

WO 2010/063701 refers to a certain *in vivo* imaging agent for use in a method to determine the presence of, or susceptibility to, PD, wherein the *in vivo* imaging agent comprises an alpha-synuclein binder labelled with an *in vivo* imaging moiety, and wherein the *in vivo* imaging agent binds to alpha-synuclein with a binding affinity.

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US 2014/0142089 relates to a method for preventing or treating a degenerative brain disease, the method comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising a specific compound, a pharmaceutically acceptable salt, an isomer, a solvate, a hydrate, and a combination thereof.

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WO 2009/155017 describes aryl or heteroaryl substituted azabenzoxazole derivatives, which are stated to be useful as tracers in positron emission tomography (PET) imaging to study amyloid deposits in brain *in vivo* to allow diagnosis of Alzheimer's disease.

15 WO 2016/033445 refers to a specific compound for imaging huntingtin protein.

WO 2017/153601 refers to the compounds that can be employed in the diagnosis, monitoring of disease progression or monitoring of drug activity, of a group of disorders and abnormalities associated with alpha-synuclein.

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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 PD. In particular, the compounds should be suitable for diagnosis of the preclinical state of 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.

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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 formula (I) as described hereinafter.

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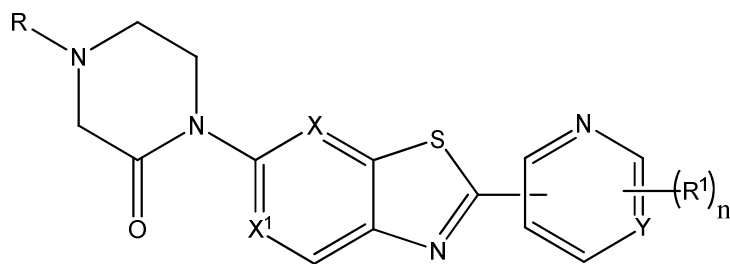
The compounds of formula (I) display high binding affinity to alpha-synuclein aggregates. Moreover, the compounds of formula (I) display high selectivity for alpha-synuclein over $\text{A}\beta$ enabling the differentiation of PD from other proteinopathies that share common clinical and pathological features. Due to their unique design features, these compounds display properties
10 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*.

15 The present disclosure discloses novel compounds of formula (I) having enhanced binding properties to alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites. Some compounds of formula (I) have improved pharmacokinetic (PK) parameters, such as brain washout and reduced unspecific retention. 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
20 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 formula (I) or a pharmaceutical composition thereof. The present disclosure provides compounds of formula (I) for use as imaging agents, particularly for diagnosis of presymptomatic and/or premotor PD
25 and/or advanced PD and/or other alpha-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 diagnostic composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier or excipient.

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The present disclosure is summarized in the following items:

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



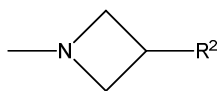
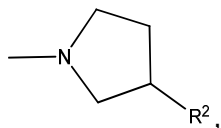
(I)

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

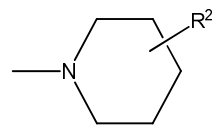
wherein

R is selected from the group consisting of hydrogen and alkyl;

R¹ is independently selected from the group consisting of fluorine,



and $-NR^3R^4$;



R² is selected from the group consisting of fluorine and hydrogen;

R³ and **R⁴** are independently selected from the group consisting of alkyl, fluoro-alkyl, alkyl-O-alkyl and hydrogen;

X and **X¹** are independently selected from the group consisting of N and CH, provided that at least one of X and X¹ is N;

Y is independently selected from the group consisting of N and CH or **Y** is C if **Y** is attached to **R¹**;

5. The compound according to any one of items 1 to 4, wherein the compound is detectably labeled, preferably with ^2H , ^3H , ^{18}F or ^{13}N , more preferably with ^{18}F .
- 5 6. A diagnostic composition comprising a compound according to any one of items 1 to 5 and optionally a pharmaceutically acceptable carrier, diluent, adjuvant and/or excipient. In another aspect, the present disclosure refers to a diagnostic composition comprising a compound as disclosed herein and optionally a pharmaceutically acceptable carrier, diluent, adjuvant and/or excipient.
- 10 7. The compound according to any one of items 1 to 5 for use in diagnostics. In yet another aspect, the present disclosure refers to the compound as disclosed herein for use in diagnostics.
- 15 8. The compound according to any one of items 1 to 5 for use in the imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites. In yet another aspect, the present disclosure refers to the compound as disclosed herein for use in the imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, preferably 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
- 20 9. The compound for use according to item 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.
- 25 10. The compound according to any one of items 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 preclinical state thereof. In yet another aspect, the present disclosure refers to the 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 preclinical state thereof.
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11. The compound for use according to item 10, wherein the disorder is selected from PD (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, Down syndrome, multiple system atrophy (including Shy-Drager syndrome, striatonigral degeneration or olivopontocerebellar atrophy), traumatic brain injury, chronic traumatic encephalopathy, motor neuron disease, 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.

disease, lysosomal storage disorders (including Kufor-Rakeb syndrome and Sanfilippo syndrome) and rapid eye movement (REM) sleep behavior disorder.

19. The method according to item 17, wherein the disorder is PD.

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20. The method according to item 17, wherein the disorder is dementia with Lewy bodies.

21. The method according to item 17, wherein the disorder is multiple system atrophy.

10 22. A method of collecting data for the diagnosis of a disorder or abnormality associated with alpha-synuclein aggregates in a patient comprising:

(a) bringing a sample or specific body part or body area of the patient suspected to contain alpha-synuclein aggregates into contact with a compound as defined in any one of items 1 to 5;

15 (b) allowing the compound to bind to the alpha-synuclein aggregates;

(c) detecting the compound bound to the alpha-synuclein aggregates; and

(d) optionally correlating the presence or absence of compound binding with the alpha-synuclein aggregates with the presence or absence of alpha-synuclein aggregates in the sample or specific body part or body area.

20 In yet another aspect, the present disclosure refers to an *in vitro* method of collecting data for the diagnosis of a disorder or abnormality associated with alpha-synuclein aggregates in a patient comprising:

(a) bringing a sample of the patient suspected to contain alpha-synuclein aggregates into contact with a compound as disclosed herein;

25 (b) allowing the compound to bind to the alpha-synuclein aggregates;

(c) detecting the compound bound to the alpha-synuclein aggregates; and

(d) optionally correlating the presence or absence of compound binding with the alpha-synuclein aggregates with the presence or absence of alpha-synuclein aggregates in the sample

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23. A method of collecting data for diagnosis of the preclinical state of a disorder or abnormality associated with alpha-synuclein aggregates in a patient comprising detecting the specific binding of a compound as defined in any one of items 1 to 5 to alpha-

synuclein aggregates in a sample or specific body part or body area of the patient which comprises the steps of:

- 5 (a) bringing the sample or specific body part or body area suspected to contain the alpha-synuclein aggregates into contact with the compound as defined in any one of items 1 to 5, which compound specifically binds to the alpha-synuclein aggregates;
- (b) allowing the compound to bind to the alpha-synuclein aggregates to form a compound/(alpha-synuclein aggregate) complex;
- (c) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
- 10 (d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregates in the sample or specific body part or body area; and

- (e) optionally comparing the amount of the compound/(alpha-synuclein aggregate) complex to a normal control value.

In yet another aspect, the present disclosure refers to an *in vitro* method of collecting data for diagnosis of the preclinical state of a disorder or abnormality associated with alpha-synuclein aggregates in a patient comprising detecting the specific binding of a compound as disclosed herein to alpha-synuclein aggregates in a sample of the patient which comprises the steps of:

- (a) bringing the sample suspected to contain the alpha-synuclein aggregates into contact with the compound as disclosed herein, which compound specifically binds to the alpha-synuclein aggregates;
- (b) allowing the compound to bind to the alpha-synuclein aggregates to form a compound/(alpha-synuclein aggregate) complex;
- (c) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
- (d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregates in the sample; and
- (e) optionally comparing the amount of the compound/(alpha-synuclein aggregate) complex to a normal control value.

24. A method of collecting data for monitoring residual disorder in a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates 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 into contact with a compound as defined in any one of items 1 to 5, which compound specifically binds to the alpha-synuclein aggregates;
- (b) allowing the compound to bind to the alpha-synuclein aggregates to form a compound/(alpha-synuclein aggregate) complex;
- (c) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
- (d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregate in the sample or specific body part or body area; and
- (e) optionally comparing the amount of the compound/(alpha-synuclein aggregate) complex to a normal control value.

In yet another aspect, the present disclosure refers to an *in vitro* method of collecting data for monitoring residual disorder in a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates who has been treated with a medicament, wherein the method comprises:

- 5 (a) bringing a sample suspected to contain alpha-synuclein aggregates into contact with a compound as disclosed herein, which compound specifically binds to the alpha-synuclein aggregates;
- (b) allowing the compound to bind to the alpha-synuclein aggregates to form a compound/(alpha-synuclein aggregate) complex;
- 10 (c) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
- (d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregate in the sample; and
- (e) optionally comparing the amount of the compound/(alpha-synuclein aggregate) complex to a normal control value.
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25. The method according to item 24, wherein step (d) is present and wherein the method further comprises steps (i) to (vi) before step (a):

- 20 (i) bringing a sample or specific body part or body area suspected to contain alpha-synuclein aggregates into contact with the compound as defined in any one of items 1 to 5, which compound specifically binds to the alpha-synuclein aggregates;
 - (ii) allowing the compound to bind to the alpha-synuclein aggregates to form a compound/(alpha-synuclein aggregate) complex;
 - (iii) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
 - 25 (iv) correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregates in the sample or specific body part or body area;
 - (v) optionally comparing the amount of the compound/(alpha-synuclein aggregate) complex to a normal control value; and
 - 30 (vi) treating the patient 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 aggregate) complex determined in step (iv) to the amount of the compound/(alpha-synuclein aggregate) complex determined in step (d).

26. The method according to item 24 or 25, wherein steps (a) to (c) and optionally steps (d) and (e) are repeated one or more times.

27. A method of collecting data for predicting responsiveness of a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates and being treated with a medicament comprising:

- (a) bringing a sample or specific body part or body area suspected to contain alpha-synuclein aggregates into contact with a compound as defined in any one of items 1 to 5, which compound specifically binds to the alpha-synuclein aggregates;
- (b) allowing the compound to bind to the alpha-synuclein aggregates to form a compound/(alpha-synuclein aggregate) complex;
- (c) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
- (d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregates in the sample or specific body part or body area; and
- (e) optionally comparing the amount of the compound/(alpha-synuclein aggregate) complex to a normal control value.

In yet another aspect, the present disclosure refers to an *in vitro* method of collecting data for predicting responsiveness of a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates and being treated with a medicament comprising:

- (a) bringing a sample suspected to contain alpha-synuclein aggregates into contact with a compound as disclosed herein, which compound specifically binds to the alpha-synuclein aggregates;
- (b) allowing the compound to bind to the alpha-synuclein aggregates to form a compound/(alpha-synuclein aggregate) complex;
- (c) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
- (d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregates in the sample; and

- (e) optionally comparing the amount of the compound/(alpha-synuclein aggregate) complex to a normal control value.

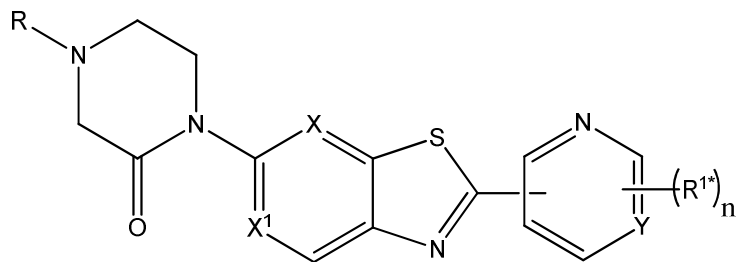
28. The method according to item 27, wherein step (d) is present and wherein the method further comprises steps (i) to (vi) before step (a):

- (i) bringing a sample or specific body part or body area suspected to contain alpha-synuclein aggregates into contact with the compound as defined in any one of items 1 to 5, which compound specifically binds to the alpha-synuclein aggregates;
- (ii) allowing the compound to bind to the alpha-synuclein aggregates to form a compound/(alpha-synuclein aggregate) complex;
- (iii) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
- (iv) correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregates in the sample or specific body part or body area;

41. The method according to any one of items 22 to 37, wherein the disorder is multiple system atrophy.
- 5 42. A method of determining the amount of alpha-synuclein aggregates in a sample or specific body part or body area of a patient comprising:
- (a) providing the sample or specific body part or body area;
 - (b) testing the sample or specific body part or body area for the presence of alpha-synuclein aggregates with a compound as defined in any one of items 1 to 5;
 - (c) determining the amount of compound bound to the alpha-synuclein aggregates; and
 - 10 (d) calculating the amount of alpha-synuclein aggregates in the sample or specific body part or body area.
- In yet another aspect, the present disclosure refers to an *in vitro* method of determining the amount of alpha-synuclein aggregates in a sample obtained from a patient comprising:
- 15 (a) testing the sample for the presence of alpha-synuclein aggregates with a compound as disclosed herein;
 - (b) determining the amount of compound bound to the alpha-synuclein aggregates; and
 - (c) calculating the amount of alpha-synuclein aggregates in the sample
- 20 43. The method according to any one of items 22 to 37, wherein the method is applied to a sample or specific body part obtained from a patient.
44. The method according to any one of items 22 to 43, wherein the sample is a tissue and/or a body fluid representative of the specific body part or body area under investigation.
- 25 45. The method according to any one of items 22 to 44, wherein alpha-synuclein aggregates include Lewy bodies and/or Lewy neurites.

46. A mixture comprising a compound as defined in any one of items 1 to 5 and at least one compound selected from an imaging agent different from the compound as defined in any one of items 1 to 5, preferably an abeta or Tau imaging agent, a pharmaceutically acceptable carrier, a diluent and an excipient. In yet another aspect, the present disclosure refers to a mixture comprising a compound as disclosed herein and at least one compound selected from an imaging agent different from the compound as disclosed herein, preferably an abeta or Tau imaging agent, a pharmaceutically acceptable carrier, a diluent and an excipient.

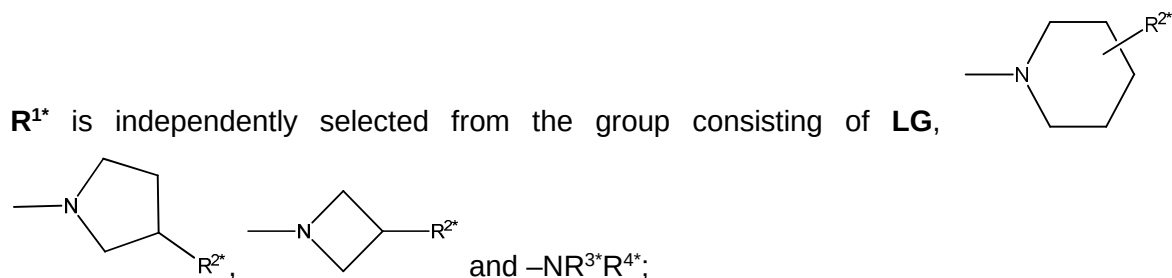
47. In yet another aspect, the present disclosure refers to a compound of formula (II)



(II)

wherein **R**, **X**, **X¹**, **Y** and **n** are as defined in item 1;

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wherein

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R^{2*} is selected from the group consisting of **LG** and hydrogen;

R^{3*} and **R^{4*}** are independently selected from the group consisting of alkyl, **LG**-alkyl, alkyl-O-alkyl, **PG** and hydrogen;

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LG is a leaving group; and

PG is an amino protecting group;

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wherein at least one of **R^{1*}**, **R^{2*}**, **R^{3*}** and **R^{4*}** contains **LG**, and

wherein **LG** is selected from halogen, trimethylammonium, C₁₋₄ alkyl sulfonate or C₆₋₁₀ aryl sulfonate, preferably **LG** is selected from the group consisting of mesylate, triflate, tosylate and nosylate.

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48. The compound according to item 47, wherein **LG** is selected from halogen, trimethylammonium, C₁₋₄ alkyl sulfonate or C₆₋₁₀ aryl sulfonate.

49. The compound according to item 48, wherein **LG** is selected from the group consisting of mesylate, triflate, tosylate and nosylate.

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50. A method for preparing the compound according to item 5, wherein the compound is labelled by ^{18}F , comprising reacting the compound according to item 47 with a ^{18}F -fluorinating agent, so that **LG** is replaced by ^{18}F . In yet another aspect, the present disclosure refers to a method for preparing the compound as disclosed herein, wherein the compound is labelled by ^{18}F , comprising reacting the compound according to claim 11 with a ^{18}F -fluorinating agent, so that **LG** is replaced by ^{18}F , preferably 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.

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51. The method according to item 50, 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.

52. Use of the compound according to any one of items 1 to 5 as an *in vitro* analytical reference or an *in vitro* screening tool. In yet another aspect, the present disclosure refers to use of the compound as disclosed herein as an *in vitro* analytical reference or an *in vitro* screening tool.

53. A test kit for use in the detection and/or diagnosis of a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, wherein the test kit comprises at least one compound as defined in any one of items 1 to 5. In yet another aspect, the present disclosure refers to a test kit for use in the detection and/or diagnosis of a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, wherein the test kit comprises at least one compound as disclosed herein.

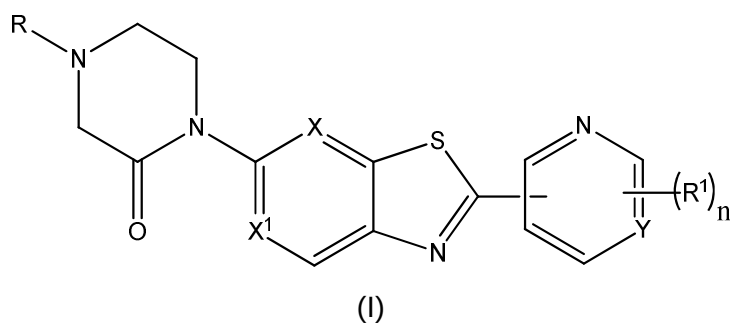
54. The test kit for use according to item 53 comprising a container containing at least one compound as defined in any one of items 1 to 5 and instructions for using the at least one compound for the purpose of binding to alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to form a compound/(alpha-synuclein aggregate including, but not limited to, Lewy bodies and/or Lewy neurites) complex and detecting the formation of the compound/(alpha-synuclein aggregate including, but not limited to, Lewy bodies and/or Lewy neurites) complex such that presence or absence of the compound/(alpha-synuclein aggregate including, but not limited to, Lewy bodies and/or Lewy neurites) complex correlates with the presence or absence of the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites.

55. A kit for preparing a radiopharmaceutical preparation, wherein the kit comprises a sealed vial containing at least one compound as defined in item 47. In yet another aspect, the present disclosure refers to a kit for preparing a radiopharmaceutical preparation, wherein the kit comprises a sealed vial containing at least one compound as disclosed herein.

The compounds, which are disclosed in the examples or in claims as well as detectably labeled derivatives, stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates, prodrugs and polymorphs thereof, are considered to be particularly suitable compounds of the present disclosure and can be used in any of the above items.

CLAIMS

1. A compound of formula (I):

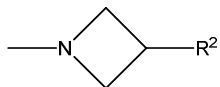
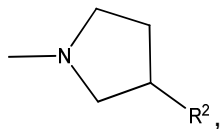


and detectably labeled derivatives, stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates, prodrugs and polymorphs thereof;

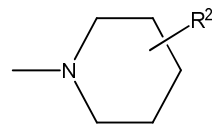
wherein

R is selected from the group consisting of hydrogen and alkyl;

R¹ is independently selected from the group consisting of fluorine,



and $-NR^3R^4$;



R² is selected from the group consisting of fluorine and hydrogen;

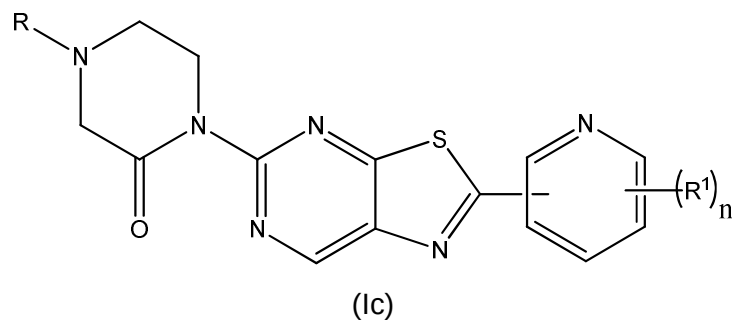
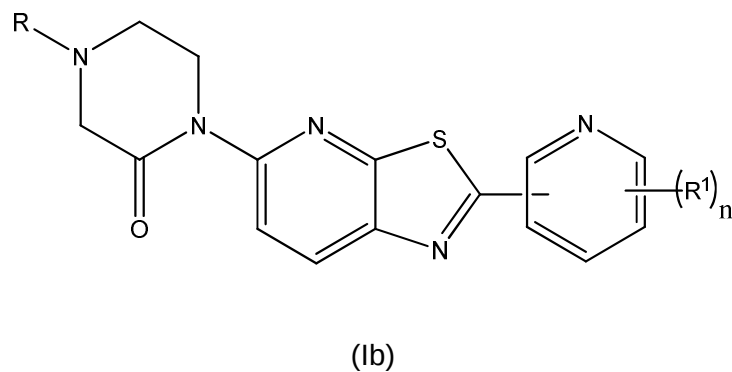
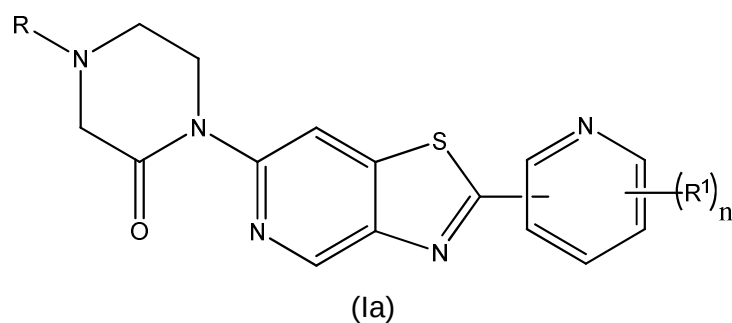
R³ and **R⁴** are independently selected from the group consisting of alkyl, fluoro-alkyl, alkyl-O-alkyl and hydrogen;

X and **X**¹ are independently selected from the group consisting of N and CH, provided that at least one of **X** and **X**¹ is N;

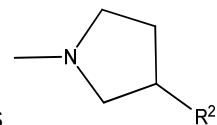
Y is independently selected from the group consisting of N and CH or **Y** is C if **Y** is attached to **R**¹;

n is 1 or 2.

2. The compound according to claim 1, which is a compound of the formula (Ia), (Ib) or (Ic):



wherein **R**, **R**¹ and **n** are as defined in claim 1.



3. The compound according to any one of claims 1 and 2, wherein **R**¹ is
4. The compound according to any one of claims 1 to 3, wherein at least one of **R**¹, **R**², **R**³ and **R**⁴ contains fluorine.
5. The compound according to any one of claims 1 to 4, wherein the compound is detectably labeled, preferably with ²H, ³H, ¹⁸F or ¹³N, more preferably with ¹⁸F.
6. A diagnostic composition comprising a compound according to any one of claims 1 to 5 and optionally 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, preferably 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.
9. 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 preclinical state thereof.
10. An *in vitro* method of collecting data for the diagnosis of a disorder or abnormality associated with alpha-synuclein aggregates in a patient comprising:
 - (a) bringing a sample of the patient suspected to contain alpha-synuclein aggregates 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;
 - (c) detecting the compound bound to the alpha-synuclein aggregates; and
 - (d) optionally correlating the presence or absence of compound binding with the alpha-synuclein aggregates with the presence or absence of alpha-synuclein aggregates in the sample.

11. An *in vitro* method of collecting data for diagnosis of the preclinical state of a disorder or abnormality associated with alpha-synuclein aggregates 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 in a sample of the patient which comprises the steps of:
- 5
- (a) bringing the sample suspected to contain the alpha-synuclein aggregates into contact with the compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates;
 - (b) allowing the compound to bind to the alpha-synuclein aggregates to form a
 - 10 compound/(alpha-synuclein aggregate) complex;
 - (c) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
 - (d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregates in the sample; and
 - 15 (e) optionally comparing the amount of the compound/(alpha-synuclein aggregate) complex to a normal control value.
12. An *in vitro* method of collecting data for monitoring residual disorder in a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates who has been
- 20 treated with a medicament, wherein the method comprises:
- (a) bringing a sample suspected to contain alpha-synuclein aggregates into contact with a compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates;
 - (b) allowing the compound to bind to the alpha-synuclein aggregates to form a
 - 25 compound/(alpha-synuclein aggregate) complex;
 - (c) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
 - (d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregate in the sample; and
 - 30 (e) optionally comparing the amount of the compound/(alpha-synuclein aggregate) complex to a normal control value.
13. The method according to claim 12, wherein step (d) is present and wherein the method further comprises steps (i) to (vi) before step (a):

- (i) bringing a sample suspected to contain alpha-synuclein aggregates into contact with the compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates;
- (ii) allowing the compound to bind to the alpha-synuclein aggregates to form a compound/(alpha-synuclein aggregate) complex;
- (iii) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
- (iv) correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregates in the sample;
- (v) optionally comparing the amount of the compound/(alpha-synuclein aggregate) complex to a normal control value; and
- (vi) 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 aggregate) complex determined in step (iv) to the amount of the compound/(alpha-synuclein aggregate) complex determined in step (d).
14. The method according to claim 12 or 13, wherein steps (a) to (c) and optionally steps (d) and (e) are repeated one or more times.
15. An *in vitro* method of collecting data for predicting responsiveness of a patient suffering from a disorder or abnormality associated with alpha-synuclein aggregates and being treated with a medicament comprising:
- (a) bringing a sample suspected to contain alpha-synuclein aggregates into contact with a compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates;
- (b) allowing the compound to bind to the alpha-synuclein aggregates to form a compound/(alpha-synuclein aggregate) complex;
- (c) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
- (d) optionally correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregates in the sample; and
- (e) optionally comparing the amount of the compound/(alpha-synuclein aggregate) complex to a normal control value.

16. The method according to claim 15, wherein step (d) is present and wherein the method further comprises steps (i) to (vi) before step (a):
- (i) bringing a sample suspected to contain alpha-synuclein aggregates into contact with the compound as defined in any one of claims 1 to 5, which compound specifically binds to the alpha-synuclein aggregates;
 - (ii) allowing the compound to bind to the alpha-synuclein aggregates to form a compound/(alpha-synuclein aggregate) complex;
 - (iii) detecting the formation of the compound/(alpha-synuclein aggregate) complex;
 - (iv) correlating the presence or absence of the compound/(alpha-synuclein aggregate) complex with the presence or absence of alpha-synuclein aggregates in the sample;
 - (v) optionally comparing the amount of the compound/(alpha-synuclein aggregate) complex to a normal control value; and
 - (vi) 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 aggregate) complex determined in step (iv) to the amount of the compound/(alpha-synuclein aggregate) complex determined in step (d).
17. The method according to claim 15 or 16, wherein steps (a) to (c) and optionally steps (d) and (e) are repeated one or more times.
18. The method according to any one of claims 10 to 17, or a compound for use according to claim 9, 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, Down syndrome, multiple system atrophy (including Shy-Drager syndrome, striatonigral degeneration or olivopontocerebellar atrophy), traumatic brain injury, chronic traumatic encephalopathy, motor neuron disease, 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.

19. The method according to any one of claims 10 to 17, or a compound for use according to claim 9, wherein the disorder is Parkinson's disease, dementia with Lewy bodies, or multiple system atrophy.

20. An *in vitro* method of determining the amount of alpha-synuclein aggregates in a sample obtained from a patient comprising:

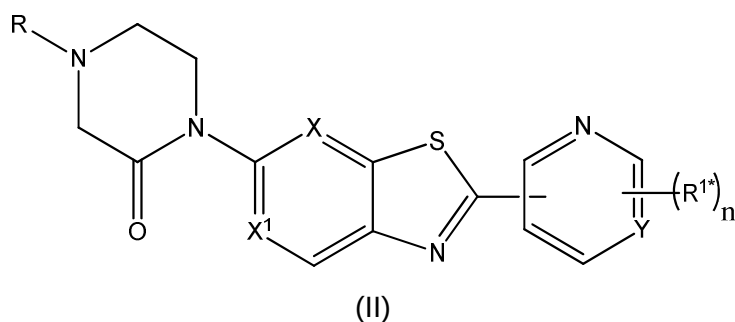
- (a) testing the sample for the presence of alpha-synuclein aggregates with a compound as defined in any one of claims 1 to 5;
- (b) determining the amount of compound bound to the alpha-synuclein aggregates; and
- (c) calculating the amount of alpha-synuclein aggregates in the sample.

21. The method according to any one of claims 10 to 20, wherein the sample is a tissue and/or a body fluid representative of a specific body part or a body area under investigation.

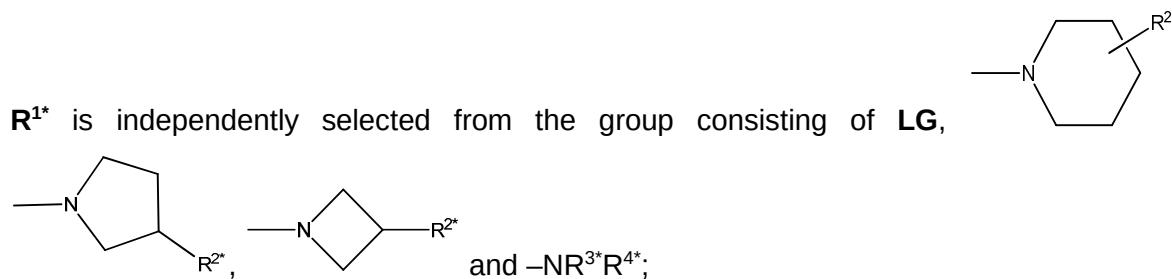
22. The method according to any one of claims 10 to 21, wherein alpha-synuclein aggregates include Lewy bodies and/or Lewy neurites.

23. 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.

24. A compound of formula (II)



wherein **R**, **X**, **X**¹, **Y** and **n** are as defined in claim 1;



wherein

R^{2*} is selected from the group consisting of **LG** and hydrogen;

R^{3*} and **R**^{4*} are independently selected from the group consisting of alkyl, **LG**-alkyl, alkyl-O-alkyl, **PG** and hydrogen;

LG is a leaving group; and

PG is an amino protecting group,

wherein at least one of **R**^{1*}, **R**^{2*}, **R**^{3*} and **R**^{4*} contains **LG**, and

wherein **LG** is selected from halogen, trimethylammonium, C₁₋₄ alkyl sulfonate or C₆₋₁₀ aryl sulfonate, preferably **LG** is selected from the group consisting of mesylate, triflate, tosylate and nosylate.

25. A method for preparing the compound according to claim 5, wherein the compound is labelled by ¹⁸F, comprising reacting the compound according to claim 11 with a ¹⁸F-fluorinating agent, so that **LG** is replaced by ¹⁸F, preferably wherein the ¹⁸F-fluorinating agent is selected from K¹⁸F, H¹⁸F, Cs¹⁸F, Na¹⁸F and tetrabutylammonium [¹⁸F]fluoride.

26. 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.

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27. A test kit for use in the detection and/or diagnosis of a disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, wherein the test kit comprises at least one compound as defined in any one of claims 1 to 5.
28. A kit for preparing a radiopharmaceutical preparation, wherein the kit comprises a sealed vial containing at least one compound as defined in claim 24.