an α-synuclein binder labelled with an *in vivo* imaging moiety, and wherein the *in vivo* imaging agent binds to α-synuclein with a binding affinity.

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.

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 the brain *in vivo* to allow diagnosis of Alzheimer's disease.

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

WO 2017/153601 and WO 2019/234243 refer to bicyclic compounds for diagnosing a-synuclein aggregates.

It was surprisingly found that a new class of compounds of formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, is capable of binding to alpha-synuclein. Thus, the compounds qualify as a PET tracer for the imaging of pathological a-syn aggregates in PD and other alpha-synucleinopathies when the inventive compounds are radiolabelled with suitable radioisotopes.

SUMMARY ~~OF THE INVENTION~~

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

Furthermore, there exists a clinical need 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 ~~invention~~ disclosure to provide compounds that are suitable in a diagnostic composition for positron emission tomography imaging of alpha-synucleinopathies, e.g., wherein the compounds are detectably labelled with ^{18}F or other labelled moieties.

The present inventors have surprisingly found that these objects can be achieved by the compounds of formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, as described hereinafter.

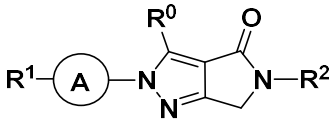
The compounds of formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, display potent binding affinity to alpha-synuclein aggregates in mammalian (e.g., human) tissues. Moreover, the compounds of formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, display potent selectivity for a-syn over other protein aggregates associated with neurodegeneration 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 the detection and quantification of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites *in vivo*, *ex vivo* and *in vitro*.

The present ~~invention~~ disclosure discloses novel compounds of formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, or of subformulae thereof, as disclosed herein, having enhanced binding properties to alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites. The compounds of this ~~invention~~ disclosure may be labelled (e.g., radiolabelled), so that they may be used for *in vitro*, *ex vivo* and *in vivo* imaging to detect alpha-synuclein aggregates

including, but not limited to, Lewy bodies and/or Lewy neurites. The present ~~invention~~ 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 subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, or a pharmaceutical composition thereof. The present ~~invention~~ disclosure provides compounds of formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, for use as diagnostic imaging agents, particularly for presymptomatic or prodromal detection of Parkinson's disease and/or other synucleinopathies, e.g., using positron emission tomography (PET). The compounds of the ~~invention~~ disclosure can serve as a biomarker for monitoring the topographic and temporal progression of the pathology, leading to improvement of clinical diagnosis study design and outcome. The present ~~invention~~ disclosure further provides a diagnostic composition comprising a compound of formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, and at least one pharmaceutically acceptable excipient, carrier, diluent or adjuvant.

The present ~~invention~~ disclosure is summarized in the following items:

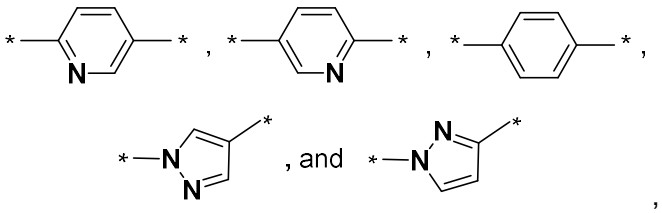
In one aspect, ~~T~~the ~~invention~~ disclosure is directed to a compound of formula (I):



(I)

or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

Ⓐ is an aryl or a heteroaryl which is directionally selected from the following:



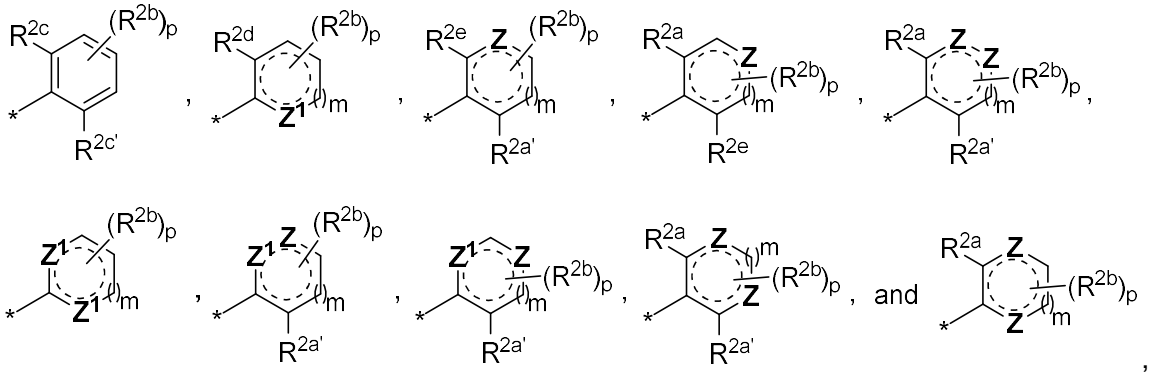
,

R^0 is H or C_1-C_4alkyl;

R^1 is -CN; or halo; or C_1-C_4alkyl; or C_1-C_4alkoxy; or -N(C_1-C_4alkyl)$_2$; or -NH(C_1-C_4alkyl); or H; or

R^1 is -NH-C_3-C_6cycloalkyl, C_3-C_6cycloalkyl, or heterocyclyl, each of which is optionally substituted with at least one halo;

R^2 is aryl, or 5-membered or 6-membered heteroaryl, wherein R^2 is selected from the following:



wherein

R^{2a}, $R^{2a'}$ are independently selected from H, or F;

R^{2b} is independently selected from F, -OH, C_1-C_4alkyl, haloC_1-C_4alkyl, -NH_2, -CN, or C_1-C_4alkoxy;

R^{2c}, $R^{2c'}$ are independently selected from H, F, OH, OCH_3, or CH_3;

R^{2d} is selected from H, F, or -OH;

R^{2e} is selected from H, OH, CH_3, or F;

Z is independently N, NH, N(C_1-C_4alkyl), N(haloC_1-C_4alkyl), O, or S;

Z^1 is independently N, NH, O, or S;

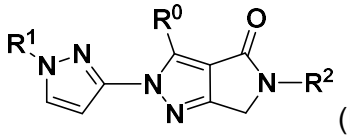
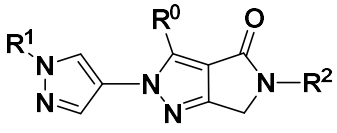
p is 0, 1 or 2;

m is 0 or 1;

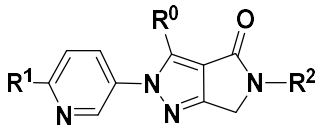
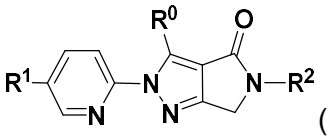
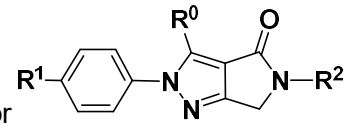
as valency permits, ⟋ is a combination of single and double bonds; and

* is the position of bonding.

~~In another aspect t~~The ~~invention~~ disclosure is also directed to a compound having the following formulae

 (IIa), or  (IIb), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof.

~~In another aspect t~~The ~~invention~~ disclosure is also directed to a compound having the following formulae


(IIIa),

(IIIb), or

(IIIc),

or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof.

~~In one aspect, t~~The compound of the formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, is for use in the imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, wherein the compound is preferably for use in positron emission tomography imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites.

In another aspect, the present disclosure is directed to a compound as described herein, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in the imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, wherein the imaging is preferably conducted by positron emission tomography.

In another aspect, the present disclosure is directed to a compound as described herein, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in diagnostics, wherein the diagnostics are preferably the diagnostics of a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites or a predisposition therefor, wherein the disease, disorder or abnormality is optionally 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), SNCA duplication carrier, Lewy Body dementia (LBD), dementia with Lewy bodies (DLB) (including “pure” Lewy body dementia), Parkinson’s disease dementia (PDD), diffuse Lewy body disease (DLBD), Alzheimer’s disease, 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 (MSA) (including Shy-Drager syndrome, striatonigral degeneration or olivopontocerebellar atrophy), traumatic brain injury, chronic traumatic encephalopathy, dementia puglistica, tauopathies (including Pick's disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration, Niemann-Pick type C1 disease, frontotemporal dementia with Parkinsonism linked to chromosome 17), Creutzfeldt-Jakob disease, Huntington's 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, Gerstmann-Straussler-Scheinker disease, inclusion-body myositis, Gaucher disease, Krabbe disease as well as other lysosomal storage disorders (including Kufor-Rakeb syndrome and Sanfilippo syndrome) and rapid eye movement (REM) sleep behavior disorder.

~~In a further aspect, t~~The present ~~invention~~ disclosure refers to a method of imaging a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, in a subject, the method comprising the steps:

(a) Administering a compound of the formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof to the subject;

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

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

In another aspect, the present disclosure is directed to a method comprising the steps:

(a) Allowing a compound as disclosed herein, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition as disclosed herein, that had been contacted with a sample or a specific body part or body area suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

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

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

wherein the method is selected from:

(i) a method of collecting data for the diagnosis of a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(ii) a method of collecting data for determining a predisposition to a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(iii) a method of collecting data for prognosing a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(iv) a method of collecting data for monitoring the progression of a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a patient; and

a method of collecting data for predicting responsiveness of a patient suffering from a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to a treatment of the disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites.

~~In a further aspect, t~~The present ~~invention~~ disclosure is directed to a method of imaging a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, in a subject, the method comprising the steps:

(a) Administering a compound of the formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof to the subject; and

(b) Imaging the brain of the subject.

~~In a further aspect, t~~The present ~~invention~~ disclosure refers to a method of positron emission tomography (PET) imaging of alpha-synuclein aggregates, including but not limited to, Lewy bodies and/or Lewy neurites, in a tissue of a subject, the method comprising the steps:

(a) Administering a compound of the formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof to the subject;

(b) Allowing the compound to penetrate into the tissue of the subject; and

(c) Collecting a positron emission tomography (PET) image of the tissue of the subject;

wherein the tissue is tissue of the central nervous system (CNS), of the eye or brain tissue, preferably wherein the tissue is brain tissue.

~~In a further aspect, t~~The present ~~invention~~ disclosure is directed a method of detecting a neurological disease, disorder or abnormality associated with alpha-synuclein aggregates, including but not limited to, Lewy bodies and/or Lewy neurites, in a subject, the method comprising the steps:

(a) Administering a compound of the formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof to the subject;

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

(c) Measuring the radioactive signal of the compound, which is bound to the alpha-synclein aggregates, including but not limited to, Lewy bodies and/or Lewy neurites.

~~In a further aspect, t~~The present ~~invention~~ disclosure is directed to a method for the detection and/or quantification of alpha-synuclein aggregates, including but not limited to, Lewy bodies and/or Lewy neurites, in a tissue of a subject, the method comprising the steps:

(a) Contacting the tissue with a compound of the formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof to the subject;

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

(c) Detecting and/or quantifying the compound bound to the alpha-synuclein aggregates, including but not limited to, Lewy bodies and/or Lewy neurites, using positron emission tomography.

~~In yet another aspect, t~~The present ~~invention~~ disclosure refers to a method of the diagnostic imaging of the brain of a subject, the method comprising the steps:

(a) Administering a compound of the formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof to the subject; and

(b) Obtaining an image of the brain of the subject using positron emission tomography.

The present ~~invention~~ disclosure is also directed to a method of collecting data for the diagnosis of a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, is also disclosed herein, wherein the method comprising the steps:

(a) Bringing a sample or a 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 of the formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof;

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

The present disclosure ~~invention~~ also refers to a method of collecting data for determining a predisposition to a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, the method comprising the steps:

(a) Bringing a sample or a 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 of the formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof;

(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 the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of the 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 a further aspect t~~The present disclosure ~~invention~~ relates to a method of collecting data for prognosing a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, wherein the method comprises the steps:

(a) Bringing a sample, a 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 of the formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof;

(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;

(d) Optionally correlating the presence or absence of the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of the 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 repeating steps (a) to (c) and, if present, optional step (d) at least one time.

~~In another aspect t~~The present disclosure ~~invention~~ is directed to a method of collecting data for monitoring the progression of a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a patient, the method comprising the steps:

(a) Bringing a sample, a 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 of the formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc),

(III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof;

(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;

(d) Optionally correlating the presence or absence of the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of the 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 repeating steps (a) to (c) and, if present, optional step (d) at least one time.

~~In a further aspect, t~~The present disclosure ~~invention~~ relates to a method of collecting data for predicting responsiveness of a patient suffering from a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to a treatment of the disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, method comprising the steps:

(a) Bringing a sample, a 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 of formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof;

(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;

(d) Optionally correlating the presence or absence of the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of the 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

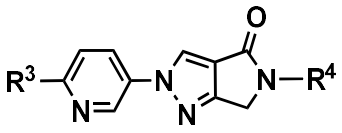
(e) Optionally repeating steps (a) to (c) and, if present, optional step (d) at least one time.

The disclosure ~~invention~~ is further directed to a diagnostic or pharmaceutical composition comprising a compound of formula (I), or subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)),

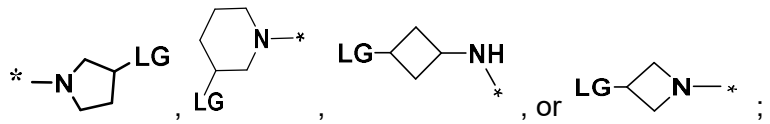
or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, and at least one pharmaceutically acceptable excipient, carrier, diluent or adjuvant.

In another aspect, the disclosure is directed to a diagnostic composition comprising a compound as disclosed herein, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, and at least one pharmaceutically acceptable excipient, carrier, diluent or adjuvant.

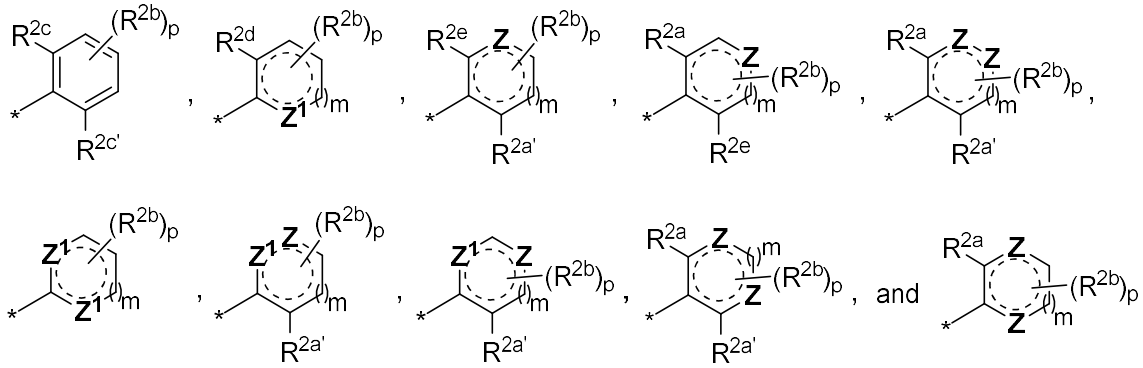
~~In another aspect t~~The ~~invention~~ disclosure is further directed to a compound of formula (IV-F)


(IV-F),

or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

R^3 is selected from  ;

R^4 is an aryl, or a 5-membered or 6-membered heteroaryl, wherein R^4 is selected from



wherein

R^{2a}, $R^{2a'}$ are independently selected from H, or F;

R^{2b} is independently selected from F, -OH, C_1-C_4alkyl, haloC_1-C_4alkyl, -NH_2, -CN, or C_1-C_4alkoxy;

R^{2c}, $R^{2c'}$ are independently selected from H, F, OH, OCH_3, or CH_3;

R^{2d} is selected from H, F, or -OH;

R^{2e} is selected from H, OH, CH_3, or F;

Z is independently N, NH, N(C_1-C_4alkyl), N(haloC_1-C_4alkyl), O, or S;

Z^1 is independently N, NH, O, or S;

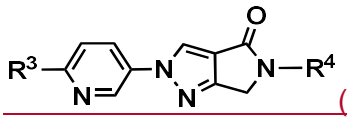
p is 0, 1 or 2;

m is 0 or 1;

as valency permits, ⸗ is a combination of single and double bonds; and

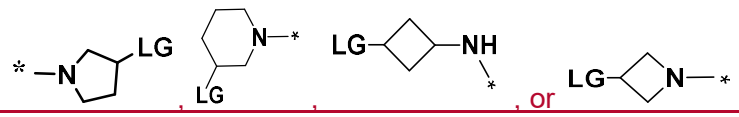
* is the position of bonding.

In another aspect, the present disclosure is directed to a compound of formula (IV-F)

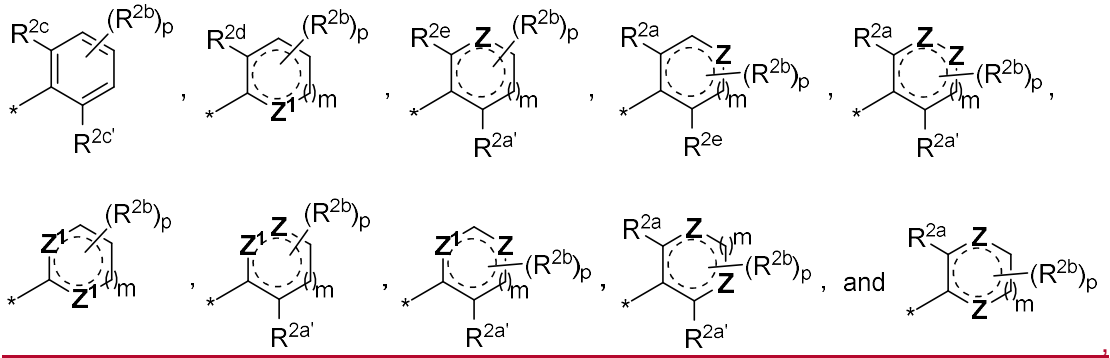


(IV-F)

or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

R^3 is selected from  ;

R^4 is an aryl or a 5-membered or 6-membered heteroaryl, wherein R^4 is selected from:



wherein

R^{2a}, $R^{2a'}$ are independently selected from H, or F;

R^{2b} is independently selected from F, -OH, C_1-C_4alkyl, haloC_1-C_4alkyl, -NH_2, -CN, or C_1-C_4alkoxy;

R^{2c}, $R^{2c'}$ are independently selected from H, F, OH, OCH_3, or CH_3;

R^{2d} is selected from H, F, or -OH;

R^{2e} is selected from H, OH, CH_3, or F;

Z is independently N, NH, N(C_1-C_4alkyl), N(haloC_1-C_4alkyl), O, or S;

Z^1 is independently N, NH, O, or S;

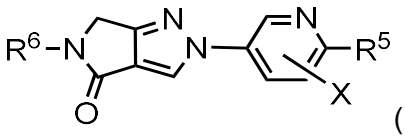
p is 0, 1 or 2;

m is 0 or 1;

as valency permits, ⟨ is a combination of single and double bonds;

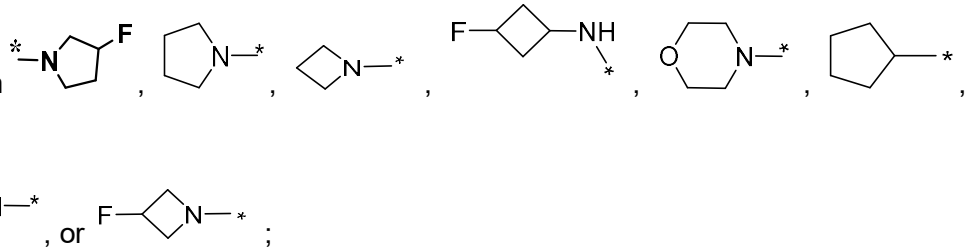
* is the position of bonding; and LG is selected from Bromo, Chloro, Iodo, C_{1-4} alkyl sulfonate and C_{6-10} aryl sulfonate, wherein the C_{6-10} aryl can be optionally substituted by $-CH_3$ or $-NO_2$.

~~In another aspect t~~The ~~invention~~ disclosure is further directed to compound of formula (IV-H)

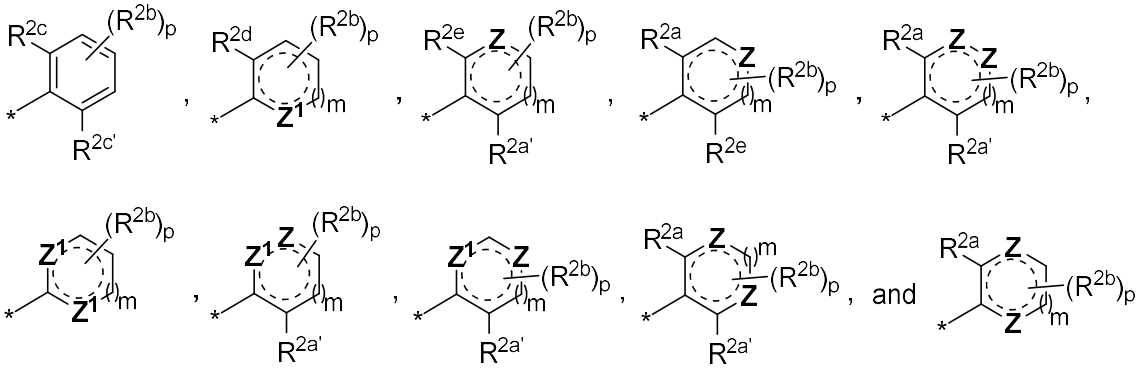


(IV-H),

or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

R^5 is selected from 

R^6 is an aryl or a 5-membered or 6-membered heteroaryl, wherein R^6 is selected from the following:



wherein

R^{2a}, R$^{2a'}$ are independently selected from H, **X** or F;

R^{2b} is independently selected from **X**, F, -OH, C_1-C_4alkyl, haloC_1-C_4alkyl, -NH_2, -CN, or C_1-C_4alkoxy, wherein C_1-C_4alkyl, haloC_1-C_4alkyl, or C_1-C_4alkoxy optionally comprise one or more **X**;

R^{2c}, R$^{2c'}$ are independently selected from **X,** H, F, OH, OCH_3, or CH_3;

R^{2d} is selected from **X**, H, F, or -OH;

R^{2e} is selected from **X**, H, OH, CH_3, or F;

Z is independently N, NH, N(C_1-C_4alkyl), N(haloC_1-C_4alkyl), O, or S;

Z^1 is independently N, NH, O, or S;

p is 0, 1 or 2;

m is 0 or 1;

as valency permits, ⟋ is a combination of single and double bonds;

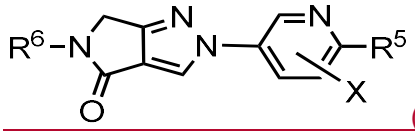
* is the position of bonding;

Fluoro is ^{19}F;

X is Bromo, Chloro, or Iodo; and

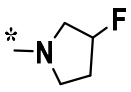
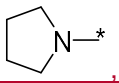
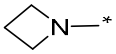
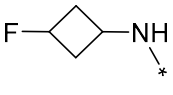
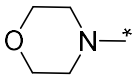
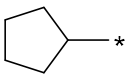
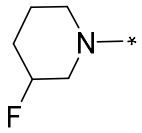
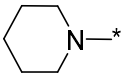
wherein R^6 comprises at least one **X**.

In another aspect, the present disclosure is directed to a compound of formula (IV-H)

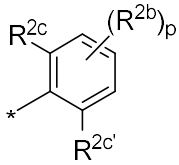
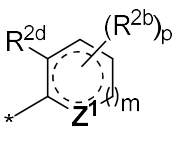
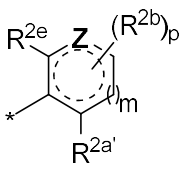
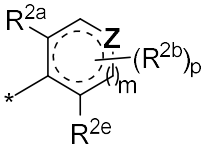
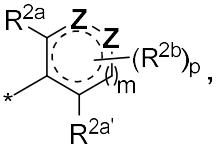


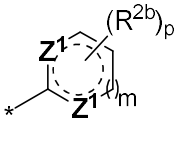
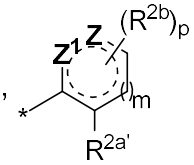
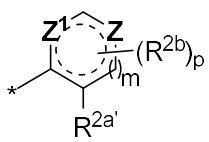
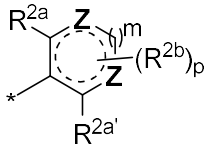
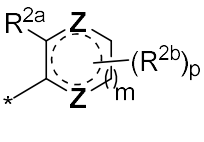
(IV-H)

or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

R^5 is selected from  ,  ,  ,  ,  ,  ,  ,  , or  ;

R^6 is an aryl or a 5-membered or 6-membered heteroaryl, wherein R^6 is selected from the following:

 ,  ,  ,  ,  ,

 ,  ,  ,  , and 

wherein

R^{2a}, $R^{2a'}$ are independently selected from H, **X** or F;

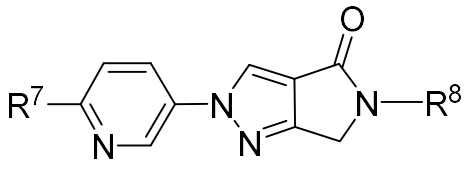
R^{2b} is independently selected from **X**, F, -OH, C_1-C_4alkyl, haloC_1-C_4alkyl, -NH_2, -CN, or C_1-C_4alkoxy, and wherein C_1-C_4alkyl, haloC_1-C_4alkyl, or C_1-C_4alkoxy optionally comprise one or more **X**;

R^{2c}, $R^{2c'}$ are independently selected from **X**, H, F, OH, OCH_3, or CH_3;
R^{2d} is selected from **X**, H, F, or -OH;
R^{2e} is selected from **X**, H, OH, CH_3, or F;
Z is independently N, NH, N(C_1-C_4alkyl), N(haloC_1-C_4alkyl), O, or S;
Z^1 is independently N, NH, O, or S;
p is 0, 1 or 2;
m is 0 or 1;
as valency permits, ⟋ is a combination of single and double bonds;
* is the position of bonding;
Fluoro is ^{19}F;
X is Bromo, Chloro, or Iodo; and
wherein R^6 comprises at least one **X**.

~~In another aspect t~~The ~~invention~~ disclosure is further directed to a method for preparing the compound of formula (III-F), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, comprising reacting the compound of formula (IV-F) with a ^{18}F-fluorinating agent, so that the Leaving Group (**LG**) is replaced by ^{18}F.

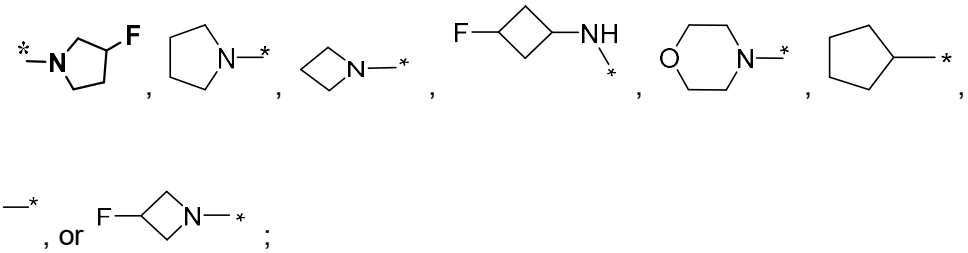
The ~~invention~~ disclosure is further directed to a method for preparing the compound of formula (III-H), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, comprising reacting the compound of formula (IV-H) with a tritating agent, so that **X** is replaced by ^3H.

In another aspect the ~~invention~~ disclosure is further directed to compound of formula (IV-J),

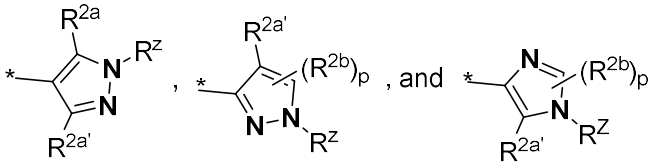


(IV-J),

or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

R^7 is selected from  ;

R^8 is selected from the following:



wherein

R^{2a}, $R^{2a'}$ are independently selected from H, or F;

R^{2b} is independently selected from F, -OH, C_1-C_4alkyl, haloC_1-C_4alkyl, -NH_2, -CN, or C_1-C_4alkoxy;

p is 0, 1 or 2;

R^z is selected from H, C_1-C_4alkyl or haloC_1-C_4alkyl;

as valency permits, ⟨ is a combination of single and double bonds;

Fluoro is ^{19}F; and

* is the position of bonding.

~~In another aspect t~~The ~~invention~~ disclosure is further directed to a method for preparing the compound of formula (III-H), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, comprising reacting the compound of formula (IV-J) with a ^3H radiolabeling agent.

In another aspect, the present disclosure is directed to a method preparing the compound as disclosed herein, comprising reacting the compound as disclosed herein with a ^3H radiolabeling agent or comprising reacting the compound as disclosed herein with a CT_3 radiolabeling agent, wherein T is ^3H.

In another aspect, the present disclosure is directed to a method of preparing the compound as disclosed herein comprising reacting the compound as disclosed herein with a ^{18}F-fluorinating agent, so that LG is replaced by ^{18}F wherein the ^{18}F-fluorinating agent is preferably selected from $K^{18}F$, $Rb^{18}F$, $Cs^{18}F$, $Na^{18}F$, $Rb^{18}F$, Kryptofix[222]$K^{18}F$, tetra(C_{1-6} alkyl) ammonium salt of ^{18}F, and tetrabutylammonium [^{18}F]fluoride.

The disclosure ~~invention~~ is further directed to the use of the compound according to compound of formula (I), or of subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, as an *in vitro* analytical reference or an *in vitro* screening tool.

In another aspect, the present disclosure is directed to use of the compound as disclosed herein, or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically

acceptable salt, hydrate, or solvate thereof, as an *in vitro* analytical reference or an *in vitro* screening tool.

The ~~invention~~ disclosure is further directed to a test kit for detection and/or diagnosis of a disease, disorder or abnormality associated with alpha-synuclein aggregates, wherein the test kit comprises at least one compound of formula (I), or of subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb), (IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof.

In another aspect, the present disclosure is directed to a test kit for the detection and/or diagnosis of a disease, disorder or abnormality associated with alpha-synuclein aggregates, wherein the test kit comprises at least one compound as disclosed herein, or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof.

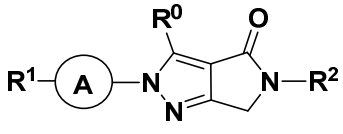
The ~~invention~~ disclosure is further directed to a kit for preparing a radiopharmaceutical preparation, wherein the kit comprises a sealed vial containing at least one compound of formula (IV-F) or (IV-H), or (IV-J), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof.

In another aspect, the present disclosure is directed to a kit for preparing a radiopharmaceutical preparation, wherein the kit comprises a sealed vial containing at least one compound as disclosed herein.

In the following, the compounds of the formulae (I), or of subformulae thereof (e.g. (IIa), (IIb), (IIIa), (IIIb),(IIIc), (III-F), (III-H)), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, are referred to as the compounds of the present ~~invention~~disclosure. The compounds of the formulae (IV-F), (IV-H) and (IV-J) will be referred to as the precursors of the compounds of the present ~~invention~~disclosure.

CLAIMS

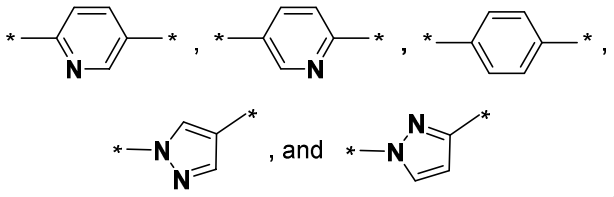
1. A compound of formula (I)


(I)

or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof,

wherein

Ⓐ is an aryl or a heteroaryl which is directionally selected from the following:

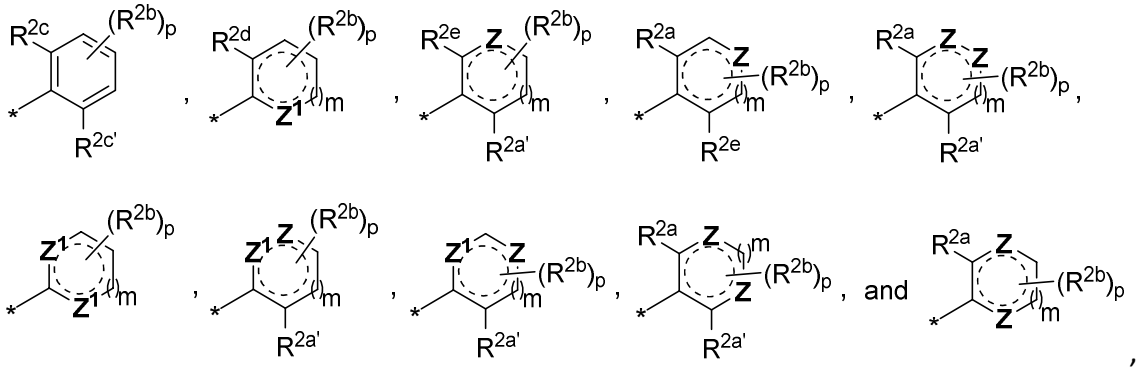


R^0 is H or C_1-C_4alkyl;

R^1 is -CN; or halo; or C_1-C_4alkyl; or C_1-C_4alkoxy; or -N(C_1-C_4alkyl)$_2$; or -NH(C_1-C_4alkyl); or H; or

R^1 is -NH-C_3-C_6cycloalkyl, C_3-C_6cycloalkyl, or heterocyclyl, each of which is optionally substituted with at least one halo;

R^2 is aryl, or 5-membered or 6-membered heteroaryl, wherein R^2 is selected from the following:



wherein

R^{2a}, $R^{2a'}$ are independently selected from H, or F;

R^{2b} is independently selected from F, OH, C_1-C_4alkyl, haloC_1-C_4alkyl, NH_2, CN, or C_1-C_4alkoxy;

R^{2c}, $R^{2c'}$ are independently selected from H, F, OH, OCH_3, or CH_3;

R^{2d} is selected from H, F, or OH;

R^{2e} is selected from H, OH, CH_3, or F;

Z is independently N, NH, N(C_1-C_4alkyl), N(haloC_1-C_4alkyl), O, or S;

Z^1 is independently N, NH, O, or S;

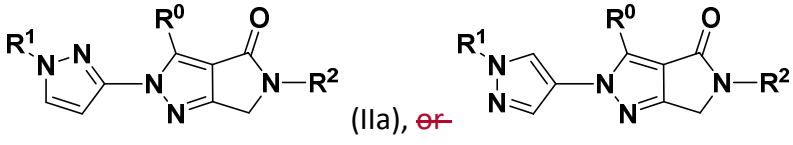
p is 0, 1 or 2;

m is 0 or 1;

as valency permits, ⋰ is a combination of single and double bonds; and

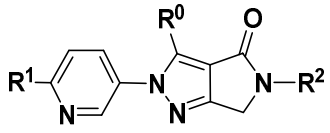
* is the position of bonding.

2. The compound according to claim 1, having a formula (IIa), ~~or~~ (IIb), (IIIa), (IIIb), or (IIIc)

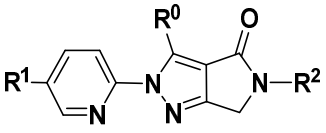


(IIa), ~~or~~

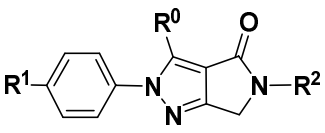
(IIb),



(IIIa),



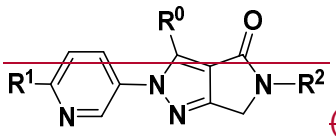
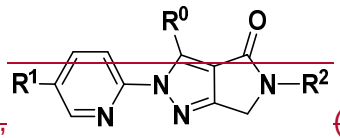
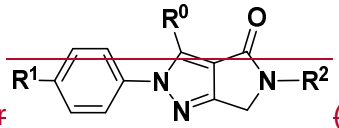
(IIIb), or



(IIIc),

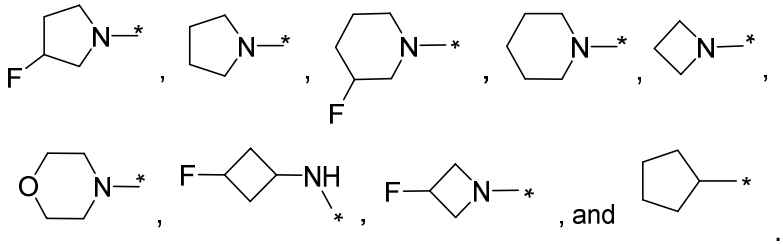
or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof.

~~3. The compound according to claim 1, having a formula (IIIa), (IIIb), or (IIIc),~~

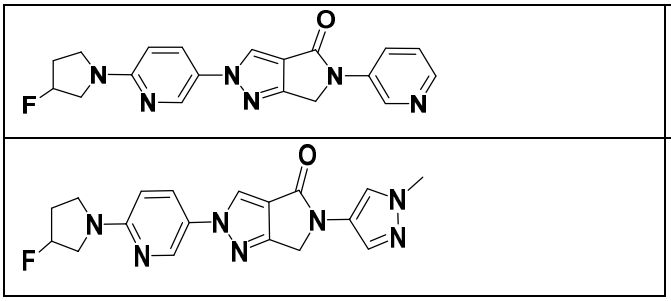
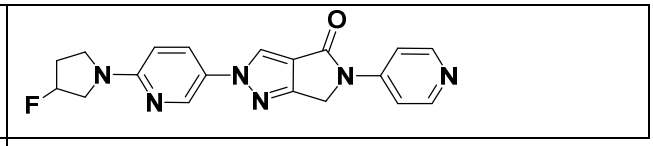

~~(IIIa),~~

~~(IIIb), or~~

~~(IIIc),~~

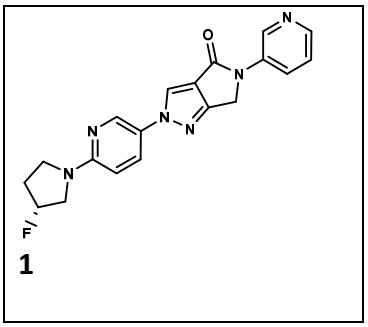
~~or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof.~~

3.The compound according to claim 1 or 2~~3~~, wherein R^1 is -NH-C_3-C_6cycloalkyl, C_3-C_6cycloalkyl, or heterocyclyl, each of which is optionally substituted with at least one halo, preferably R^1 is selected from the following:


, and .

4~~5~~. The compound of formula (I) according to claim 1, wherein the compound is selected from: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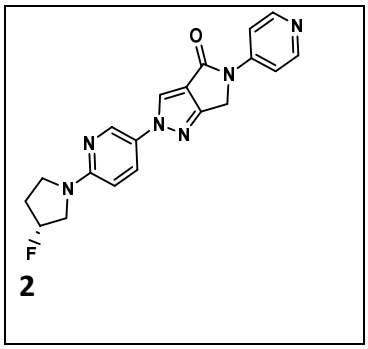
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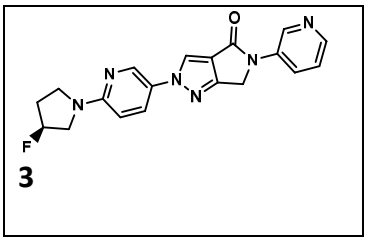
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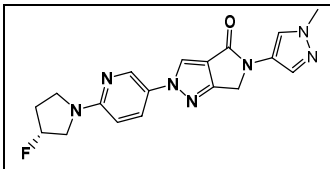

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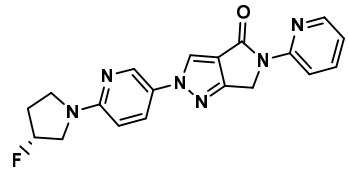

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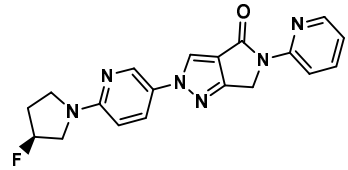

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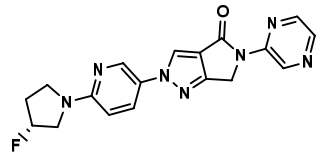

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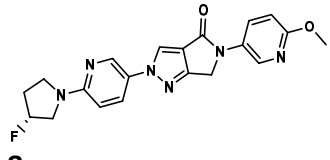

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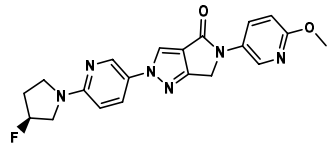

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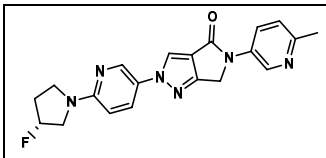

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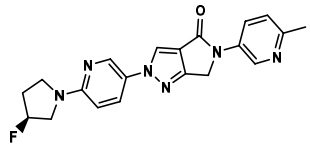

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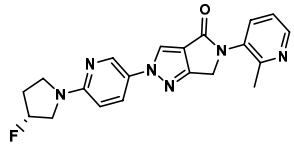

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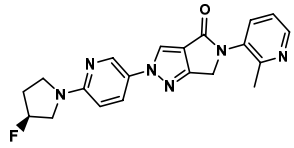

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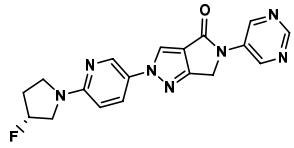

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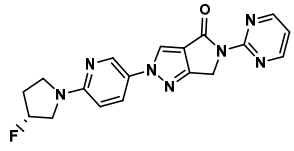

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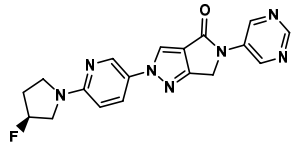

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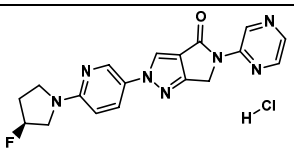

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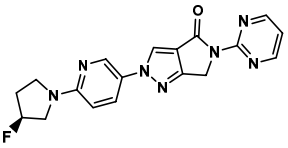

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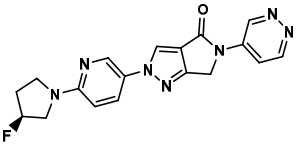

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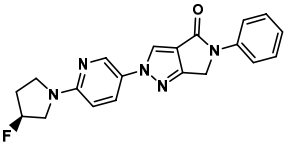

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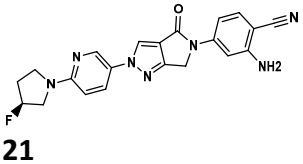

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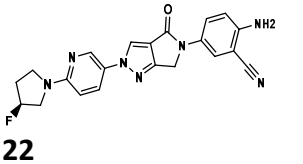

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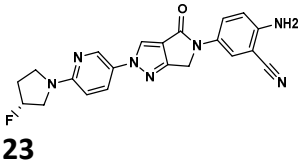

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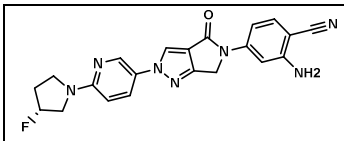

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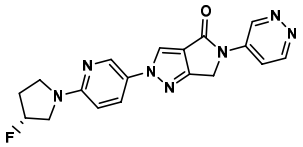

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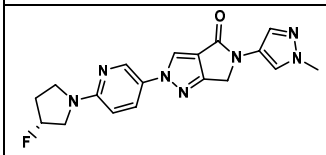

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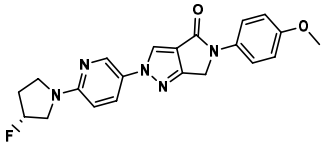

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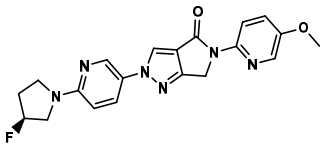

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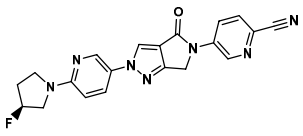

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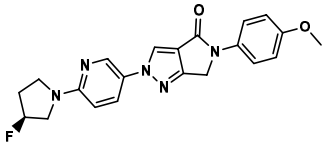

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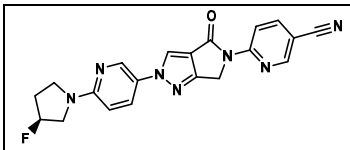

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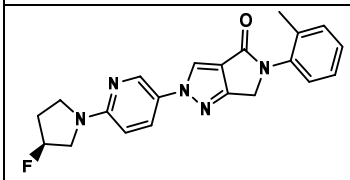

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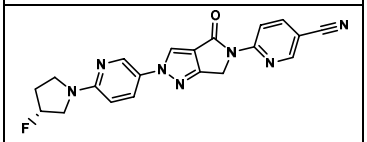

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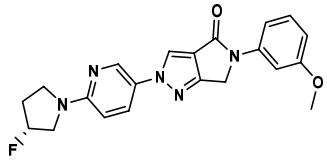

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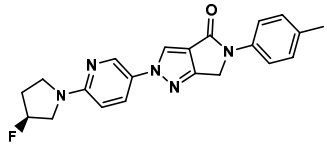

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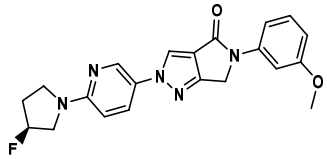

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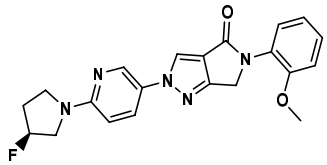

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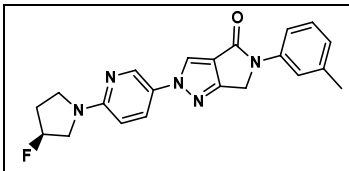

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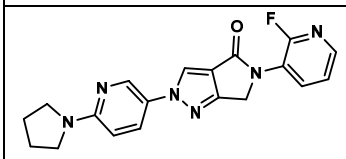

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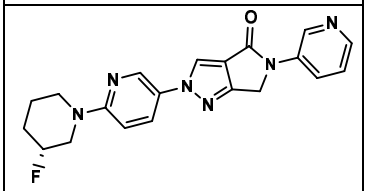

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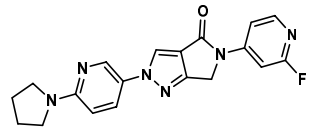

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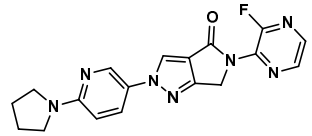

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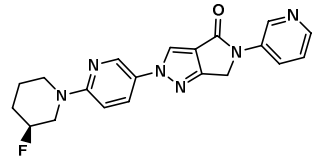

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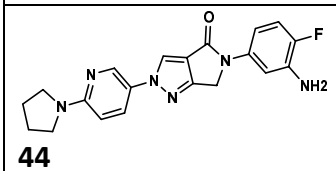

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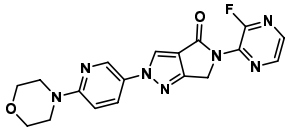
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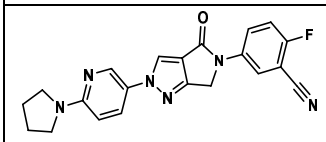
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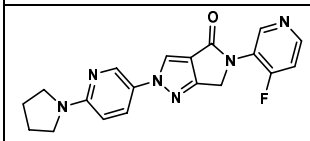
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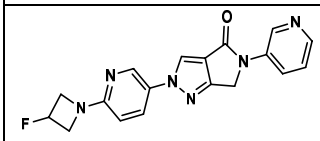
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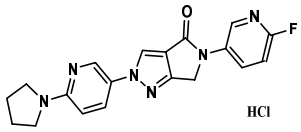
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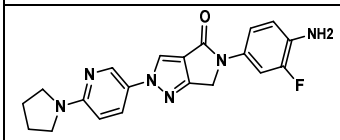
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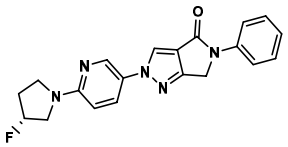
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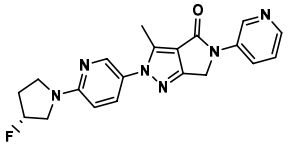
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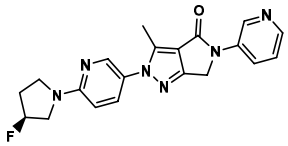
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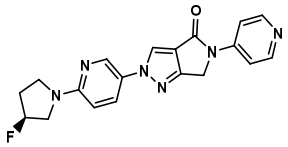
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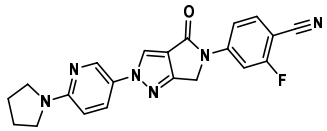
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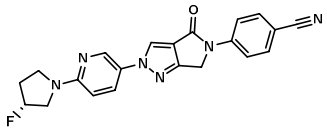
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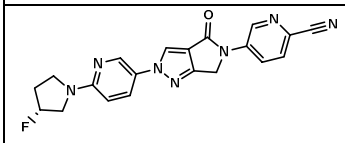
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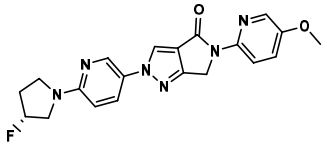
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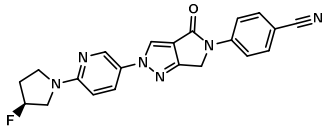
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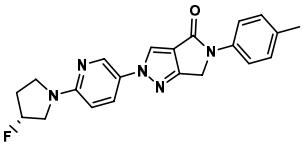
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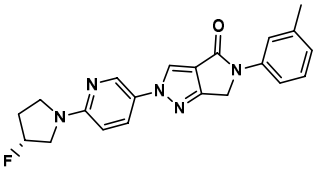
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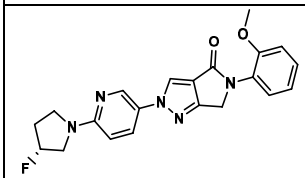
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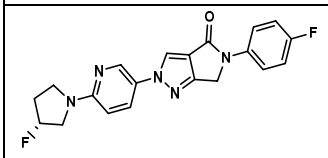
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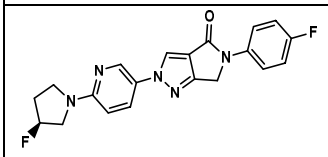
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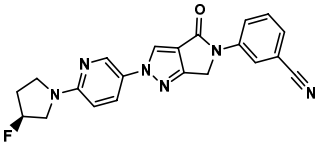
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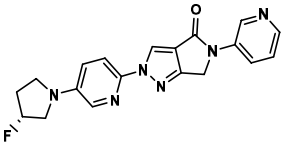
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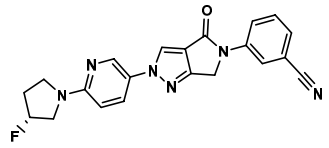

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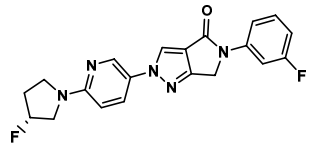

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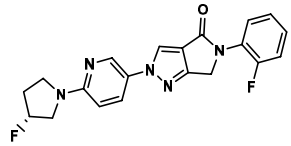

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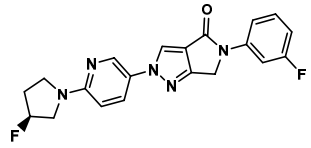

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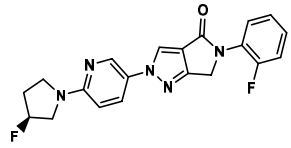

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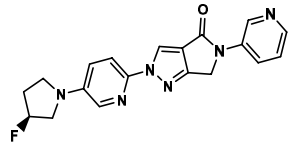

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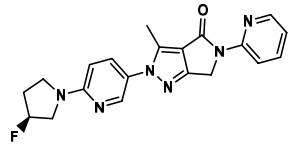

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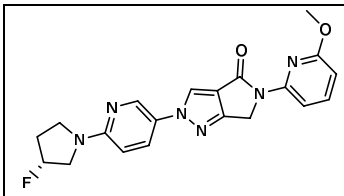

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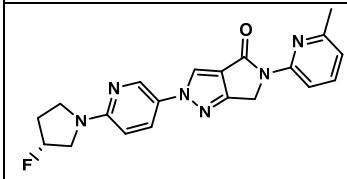

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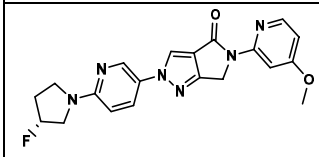

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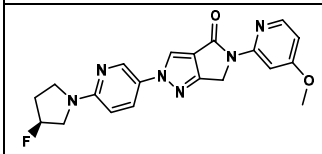

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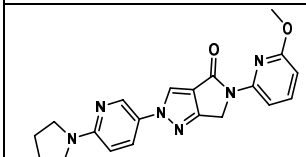

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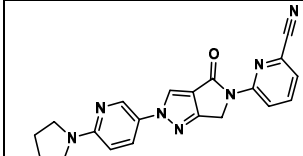

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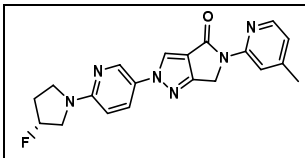

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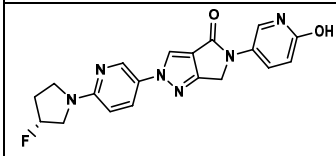

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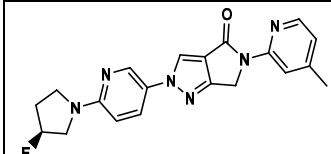

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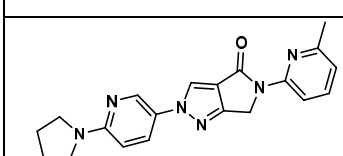

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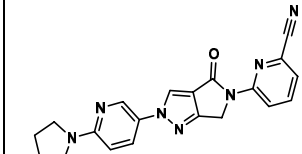

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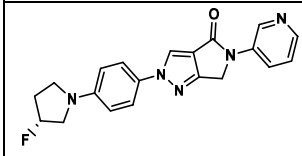

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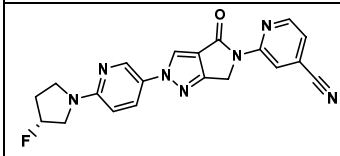

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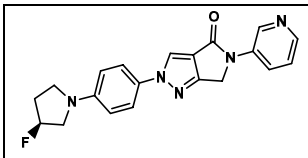

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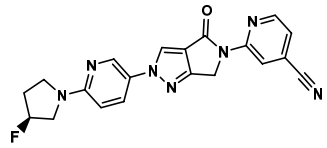

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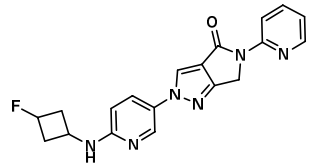

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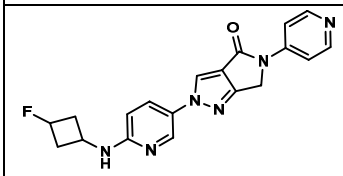

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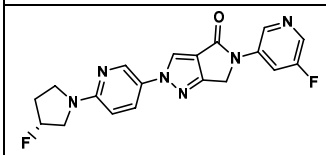

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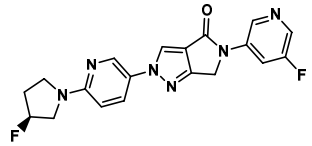

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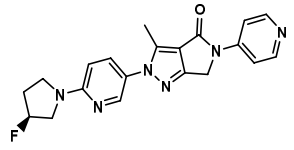

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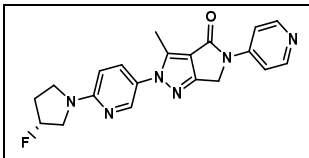

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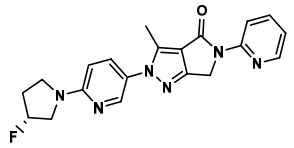

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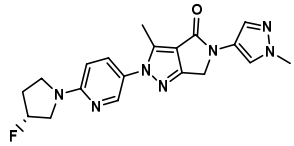

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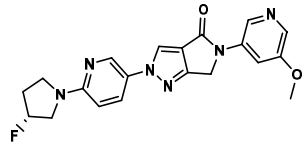

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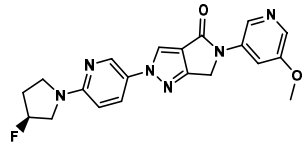

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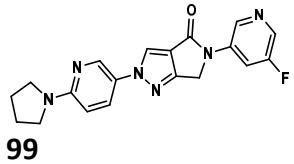

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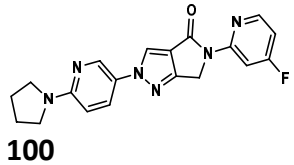

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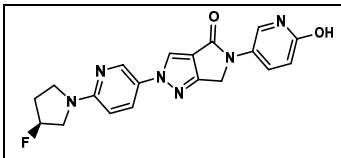

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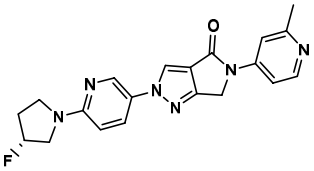

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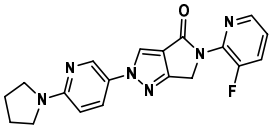

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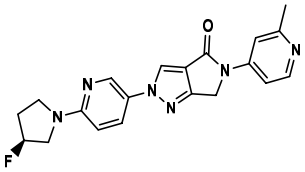

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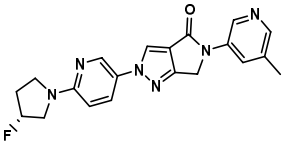

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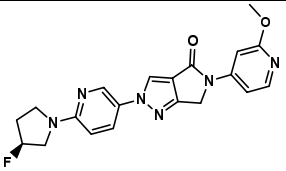

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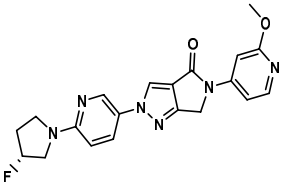

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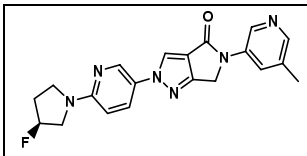

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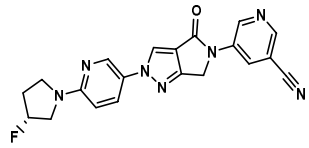

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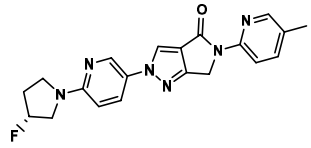

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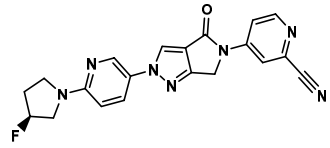

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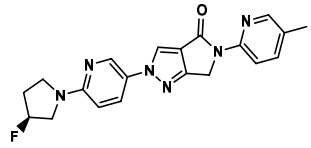

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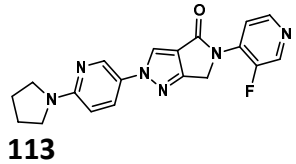

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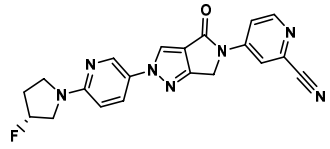

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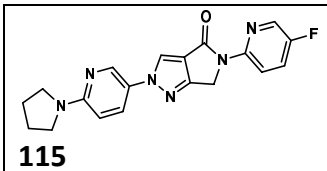

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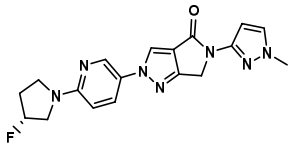

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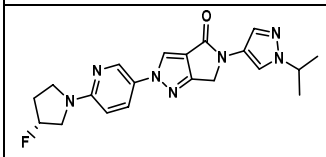

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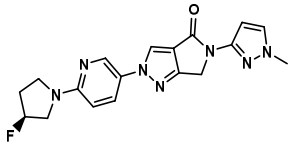

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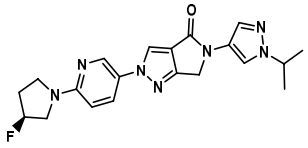

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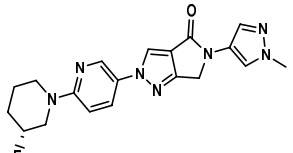

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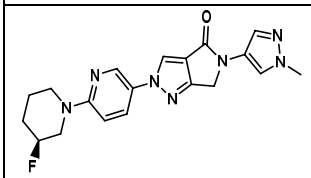

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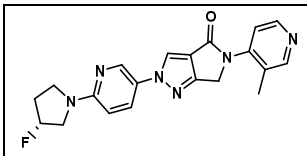

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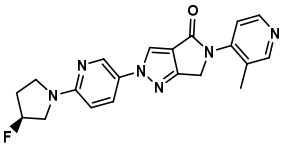

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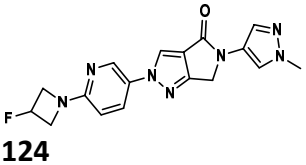

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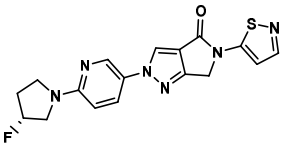

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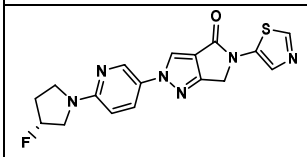

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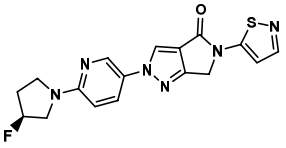

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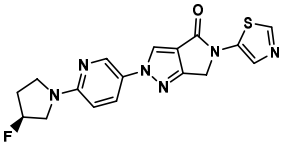

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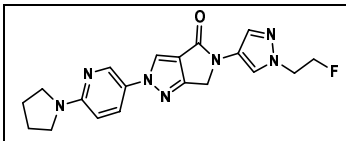

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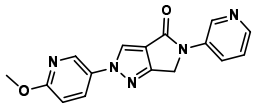

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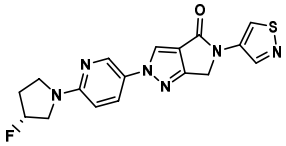

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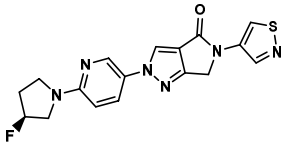

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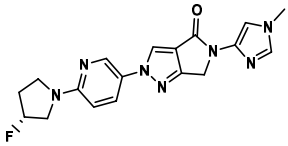

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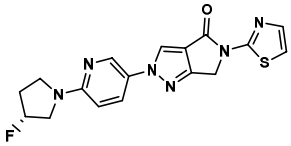

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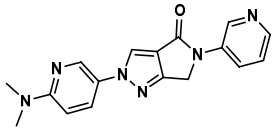

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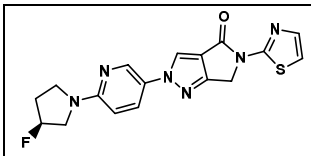

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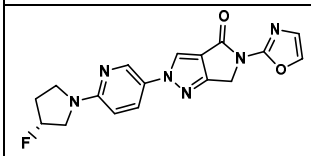

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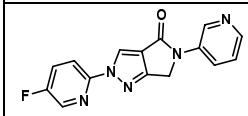

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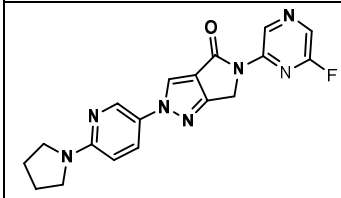

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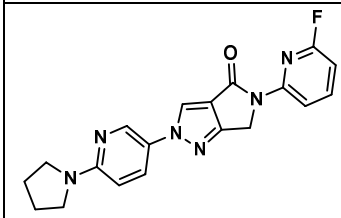

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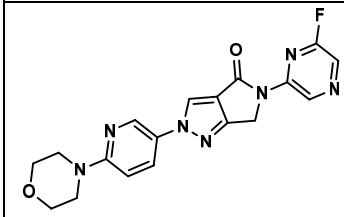

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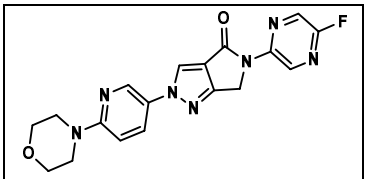

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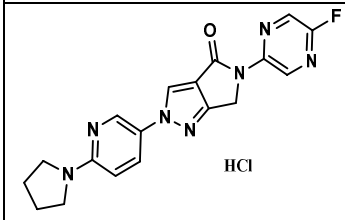

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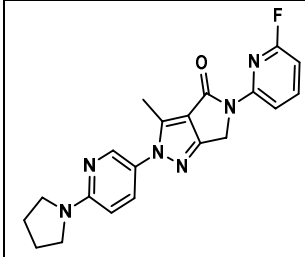

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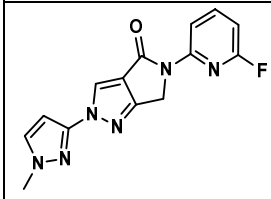

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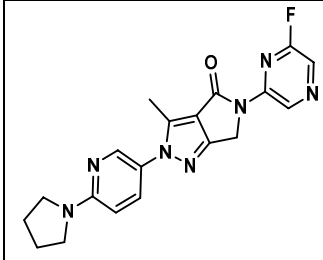

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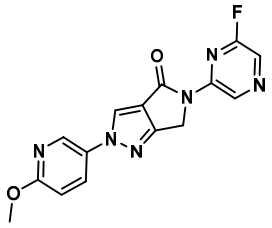

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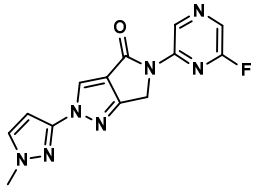

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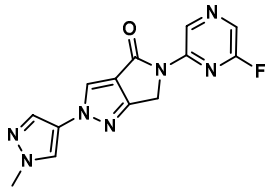

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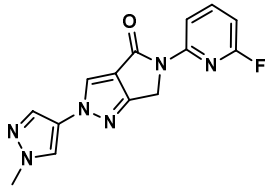

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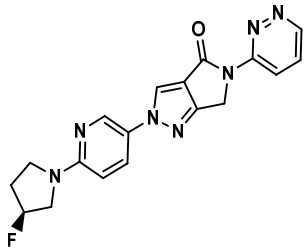

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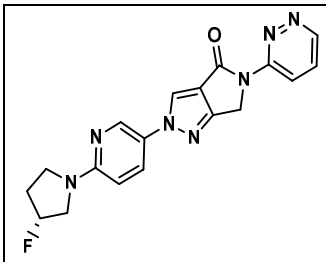

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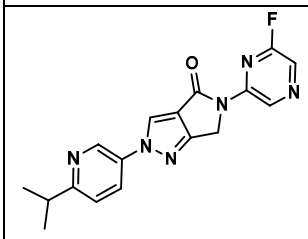

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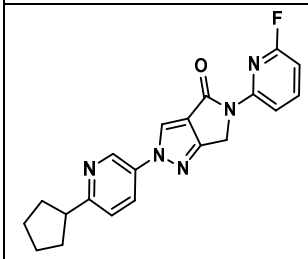

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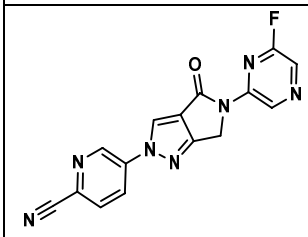

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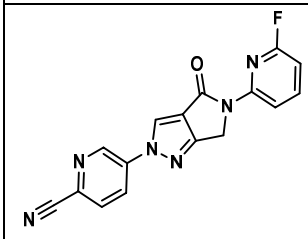

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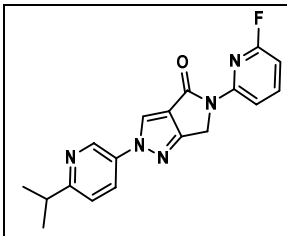

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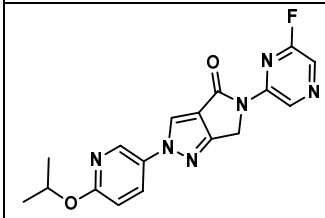

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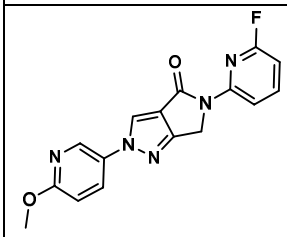

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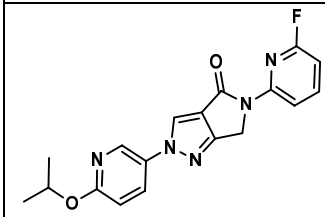

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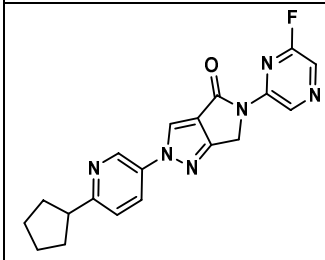

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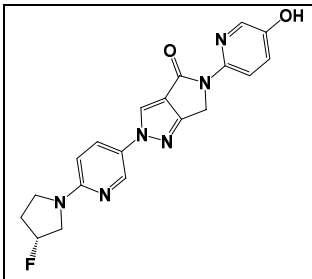

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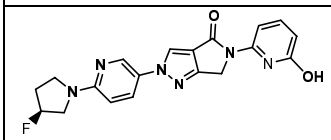

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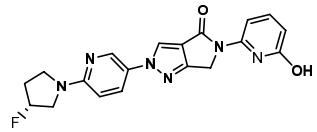

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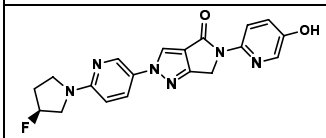

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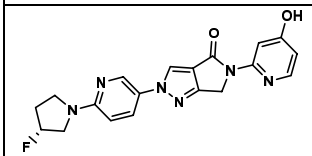

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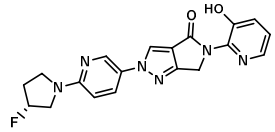

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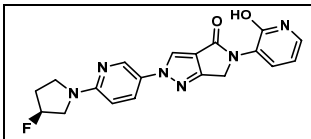

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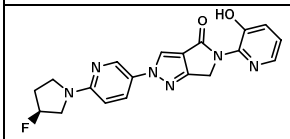

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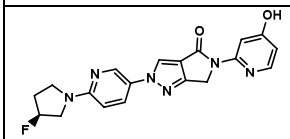

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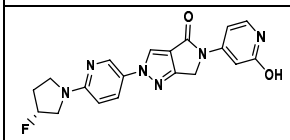
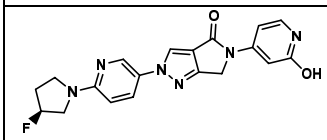


171



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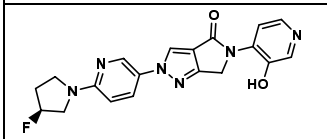

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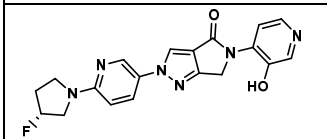

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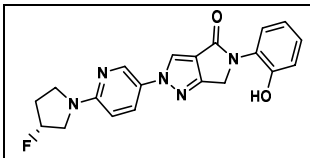

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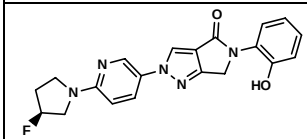

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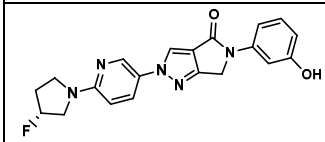

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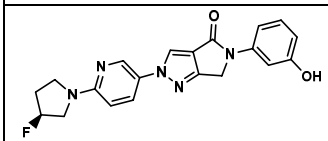

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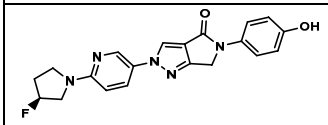

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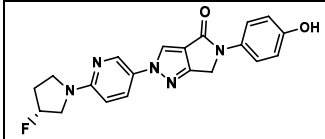

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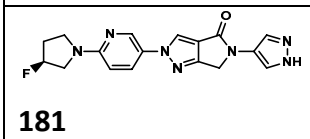

181

or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof.

5~~6~~. The compound of formula (I) according to any one of the preceding claims, wherein the compound is a detectably labelled compound, wherein the detectably labelled compound optionally comprises a detectable label selected from a radioisotope, preferably ^{2}H, ^{3}H or ^{18}F.

~~7. The compound of formula (I) according to claim 6, wherein the detectably labelled compound comprises a detectable label selected from a radioisotope, preferably ^{2}H, ^{3}H or ^{18}F.~~

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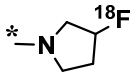
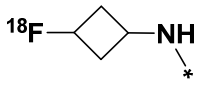
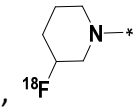
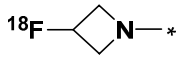
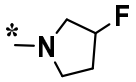
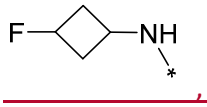
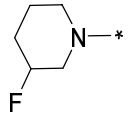
~~8~~6. The compound of formula (I) according to claim ~~6 or 7~~5, wherein $\mathbf{R^1}$ is  ,  ,  , or  , or  wherein $\mathbf{R^1}$ is  ,  ,  , or  , wherein F means ^{19}F; and the compound of formula (I) is detectably labelled at least at one available position by ^{3}H (Tritium).

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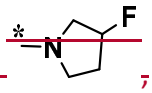
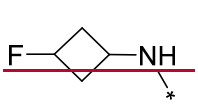
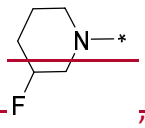
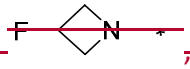
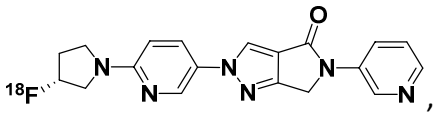
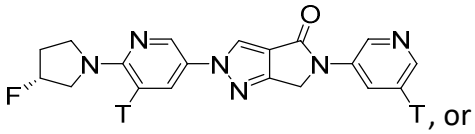
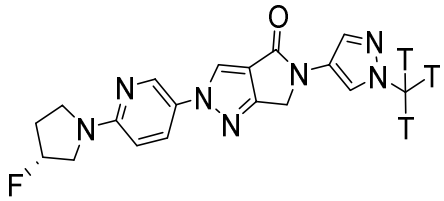
~~9. The compound of formula (I) according to claim 6 or 7, wherein $\mathbf{R^1}$ is~~  ~~,~~  ~~,~~  ~~, or~~  ~~, wherein F means ^{19}F; and the compound of formula (I) is detectably labelled at least at one available position by ^{3}H (Tritium).~~

20 7~~10~~. The compound according to claim 5 or~~any one of claims~~ 6~~ to 9~~, wherein the detectably labelled compound is

 ,





wherein T means ^{3}H (Tritium) and F means ^{19}F;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

8~~11~~. The compound according to any one of claims 5~~6~~ to 7~~10~~, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in the imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, wherein the imaging is preferably conducted by positron emission tomography.

~~12. The compound according to any one of claims 6 to 10, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in positron emission tomography imaging of alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites.~~

~~13~~9. The compound for use according to claim 8~~11 or 12~~, wherein the use is for *in vitro* imaging, *ex vivo* imaging, or *in vivo* imaging, preferably the use is for *in vivo* imaging, more preferably the use is for brain imaging.

10~~14~~. The compound according to any one of claims 5~~6~~ to 7~~10~~, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in diagnostics, wherein the diagnostics are preferably the diagnostics of a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites or a predisposition therefor, wherein the disease, disorder or

abnormality is optionally 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), SNCA duplication carrier, Lewy Body dementia (LBD), dementia with Lewy bodies (DLB) (including “pure” Lewy body dementia), Parkinson’s disease dementia (PDD), diffuse Lewy body disease (DLBD), Alzheimer’s disease, 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 (MSA) (including Shy-Drager syndrome, striatonigral degeneration or olivopontocerebellar atrophy), traumatic brain injury, chronic traumatic encephalopathy, dementia puglistica, tauopathies (including Pick's disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration, Niemann-Pick type C1 disease, frontotemporal dementia with Parkinsonism linked to chromosome 17), Creutzfeldt-Jakob disease, Huntington's 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, Gerstmann-Straussler-Scheinker disease, inclusion-body myositis, Gaucher disease, Krabbe disease as well as other lysosomal storage disorders (including Kufor-Rakeb syndrome and Sanfilippo syndrome) and rapid eye movement (REM) sleep behavior disorder.

~~15. The compound for use according to claim 14, wherein the diagnostics are the diagnostics of a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites or a predisposition therefor, wherein the disease, disorder or abnormality is optionally 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), SNCA duplication carrier, Lewy Body dementia (LBD), dementia with Lewy bodies (DLB) (including “pure” Lewy body dementia), Parkinson’s disease dementia (PDD), diffuse Lewy body disease~~

~~(DLBD), Alzheimer's disease, 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 (MSA) (including Shy-Drager syndrome, striatonigral degeneration or olivopontocerebellar atrophy), traumatic brain injury, chronic traumatic encephalopathy, dementia puglistica, tauopathies (including Pick's disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration, Niemann-Pick type C1 disease, frontotemporal dementia with Parkinsonism linked to chromosome 17), Creutzfeldt-Jakob disease, Huntington's 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, Gerstmann-Straussler-Scheinker disease, inclusion-body myositis, Gaucher disease, Krabbe disease as well as other lysosomal storage disorders (including Kufor-Rakeb syndrome and Sanfilippo syndrome) and rapid eye movement (REM) sleep behavior disorder.~~

11~~16~~. The compound for use according to claim 10~~15~~, wherein the disease is Parkinson's disease, multiple system atrophy, dementia with Lewy bodies, Parkinson's disease dementia, SNCA duplication carrier, or Alzheimer's disease.

~~17. The compound for use according to claim 15, wherein the disease is multiple system atrophy.~~

~~18. The compound for use according to claim 15, wherein the disease is dementia with Lewy bodies.~~

~~19. The compound for use according to claim 15, wherein the disease is Parkinson's disease dementia.~~

~~20. The compound for use according to claim 15, wherein the disease is SNCA duplication carrier.~~

~~21. The compound for use according to claim 15, wherein the disease is Alzheimer's disease.~~

~~22. The compound for use according to any one of claims 11 to 21, wherein the use is in a human.~~

~~23~~12. A diagnostic composition comprising a compound according to any one of claims 5~~6~~ to 7~~10~~, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, and at least one pharmaceutically acceptable excipient, carrier, diluent or adjuvant.

~~24. A method of imaging a disease, disorder or abnormality associated with alpha synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, in a subject, the method comprising the steps:~~

~~(a) Administering a compound according to any one of claims 6 to 10, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 23 to the subject;~~

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

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

~~25. A method of imaging a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, in a subject, the method comprising the steps:~~

(a) Administering a compound according to any one of claims 6 to 10, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 23 to the subject; and

(b) Imaging the brain of the subject.

26. A method of imaging a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, in a subject according to claim 24 or 25, the method comprising the steps:

(a) Administering a compound according to any one of claims 6 to 10, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 23 to the subject;

(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) Generating an image representative of the location and/or amount of the compound bound to the alpha-synuclein aggregates, including, but not limited to, Lewy bodies and/or Lewy neurites.

27. A method of positron emission tomography (PET) imaging of alpha-synuclein aggregates, including but not limited to, Lewy bodies and/or Lewy neurites, in a tissue of a subject, the method comprising the steps:

(a) Administering a compound according to any one of claims 6 to 10, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 23 to the subject;

(b) Allowing the compound to penetrate into the tissue of the subject; and

(c) Collecting a positron emission tomography (PET) image of the tissue of the subject;

wherein the tissue is tissue of the central nervous system (CNS), of the eye or brain tissue, preferably wherein the tissue is brain tissue.

28. A method of detecting a neurological disease, disorder or abnormality associated with alpha-synuclein aggregates, including but not limited to, Lewy bodies and/or Lewy neurites, in a subject, the method comprising the steps:

(a) Administering a compound according to any one of claims 6 to 10, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 23 to the subject;

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

(c) Measuring the radioactive signal of the compound, which is bound to the alpha-synclein aggregates, including but not limited to, Lewy bodies and/or Lewy neurites.

29. A method for the detection and/or quantification of alpha-synuclein aggregates, including but not limited to, Lewy bodies and/or Lewy neurites, in a tissue of a subject, the method comprising the steps:

(a) Contacting the tissue with a compound according to any one of claims 6 to 10, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 23 to the subject;

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

(c) Detecting and/or quantifying the compound bound to the alpha-synuclein aggregates, including but not limited to, Lewy bodies and/or Lewy neurites, using positron emission tomography.

30. A method of the diagnostic imaging of the brain of a subject, the method comprising the steps:

(a) Administering a compound according to any one of claims 6 to 10, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 23 to the subject; and

~~(b) Obtaining an image of the brain of the subject using positron emission tomography.~~

~~31~~13. A method ~~of collecting data for the diagnosis of a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, the method~~ comprising the steps:

~~(a) Bringing a sample or a 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 according to any one of claims 6 to 10, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 23;~~

(~~b~~a) Allowing ~~the~~ a compound according to any one of claims 5 to 7, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 12, that had been contacted with a sample or a specific body part or body area suspected to contain alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, to bind to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

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

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

wherein the method is selected from:

(i) a method of collecting data for the diagnosis of a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(ii) a method of collecting data for determining a predisposition to a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(iii) a method of collecting data for prognosing a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites;

(iv) a method of collecting data for monitoring the progression of a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a patient; and

(v) a method of collecting data for predicting responsiveness of a patient suffering from a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to a treatment of the disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites.

~~32. A method of collecting data for determining a predisposition to a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, the method comprising the steps:~~

~~(a) Bringing a sample or a 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 according to any one of claims 6 to 10, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 23;~~

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

with the presence or absence of the 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. A method of collecting data for prognosing a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, wherein the method comprises the steps:

(a) Bringing a sample, a 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 according to any one of claims 6 to 10, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 23;

(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;

(d) Optionally correlating the presence or absence of the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of the 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 repeating steps (a) to (c) and, if present, optional step (d) at least one time.

34. A method of collecting data for monitoring the progression of a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in a patient, the method comprising the steps:

(a) Bringing a sample, a 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 according to any one of claims 6 to 10, or a

~~stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 23;~~

~~(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;~~

~~(d) Optionally correlating the presence or absence of the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of the 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 repeating steps (a) to (c) and, if present, optional step (d) at least one time.~~

~~35. A method of collecting data for predicting responsiveness of a patient suffering from a disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites to a treatment of the disease, disorder or abnormality associated with alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites, method comprising the steps:~~

~~(a) Bringing a sample, a 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 according to any one of claims 6 to 10, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof; or a diagnostic composition according to claim 23;~~

~~(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;~~

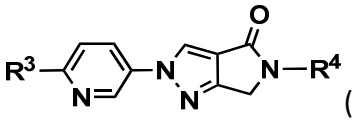
~~(d) Optionally correlating the presence or absence of the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in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

~~(e) Optionally repeating steps (a) to (c) and, if present, optional step (d) at least one time.~~

~~36~~14. The method of claim 13~~any one of claims 31 to 35~~, wherein the step of optionally correlating the presence or absence of the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample or specific body part or body area; comprises

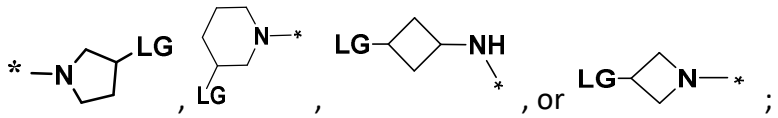
- determining in which amount of the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy;
- correlating the amount of the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the amount of the 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
- optionally comparing the amount of the amount of the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample or specific body part or body area to a normal control value in a healthy control subject.

15~~37~~. A compound of formula (IV-F)



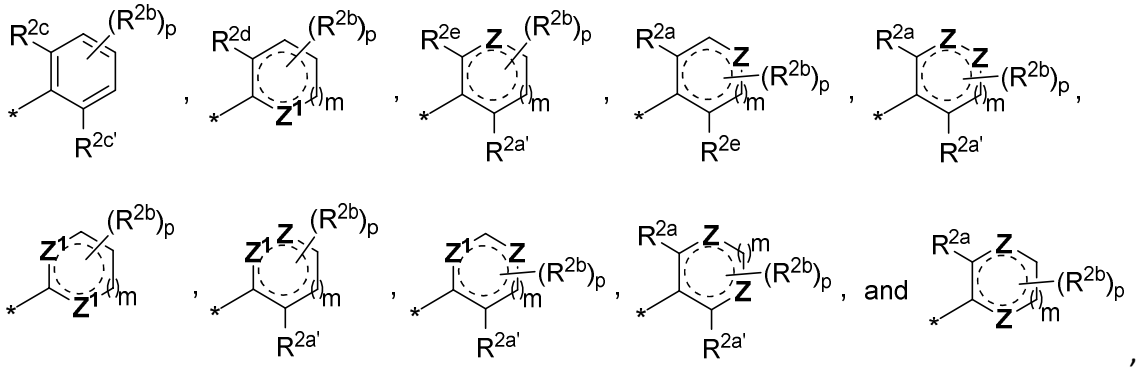
(IV-F)

or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

R^3 is selected from 

;

R^4 is an aryl or a 5-membered or 6-membered heteroaryl, wherein R^4 is selected from:



wherein

R^{2a}, $R^{2a'}$ are independently selected from H, or F;

R^{2b} is independently selected from F, -OH, C_1-C_4alkyl, haloC_1-C_4alkyl, -NH_2, -CN, or C_1-C_4alkoxy;

R^{2c}, $R^{2c'}$ are independently selected from H, F, OH, OCH_3, or CH_3;

R^{2d} is selected from H, F, or -OH;

R^{2e} is selected from H, OH, CH_3, or F;

Z is independently N, NH, N(C_1-C_4alkyl), N(haloC_1-C_4alkyl), O, or S;

Z^1 is independently N, NH, O, or S;

p is 0, 1 or 2;

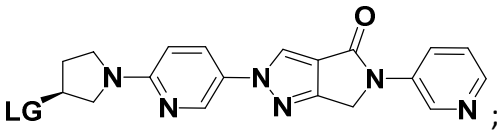
m is 0 or 1;

as valency permits, ⸗ is a combination of single and double bonds; ~~and~~

* is the position of bonding; and LG is selected from Bromo, Chloro, Iodo, C_{1-4} alkyl sulfonate and C_{6-10} aryl sulfonate, wherein the C_{6-10} aryl can be optionally substituted by –CH_3 or –NO_2.

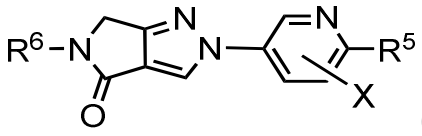
~~38. The compound of formula (IV-F) according to claim 37, wherein LG is selected from Bromo, Chloro, Iodo, C_{1-4} alkyl sulfonate and C_{6-10} aryl sulfonate, wherein the C_{6-10} aryl can be optionally substituted by –CH_3 or –NO_2.~~

16~~39~~. The compound of formula (IV-F) according to claim 15~~37 or 38~~, which is



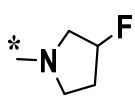
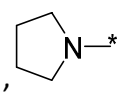
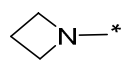
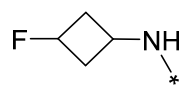
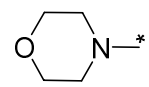
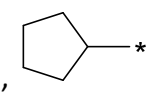
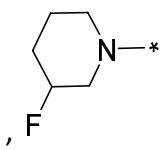
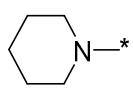
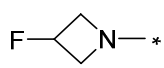
or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein **LG** is mesylate or nosylate.

~~40~~17. A compound of formula (IV-H)

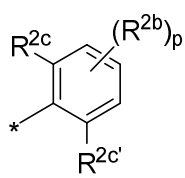
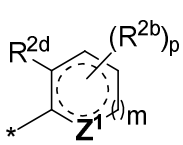
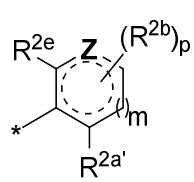
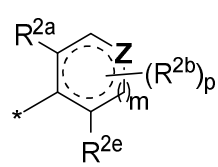
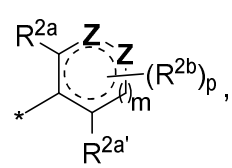


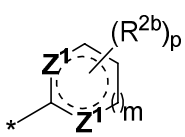
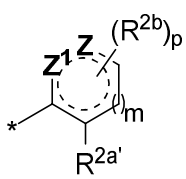
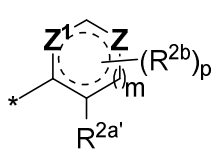
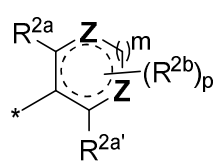
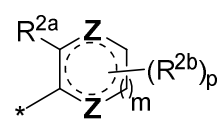
(IV-H)

or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

R^5 is selected from  ,  ,  ,  ,  ,  ,  ,  , or  ;

R^6 is an aryl or a 5-membered or 6-membered heteroaryl, wherein R^6 is selected from the following:

 ,  ,  ,  ,  ,

 ,  ,  ,  , and 

wherein

R^{2a}, $R^{2a'}$ are independently selected from H, **X** or F;

R^{2b} is independently selected from **X**, F, -OH, C_1-C_4alkyl, haloC_1-C_4alkyl, -NH_2, -CN, or C_1-C_4alkoxy, and wherein C_1-C_4alkyl, haloC_1-C_4alkyl, or C_1-C_4alkoxy optionally comprise one or more **X**;

R^{2c}, $R^{2c'}$ are independently selected from **X,** H, F, OH, OCH_3, or CH_3;

R^{2d} is selected from **X**, H, F, or -OH;

R^{2e} is selected from **X**, H, OH, CH_3, or F;

Z is independently N, NH, N(C_1-C_4alkyl), N(haloC_1-C_4alkyl), O, or S;

Z^1 is independently N, NH, O, or S;

p is 0, 1 or 2;

m is 0 or 1;

as valency permits, ⸗ is a combination of single and double bonds;

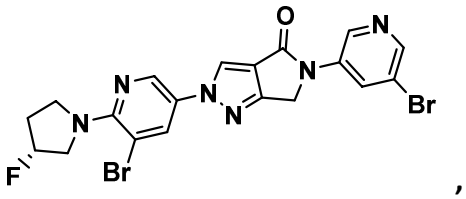
* is the position of bonding;

Fluoro is ^{19}F;

X is Bromo, Chloro, or Iodo; and

wherein R^6 comprises at least one **X**.

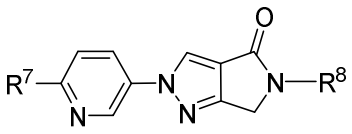
18~~41~~. The compound of formula (IV-H) according to claim 17~~40~~, which is



,

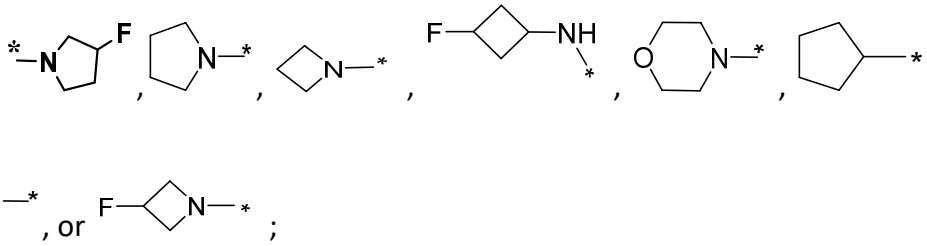
or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

19~~42~~. A compound of formula (IV-J)

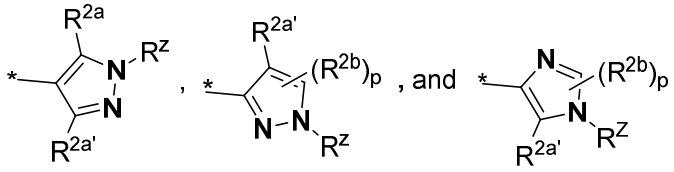


(IV-J),

or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

R^7 is selected from 

R^8 is selected from the following:



wherein

R^{2a}, $R^{2a'}$ are independently selected from H, or F;

R^{2b} is independently selected from F, -OH, C_1-C_4alkyl, haloC_1-C_4alkyl, -NH_2, -CN, or C_1-C_4alkoxy;

p is 0, 1 or 2;

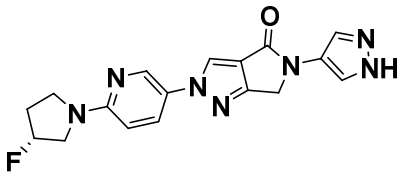
R^z is selected from H, C_1-C_4alkyl or haloC_1-C_4alkyl;

as valency permits,  is a combination of single and double bonds;

Fluoro is ^{19}F; and

***** is the position of bonding.

20<u>43</u>. The compound of formula (IV-J) according to claim 19<u>42</u>, which is



or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

21<u>44</u>. A method of preparing the compound according to <u>claim 5</u>~~claims 6, 7~~ or <u>6</u>~~8~~ comprising reacting the compound according to any one of claims <u>15 or 16</u>~~37 to 39~~ with a ^{18}F-fluorinating agent, so that LG is replaced by ^{18}F <u>wherein the ^{18}F-fluorinating agent is</u>

preferably selected from $K^{18}F$, $Rb^{18}F$, $Cs^{18}F$, $Na^{18}F$, $Rb^{18}F$, Kryptofix[222]$K^{18}F$, tetra(C_{1-6} alkyl) ammonium salt of ^{18}F, and tetrabutylammonium [^{18}F]fluoride.

~~45. The method according to claim 44, wherein the ^{18}F-fluorinating agent is selected from $K^{18}F$, $Rb^{18}F$, $Cs^{18}F$, $Na^{18}F$, $Rb^{18}F$, Kryptofix[222]$K^{18}F$, tetra(C_{1-6} alkyl) ammonium salt of ^{18}F, and tetrabutylammonium [^{18}F]fluoride.~~

2246. A method of preparing the compound according to claim 5~~claims 6, 7~~ or 6~~8~~, comprising reacting the compound according to claim 1740 or 1841 with a ^3H radiolabeling agent or comprising reacting the compound according to claim 19 or 20 with a CT_3 radiolabeling agent, wherein T is ^3H.

~~47. A method of preparing the compound according to claims 6, 7, or 8 comprising reacting the compound according to claim 39 or 40 with a CT_3 radiolabeling agent, wherein T is ^3H.~~

2348. Use of the compound according to any one of claims 1 to 710, or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, as an *in vitro* analytical reference or an *in vitro* screening tool.

2449. A test kit for the detection and/or diagnosis of a disease, 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 710, or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof.

2550. A kit for preparing a radiopharmaceutical preparation, wherein the kit comprises a sealed vial containing at least one compound as defined in any claims 1537 to 2043.