled), so that they may be used for *ex vivo* and *in vivo* imaging to detect alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites. The present disclosure provides methods for the detection of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, *ex vivo* using a compound of formulae (I) and (II) or a pharmaceutical composition thereof. The present disclosure provides compounds of formulae (I) and (II) for use as diagnostic imaging agents, particularly for presymptomatic detection of Parkinson's disease and/or other α-synucleinopathies, e.g., using positron emission tomography (PET). The disclosure would serve as a biomarker for monitoring of topographic progression of pathology, leading to improvement of clinical diagnosis and clinical study design. The present disclosure further provides a pharmaceutical composition comprising a compound of formula (I) or (II) and a pharmaceutically acceptable carrier or excipient.

In one aspect, the present disclosure refers to a compound of formula (IIa):

$–(O–CH_2CH_2)_n–R^d$, =O, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, and alkynyl;

for each occurrence, $\mathbf{R^E}$ is independently selected from the group consisting of halogen, CN, $–O–R^{10}$, $–NR^{10}R^{11}$, $–CONR^{10}R^{11}$, $–N(R^{10})–C(O)–R^{11}$, $–N(R^{10})–C(O)–O–R^{11}$, $–(O–CH_2CH_2)_n–R^d$, =O, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, and alkynyl, wherein alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, and alkynyl can be optionally substituted, or if more than one group R^E is present and two of the groups R^E are adjacent, they can optionally be taken together and can form a 5- to 8-membered ring containing carbon atoms and optionally one or more heteroatoms selected from O, S, or N or optionally one or more heteroatom (e.g., N, O and/or S)-containing moieties and wherein the 5- to 8-membered ring may be substituted;

for each occurrence, $\mathbf{R^{10}}$ is independently selected from the group consisting of: hydrogen, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl can be optionally substituted;

for each occurrence, $\mathbf{R^{11}}$ is independently selected from the group consisting of: hydrogen, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl can be optionally substituted;

for each occurrence, **n** is independently 1 to 4.

In another aspect, the present disclosure refers to a method of imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, wherein an effective amount of a compound as disclosed herein is to be administered to a patient in need thereof.

In another aspect, the present disclosure refers to a method of detecting the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites or a predisposition therefor in a subject, wherein the method comprises that a compound as disclosed herein is to be administered to a patient in need thereof, thereby allowing the detection of the alpha-synuclein aggregates.

In another aspect, the present dislocsure refers to a method of collecting data for the diagnosis of a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a patient comprising:
(a) bringing a sample ~~or specific body part or body area~~ of the patient suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with a compound as defined herein;
(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;
(c) detecting the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites; and
(d) optionally correlating the presence or absence of compound binding with the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~.

In another aspect, the present dislocsure refers to a method of collecting data for determining a predisposition to a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a patient comprising detecting the specific binding of a compound as defined herein to alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a sample ~~or specific body part or body area~~ of the patient which comprises the steps of:

(a) bringing the sample ~~or specific body part or body area~~ suspected to contain the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with the compound as defined herein, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(c) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~; and

(e) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value.

In another aspect, the present dislocsure refers to a method of collecting data for monitoring residual disorder in a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites who has been treated with a medicament, wherein the method comprises:

(a) bringing a sample ~~or specific body part or body area~~ suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with a compound as defined herein, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(c) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~; and

(e) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value.

In another aspect, the present dislocsure refers to a method of collecting data for predicting responsiveness of a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites and being treated with a medicament comprising:

(a) bringing a sample ~~or specific body part or body area~~ suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with a compound as defined herein, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;
(c) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;
(d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~; and
(e) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value.

In another aspect, the present dislocsure refers to a method of determining the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a patient comprising:
(a) bringing a sample ~~or specific body part or body area~~ of the patient suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with a compound as defined herein;
(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;
(c) detecting the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites; and
(d) optionally correlating the presence or absence of compound binding with the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~.

In another aspect, the present dislocsure refers to a method of determining the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a patient comprising detecting the specific binding of a compound as defined herein to alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a sample ~~or specific body part or body area~~ of the patient which comprises the steps of:
(a) bringing the sample ~~or specific body part or body area~~ suspected to contain the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with the compound as defined herein, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;
(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;
(c) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;
(d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~; and
(e) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value.

In another aspect, the present dislocsure refers to a method of monitoring residual disorder in a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates

including, but not limited to, Lewy bodies and/or Lewy neurites who has been treated with a medicament, wherein the method comprises:

(a) bringing a sample ~~or specific body part or body area~~ suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with a compound as defined herein, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(c) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~; and

(e) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value.

In another aspect, the present dislocsure refers to a method of predicting responsiveness of a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites and being treated with a medicament comprising:

(a) bringing a sample ~~or specific body part or body area~~ suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with a compound as defined herein, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(c) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~; and

(e) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value.

In another aspect, the present dislocsure refers to a method of determining the amount of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a sample ~~or specific body part or body area~~ of a patient comprising:

(a) testing a sample ~~or specific body part or body area~~ for the presence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with a compound as defined herein;

(b) determining the amount of compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites; and

(c) calculating the amount of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~.

In another aspect, the present dislocsure refers to a mixture comprising a compound as defined herein and at least one compound selected from an imaging agent different from the compound as defined herein, preferably an abeta or tau imaging agent, a pharmaceutically acceptable carrier, a diluent and an excipient.

~~In another aspect, the present disclosure refers to a use of the compound as disclosed herein in the manufacture of a medicament for treating, alleviating or preventing a disorder or abnormality associated with alpha-synuclein aggregates, wherein the disorder is selected from the group consisting of Parkinson's disease (including sporadic, familial with alpha-synuclein mutations, familial with mutations other than alpha-synuclein, pure autonomic failure or Lewy body dysphagia), dementia with Lewy bodies (including "pure" Lewy body dementia), sporadic Alzheimer's disease, familial Alzheimer's disease with APP mutations, familial Alzheimer's disease with PS-1, PS-2 or other mutations, familial British dementia, Lewy body variant of Alzheimer's disease, normal aging (including Down syndrome), multiple system atrophy (including Shy-Drager syndrome, striatonigral degeneration or olivopontocerebellar atrophy), traumatic brain injury, chronic traumatic encephalopathy, tauopathies (including Pick's disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration or Niemann-Pick type C1 disease), motor neuron disease, amyotrophic lateral sclerosis (including sporadic, familial or ALS-dementia complex of Guam), neuroaxonal dystrophy, neurodegeneration with brain iron accumulation type 1 (including Hallervorden-Spatz syndrome), prion diseases, ataxia telangiectatica, Meige's syndrome, subacute sclerosing panencephalitis, Gaucher disease, lysosomal storage disorders (including Kufor-Rakeb syndrome and Sanfilippo syndrome) and rapid eye movement (REM) sleep behavior disorder, preferably Parkinson's disease.~~

In another aspect, the present disclosure refers to a diagnostic composition comprising a compound as disclosed herein and a pharmaceutically acceptable carrier, diluent, adjuvant and/or excipient.

In another aspect, the present disclosure refers to a compound as disclosed herein for use in diagnostics.

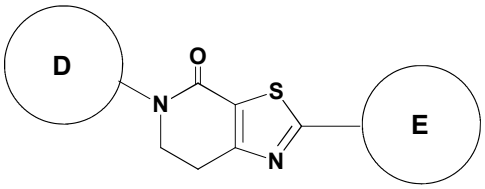
In another aspect, the present disclosure refers to a as disclosed herein for use in the imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites.

In another aspect, the present disclosure refers to a compound as disclosed herein for use in the diagnostics of a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites or a predisposition therefor.

In another aspect, the present disclosure refers to a compound of formula (IVa) or (IVb)

CLAIMS

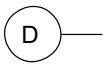
1. A compound of formula (IIa):



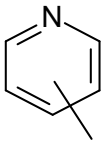
(IIa)

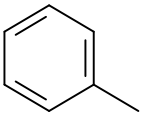
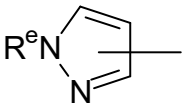
and all detectably labeled derivatives, stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof;

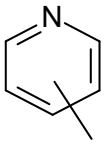
wherein

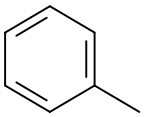
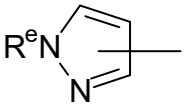


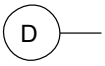
is selected from the group consisting of



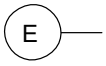
, 
, 

, hydrogen and alkyl, wherein 

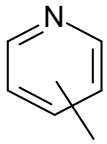
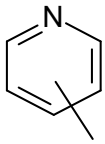
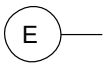
, 
, 

, and alkyl can be attached at any available position, and wherein 

can be optionally substituted by one or more substituents R^D;



is selected from the group consisting of


, wherein  can be attached at any available position, and wherein  can be optionally substituted by one or more substituents R^E;

for each occurrence, $\mathbf{R^d}$ is independently selected from the group consisting of halogen, –OH, –O–alkyl and hydrogen;

for each occurrence, $\mathbf{R^e}$ is independently selected from the group consisting of hydrogen, $–(CH_2CH_2–O)_n–R^f$, $–(CH_2CH_2–O)_n–(CH_2CH_2)–R^d$, alkyl, carbocyclyl and heterocyclyl, wherein alkyl, carbocyclyl and heterocyclyl can be optionally substituted,

for each occurrence, $\mathbf{R^f}$ is independently selected from the group consisting of hydrogen, and alkyl, wherein alkyl can be optionally substituted;

for each occurrence, $\mathbf{R^D}$ is independently selected from the group consisting of halogen, CN, $–O–R^{10}$, $–NR^{10}R^{11}$, $–CONR^{10}R^{11}$, $–N(R^{10})–C(O)–R^{11}$, $–N(R^{10})–C(O)–O–R^{11}$, $–(O–CH_2CH_2)_n–R^d$, =O, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, and alkynyl;

for each occurrence, $\mathbf{R^E}$ is independently selected from the group consisting of halogen, CN, $–O–R^{10}$, $–NR^{10}R^{11}$, $–CONR^{10}R^{11}$, $–N(R^{10})–C(O)–R^{11}$, $–N(R^{10})–C(O)–O–R^{11}$, $–(O–CH_2CH_2)_n–R^d$, =O, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, and alkynyl, wherein alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, and alkynyl can be optionally substituted, or if more than one group R^E is present and two of the groups R^E are adjacent, they can optionally be taken together and can form a 5- to 8-membered ring containing carbon atoms and optionally one or more heteroatoms selected from O, S, or N or optionally one or more heteroatom (e.g., N, O and/or S)-containing moieties and wherein the 5- to 8-membered ring may be substituted;

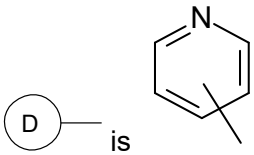
for each occurrence, $\mathbf{R^{10}}$ is independently selected from the group consisting of: hydrogen, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein alkyl,

carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl can be optionally substituted;

for each occurrence, **R^{11}** is independently selected from the group consisting of: hydrogen, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl can be optionally substituted;

for each occurrence, **n** is independently 1 to 4.

2. The compound according to claim 1, wherein



is , which is optionally substituted by R^D.

3. The compound according to claim 1 or 2, wherein R^E is independently selected from the group consisting of halogen, –CN, –O–R^{10}, –$NR^{10}R^{11}$, –N(R^{10})–C(O)–O–R^{11}, –(O–$CH_2CH_2)_n$–R^d, optionally substituted alkyl, and optionally substituted heterocyclyl.

4. The compound according to claim 3, wherein R^E is independently selected from the group consisting of halogen and optionally substituted heterocyclyl.

5. The compound according to any one of claims 1 to 4, wherein the compound is detectably labeled, preferably with ^{2}H, ^{3}H, ^{18}F, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{11}C, ^{13}N, ^{15}O, and ^{77}Br, more preferably with ^{18}F.

6. A diagnostic composition comprising a compound according to any one of claims 1 to 5 and a pharmaceutically acceptable carrier, diluent, adjuvant and/or excipient.

7. The compound according to any one of claims 1 to 5 for use in diagnostics.

8. The compound according to any one of claims 1 to 5 for use in the imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites.

9. The compound for use according to claim 8, wherein the compound is for use in the positron emission tomography imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites.

10. The compound according to any one of claims 1 to 5 for use in the diagnostics of a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites or a predisposition therefor.

11. The compound for use according to claim 10, wherein the disorder is selected from Parkinson's disease (including sporadic, familial with alpha-synuclein mutations, familial with mutations other than alpha-synuclein, pure autonomic failure or Lewy body dysphagia), dementia with Lewy bodies (including “pure” Lewy body dementia), sporadic Alzheimer’s disease, familial Alzheimer's disease with APP mutations, familial Alzheimer's disease with PS-1, PS-2 or other mutations, familial British dementia, Lewy body variant of Alzheimer’s disease, normal aging (including Down syndrome), multiple system atrophy (including Shy-Drager syndrome, striatonigral degeneration or olivopontocerebellar atrophy), traumatic brain injury, chronic traumatic encephalopathy, tauopathies (including Pick's disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration or Niemann-Pick type C1 disease), motor neuron disease, amyotrophic lateral sclerosis (including sporadic, familial or ALS-dementia complex of Guam), neuroaxonal dystrophy, neurodegeneration with brain iron accumulation type 1 (including Hallervorden-Spatz syndrome), prion diseases, ataxia telangiectatica, Meige’s syndrome, subacute sclerosing panencephalitis, Gaucher disease, lysosomal storage disorders (including Kufor-Rakeb syndrome and Sanfilippo syndrome) and rapid eye movement (REM) sleep behavior disorder, preferably Parkinson's disease.

12. A method of imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, wherein an effective amount of a compound according to any one of claims 1 to 5 is to be administered to a patient in need thereof.

13. The method according to claim 12, wherein the method is positron emission tomography imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites.

14. A method of detecting the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites or a predisposition therefor in a subject, wherein the method comprises that a compound according to any one of claims 1 to 5 is to be administered to a patient in need thereof, thereby allowing the detection of the alpha-synuclein aggregates.

15. A method of collecting data for the diagnosis of a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a patient comprising:
    (a) bringing a sample ~~or specific body part or body area~~ of the patient suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with a compound as defined in any one of claims 1 to 5;
    (b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;
    (c) detecting the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites; and
    (d) optionally correlating the presence or absence of compound binding with the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~.

16. A method of collecting data for determining a predisposition to a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a patient comprising detecting the specific binding of a compound as defined in any one of claims 1 to 5 to alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a sample ~~or specific body part or body area~~ of the patient which comprises the steps of:
    (a) bringing the sample ~~or specific body part or body area~~ suspected to contain the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with the compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(c) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~; and

(e) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value.

17. A method of collecting data for monitoring residual disorder in a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites who has been treated with a medicament, wherein the method comprises:

(a) bringing a sample ~~or specific body part or body area~~ suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with a compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(c) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~; and

(e) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value.

18. The method according to claim 17, wherein step (d) is present and wherein the method further comprises steps (i) to (vi) before step (a):

(i) bringing a sample ~~or specific body part or body area~~ suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with the compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(ii) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(iii) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(iv) correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~;

(v) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value; and

(vi) ~~treating~~ wherein the patient is to be treated with the medicament;

and wherein the method further comprises step (A) after step (d) or step (e):

(A) comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex determined in step (iv) to the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex determined in step (d).

19. The method according to claim 17 or 18, wherein steps (a) to (c) and optionally steps (d) and (e) are repeated one or more times.

20. A method of collecting data for predicting responsiveness of a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites and being treated with a medicament comprising:

(a) bringing a sample ~~or specific body part or body area~~ suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with a compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(c) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~; and

(e) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value.

21. The method according to claim 20, wherein step (d) is present and wherein the method further comprises steps (i) to (vi) before step (a):

(i) bringing a sample ~~or specific body part or body area~~ suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with the compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(ii) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(iii) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(iv) correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~;

(v) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value; and

(vi) ~~treating~~ wherein the patient is to be treated with the medicament;

and wherein the method further comprises step (A) after step (d) or step (e):

(A) comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex determined in step (iv) to the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex determined in step (d).

22. The method according to claim 20 or 21, wherein steps (a) to (c) and optionally steps (d) and (e) are repeated one or more times.

23. A method of determining the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a patient comprising:

(a) bringing a sample ~~or specific body part or body area~~ of the patient suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with a compound as defined in any one of claims 1 to 5;

(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(c) detecting the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites; and

(d) optionally correlating the presence or absence of compound binding with the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~.

24. A method of determining the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a patient comprising detecting the specific binding of a compound as defined in any one of claims 1 to 5 to alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a sample ~~or specific body part or body area~~ of the patient which comprises the steps of:

(a) bringing the sample ~~or specific body part or body area~~ suspected to contain the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with the compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(c) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~; and

(e) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value.

25. A method of monitoring residual disorder in a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites who has been treated with a medicament, wherein the method comprises:

(a) bringing a sample ~~or specific body part or body area~~ suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with a compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(c) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~; and

(e) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value.

26. The method according to claim 25, wherein step (d) is present and wherein the method further comprises steps (i) to (vi) before step (a):

(i) bringing a sample ~~or specific body part or body area~~ suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with the compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(ii) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(iii) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(iv) correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~;

(v) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value; and

(vi) ~~treating~~ wherein the patient is to be treated with the medicament;

and wherein the method further comprises step (A) after step (d) or step (e):

(A) comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex determined in step (iv) to the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex determined in step (d).

27. The method according to claim 25 or 26, wherein steps (a) to (c) and optionally steps (d) and (e) are repeated one or more times.

28. A method of predicting responsiveness of a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites and being treated with a medicament comprising:

(a) bringing a sample ~~or specific body part or body area~~ suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with a compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(b) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(c) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~; and

(e) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value.

29. The method according to claim 28, wherein step (d) is present and wherein the method further comprises steps (i) to (vi) before step (a):

(i) bringing a sample ~~or specific body part or body area~~ suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites into contact with the compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(ii) allowing the compound to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(iii) detecting the formation of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex;

(iv) correlating the presence or absence of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex with the presence or absence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~;

(v) optionally comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex to a normal control value; and

(vi) ~~treating~~ wherein the patient is to be treated with the medicament;

and wherein the method further comprises step (A) after step (d) or step (e):

(A) comparing the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex determined in step (iv) to the amount of the compound/(alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites) complex determined in step (d).

30. The method according to claim 28 or 29, wherein steps (a) to (c) and optionally steps (d) and (e) are repeated one or more times.

31. The method according to any one of claims 15 to 30, wherein the patient is suspected to be suffering from a disorder selected from Parkinson's disease (including sporadic, familial with alpha-synuclein mutations, familial with mutations other than alpha-synuclein, pure autonomic failure or Lewy body dysphagia), dementia with Lewy bodies (including “pure” Lewy body dementia), sporadic Alzheimer’s disease, familial Alzheimer's disease with APP mutations, familial Alzheimer's disease with PS-1, PS-2 or other mutations, familial British dementia, Lewy body variant of Alzheimer’s disease, normal aging (including Down

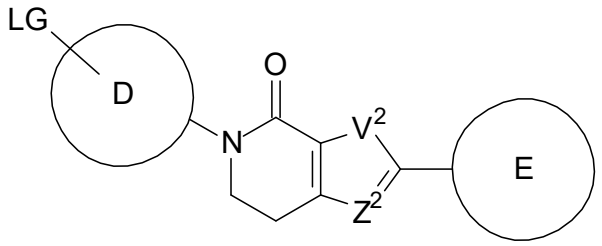
syndrome), multiple system atrophy (including Shy-Drager syndrome, striatonigral degeneration or olivopontocerebellar atrophy), traumatic brain injury, chronic traumatic encephalopathy, tauopathies (including Pick's disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration or Niemann-Pick type C1 disease), motor neuron disease, amyotrophic lateral sclerosis (including sporadic, familial or ALS-dementia complex of Guam), neuroaxonal dystrophy, neurodegeneration with brain iron accumulation type 1 (including Hallervorden-Spatz syndrome), prion diseases, ataxia telangiectatica, Meige's syndrome, subacute sclerosing panencephalitis, Gaucher disease, lysosomal storage disorders (including Kufor-Rakeb syndrome and Sanfilippo syndrome) and rapid eye movement (REM) sleep behavior disorder, preferably Parkinson's disease.

32. A method of determining the amount of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a sample ~~or specific body part or body area~~ of a patient comprising:
    (a) testing a sample ~~or specific body part or body area~~ for the presence of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with a compound as defined in any one of claims 1 to 5;
    (b) determining the amount of compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites; and
    (c) calculating the amount of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample ~~or specific body part or body area~~.

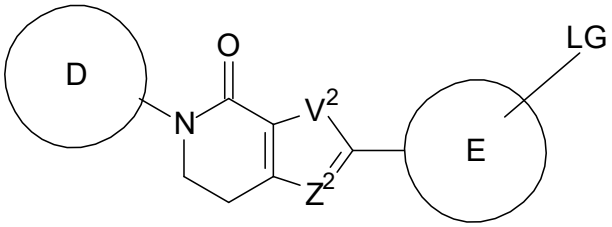
33. The method according to any one of claims 15 to 32, wherein the sample is to be obtained from a tissue and/or a body fluid representative of ~~the~~ a specific body part or body area under investigation.

34. A mixture comprising a compound as defined in any one of claims 1 to 5 and at least one compound selected from an imaging agent different from the compound as defined in any one of claims 1 to 5, preferably an abeta or tau imaging agent, a pharmaceutically acceptable carrier, a diluent and an excipient.

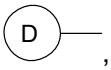
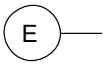
35. A compound of formula (IVa) or (IVb)



(IVa)



(IVb)

wherein R^e, R^D,  , and  are as defined in claim 1;
V^2 is S and Z^2 is N; and
LG is a leaving group.

36. The compound according to claim 35, whererin LG is selected from nitro, halogen, trimethylammonium, C_{1-4} alkyl sulfonate or C_{6-10} aryl sulfonate.

37. A method for preparing the compound according to claim 5, wherein the compound is labelled by ^{18}F, comprising reacting the compound according to claim 35 or 36 with a ^{18}F-fluorinating agent, so that LG is replaced by ^{18}F.

38. The method according to claim 37, wherein the ^{18}F-fluorinating agent is selected from $K^{18}F$, $H^{18}F$, $Cs^{18}F$, $Na^{18}F$ and tetrabutylammonium [^{18}F]fluoride.

39. Use of the compound according to any one of claims 1 to 5 as an *in vitro* analytical reference or an *in vitro* screening tool.

40. A test kit for detection and/or diagnosis of a disorder or abnormality associated with alpha-synuclein aggregates, wherein the test kit comprises at least one compound as defined in any one of claims 1 to 5.

41. The test kit according to claim ~~37~~ 40 comprising a container containing at least one compound as defined in any one of claims 1 to 5 and instructions for using the at least one compound for the purpose of binding to alpha-synuclein aggregates to form a compound/protein complex and detecting the formation of the compound/protein complex such that presence or absence of the compound/protein complex correlates with the presence or absence of the alpha-synuclein aggregates.

42. A kit for preparing a radiopharmaceutical preparation, wherein the kit comprises a sealed vial containing at least one compound as defined in claim 35 or 36.