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.

The present 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 an *in vitro* 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 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;

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.

The present 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.

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

The 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 detectably labelled compound as disclosed herein, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein the detectably labelled compound is radioisotope-labelled.

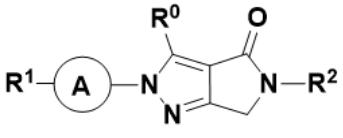
The disclosure is further directed to a kit for preparing a radiopharmaceutical preparation, wherein the kit comprises a sealed vial containing at least one compound of formula (IV-F) or (IV-H), or (IV-J), or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt,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

CLAIMS

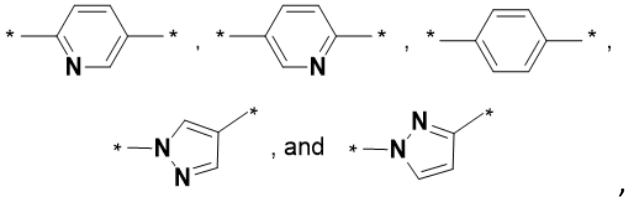
1. A compound of formula (I)


(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:

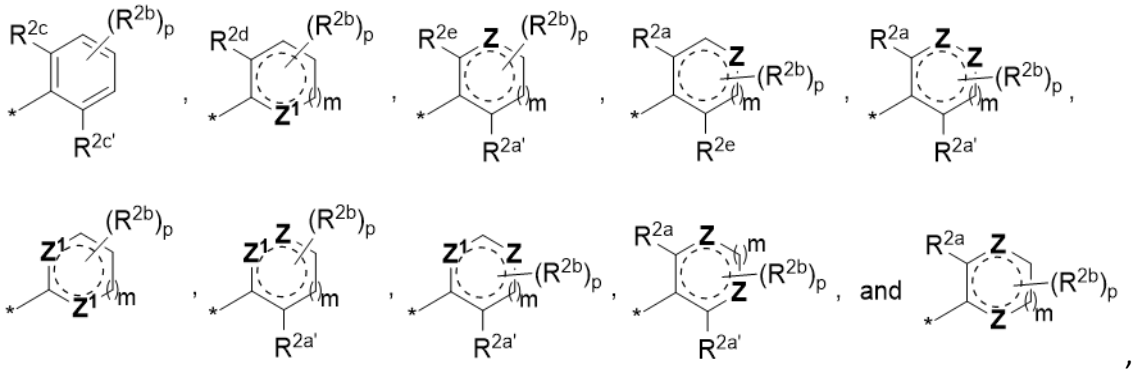


R^0 is H or C_1-C_4alkyl;

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;

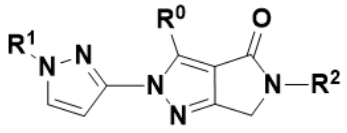
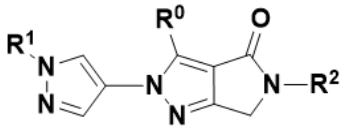
p is 0, 1 or 2;

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), (IIb), (IIIa), (IIIb), or (IIIc)


(IIa),

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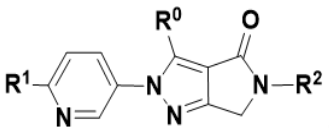
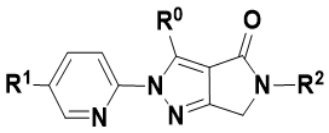
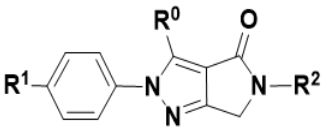
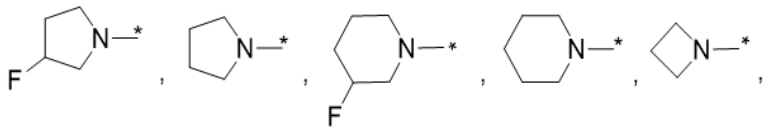

(IIIa),

(IIIb), or

(IIIc),

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

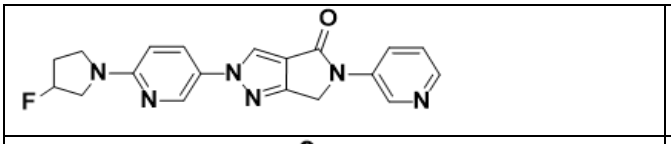
3.The compound according to claim 1 or 2, wherein R^1 is -NH-C_3-C_6cycloalkyl, C_3-C_6cycloalkyl, or heterocyclyl, each of which is optionally substituted with at least one halo, preferably R^1 is selected from the following:

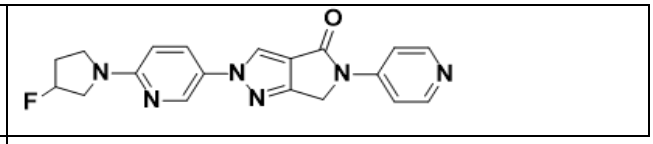


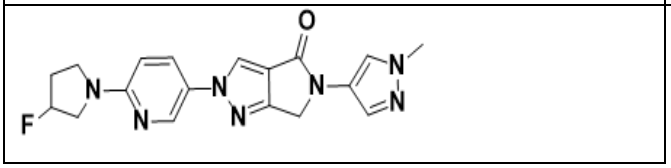
and

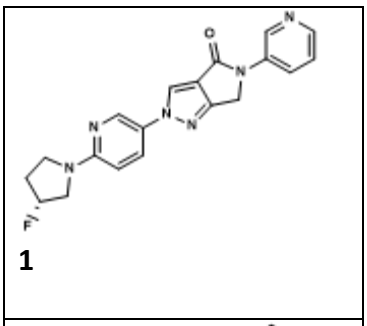
.

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









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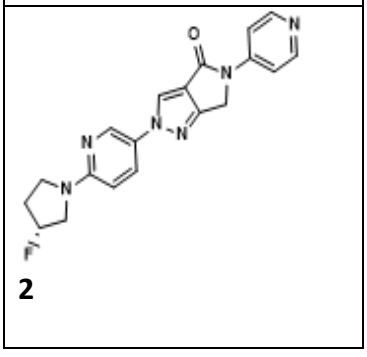

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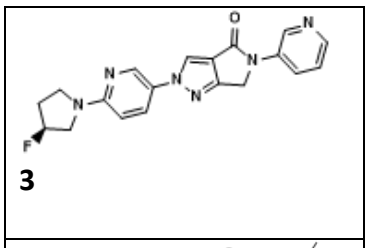

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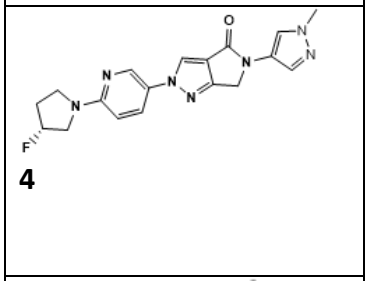

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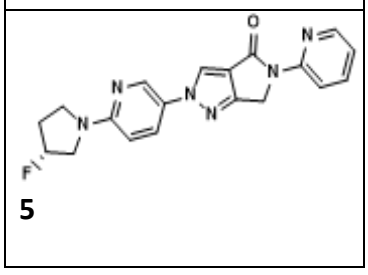

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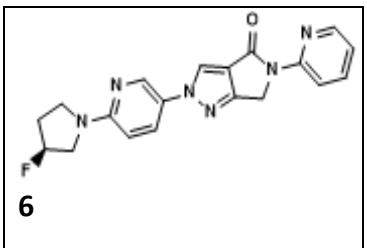

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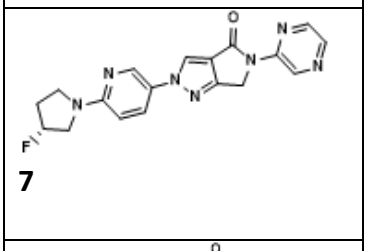

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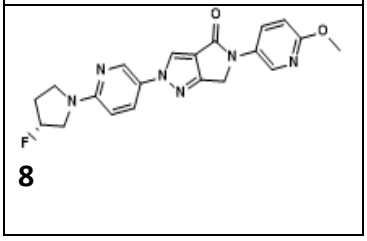

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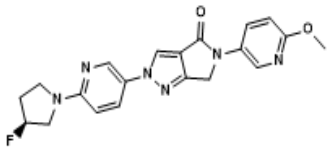

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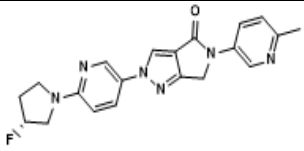

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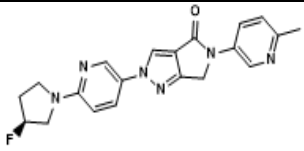

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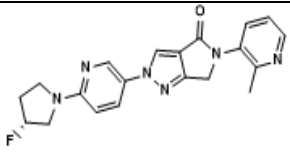

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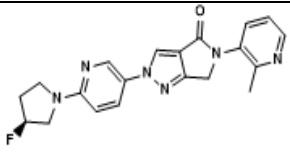

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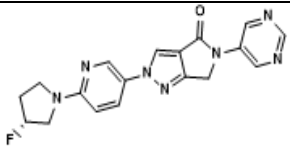

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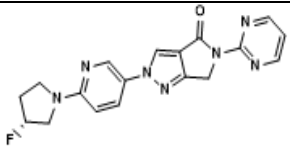

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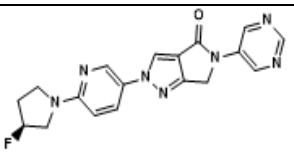

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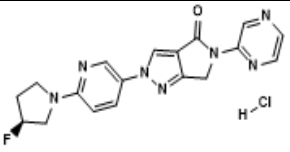

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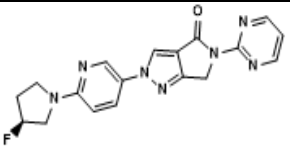

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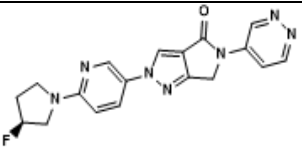

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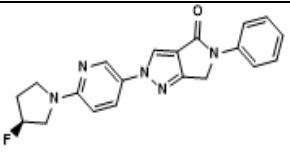

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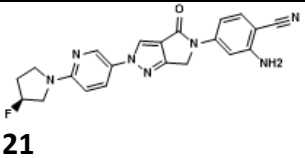

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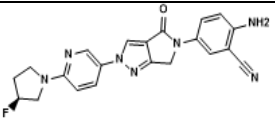

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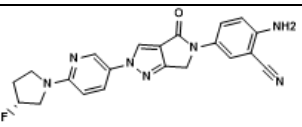

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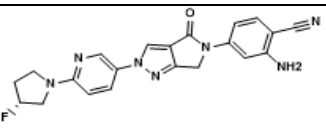

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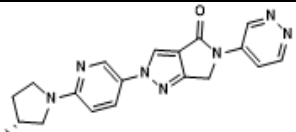

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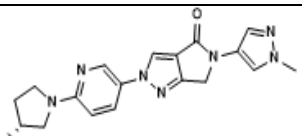

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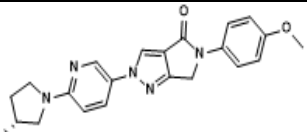

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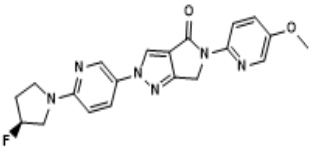

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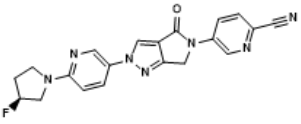

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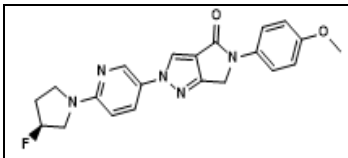

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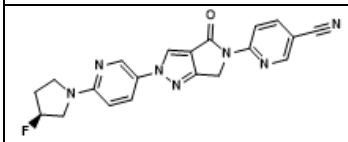

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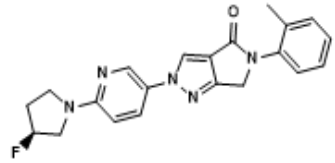

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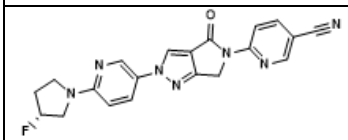

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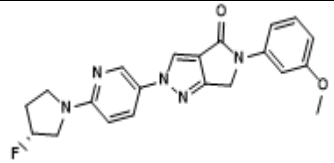

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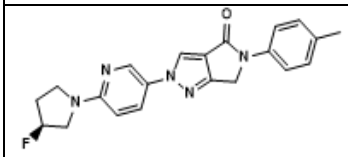

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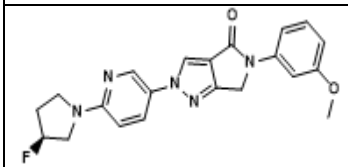

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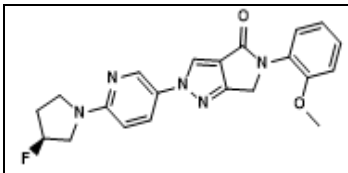

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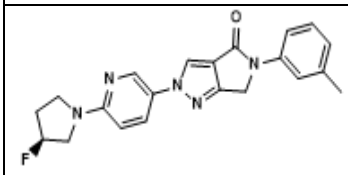

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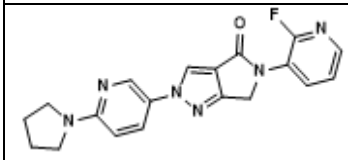

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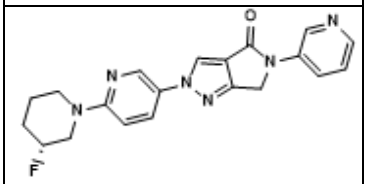

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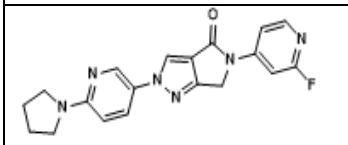

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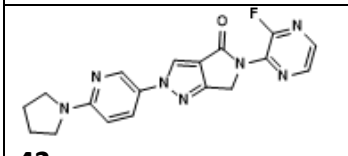

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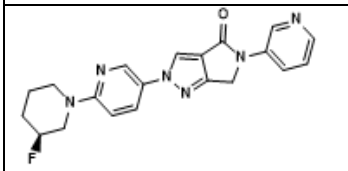

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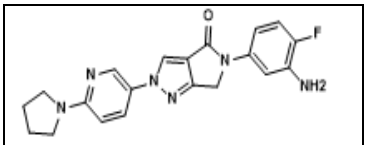

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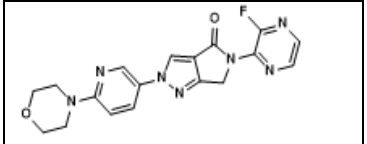

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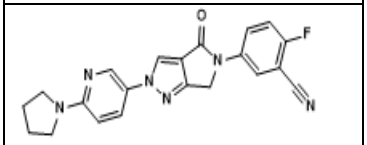

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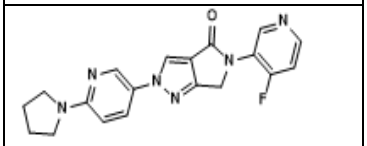

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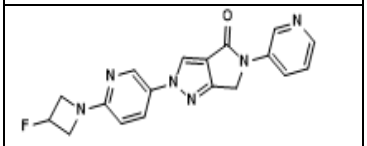

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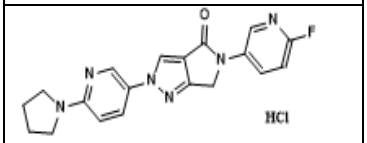

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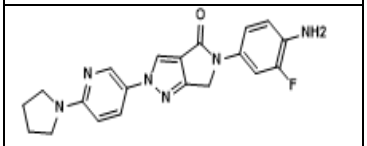

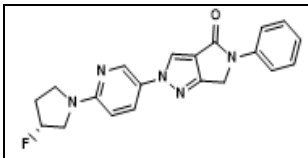

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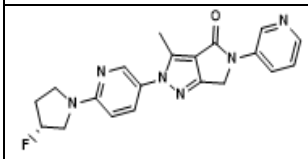

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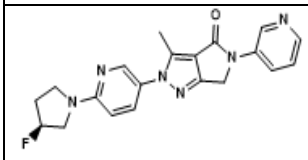

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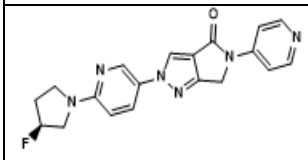

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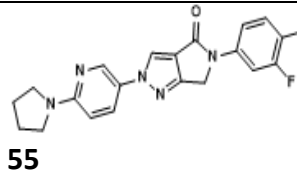

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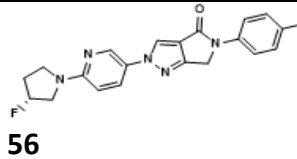

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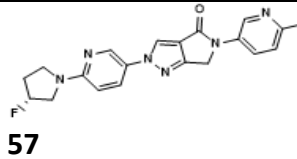

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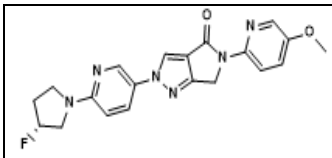

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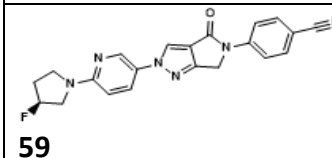

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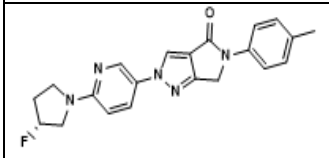

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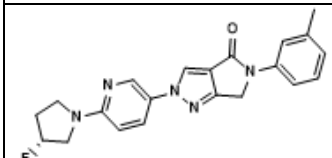

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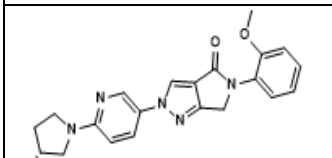

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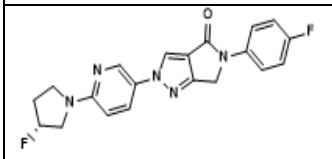

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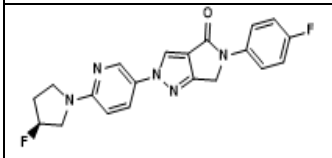

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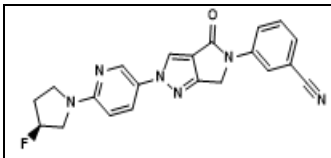

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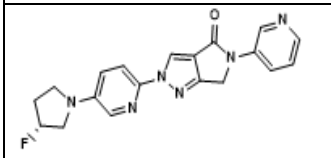

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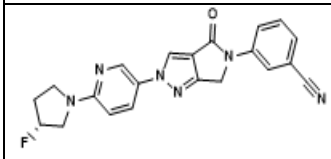

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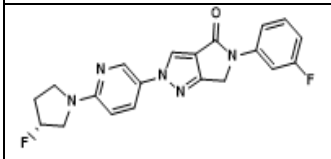

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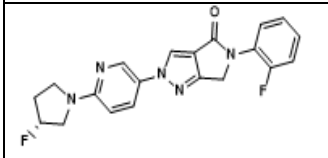

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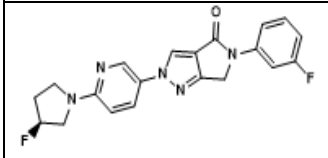

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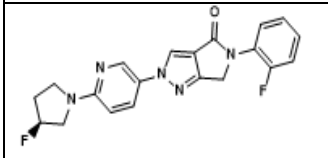

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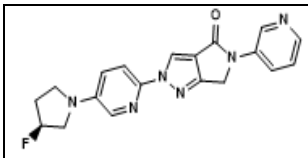

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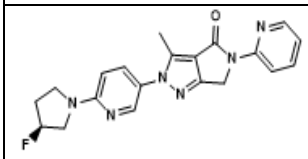

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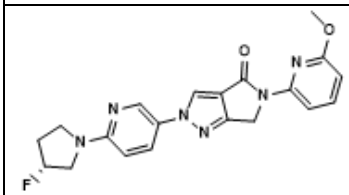

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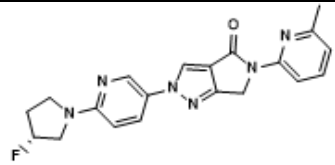

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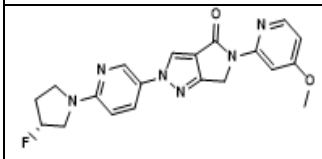

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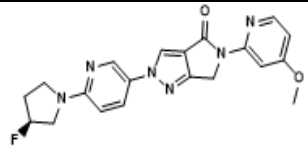

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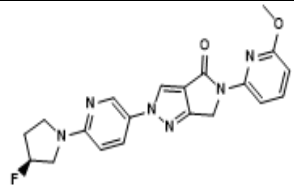

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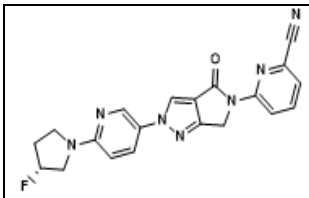

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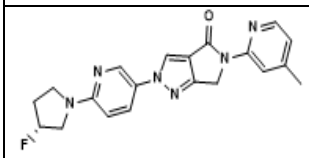

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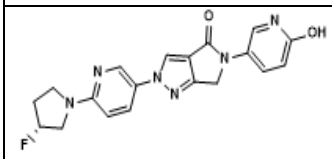

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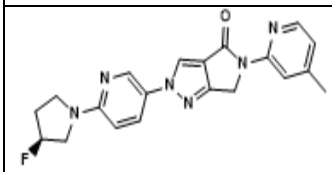

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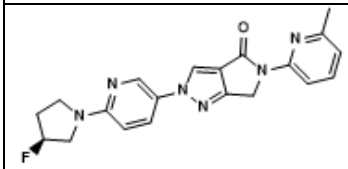

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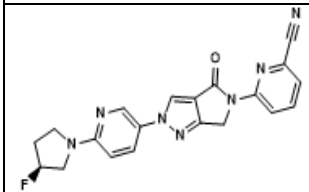

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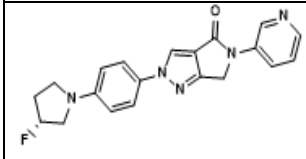

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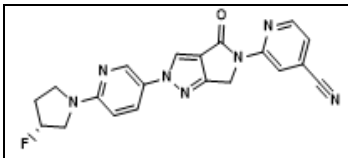

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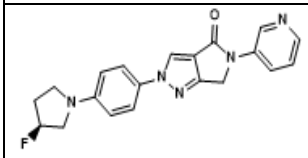

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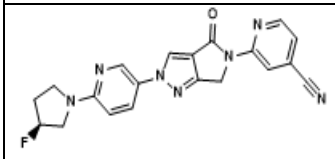

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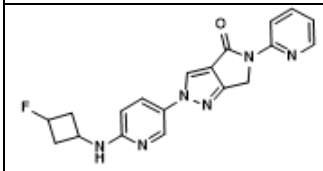

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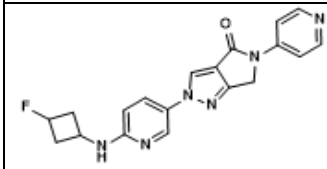

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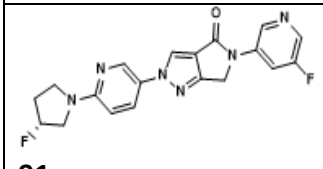

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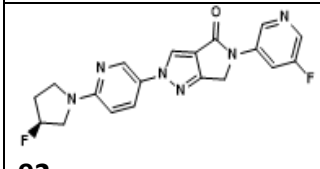

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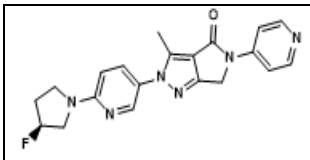

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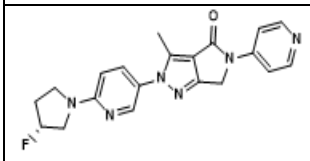

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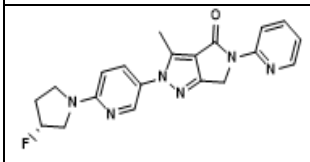

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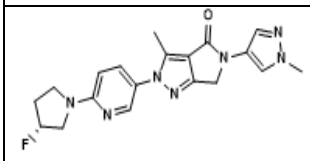

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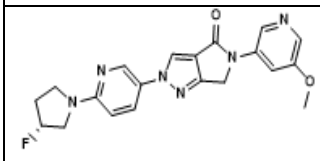

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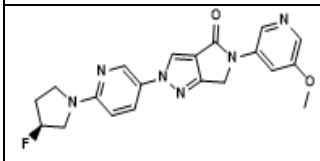

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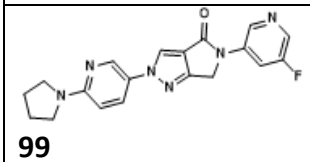

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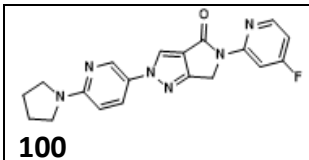

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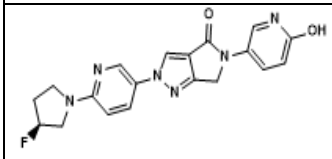

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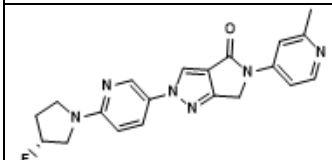

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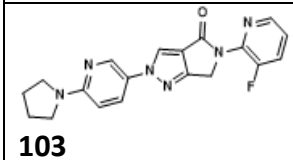

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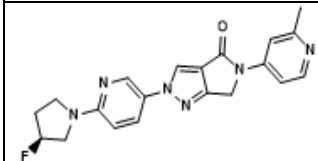

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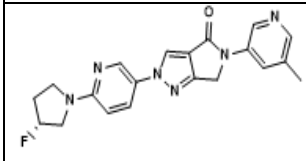

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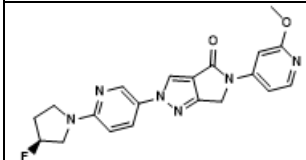

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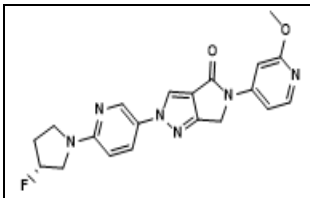

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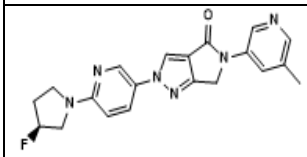

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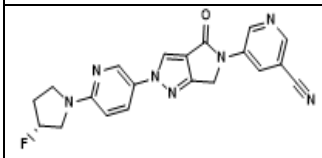

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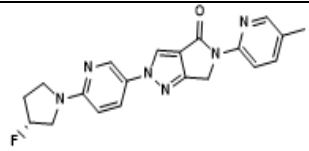

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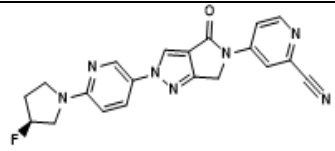

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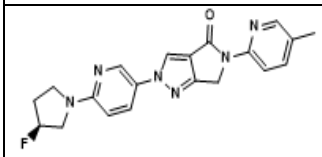

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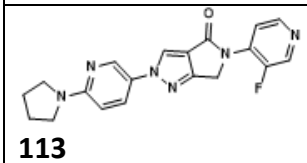

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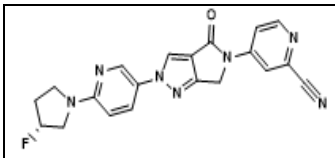

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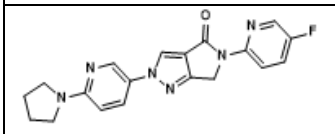

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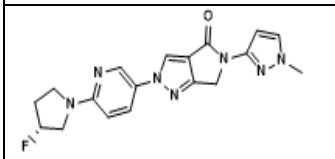

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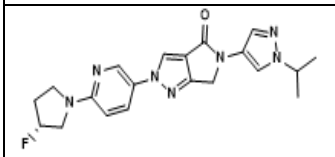

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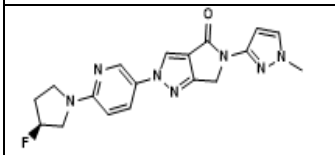

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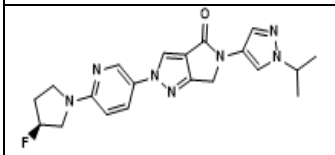

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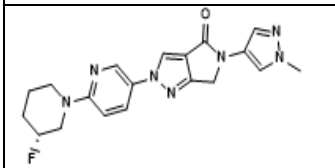

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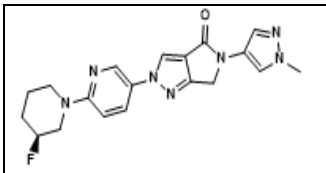

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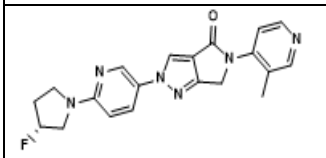

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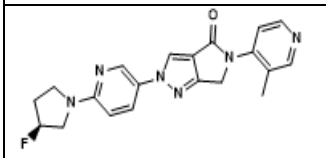

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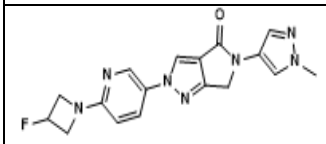

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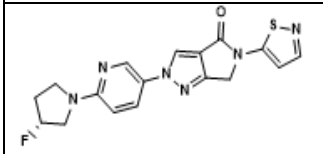

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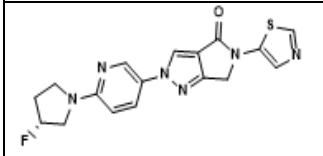

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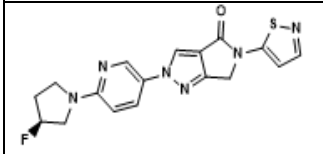

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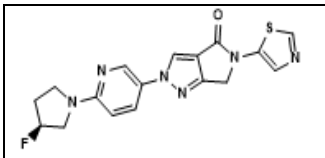

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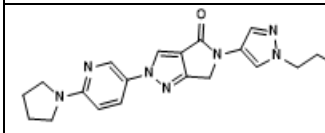

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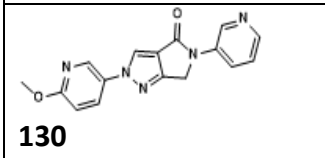

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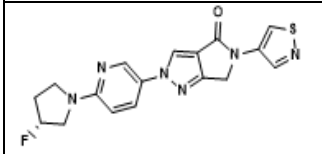

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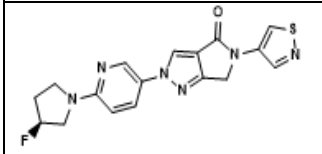

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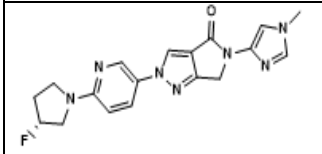

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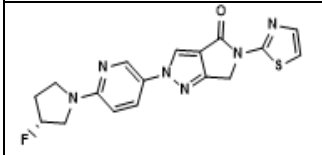

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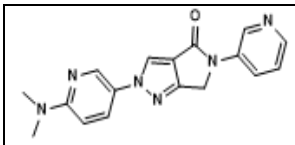

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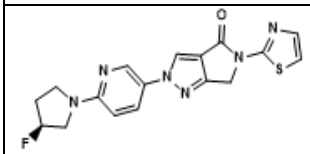

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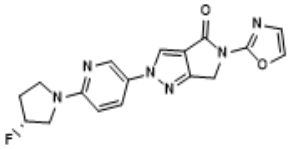

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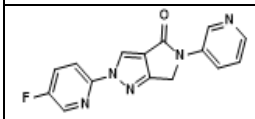

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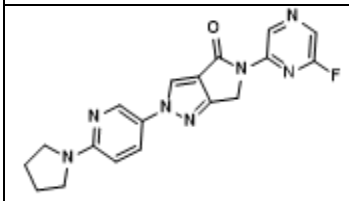

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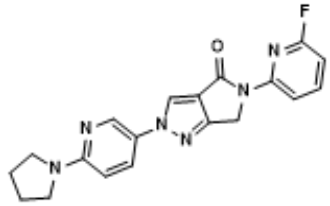

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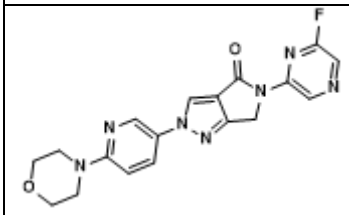

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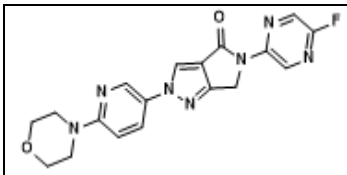

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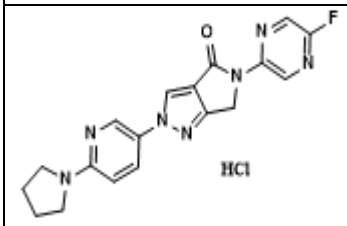

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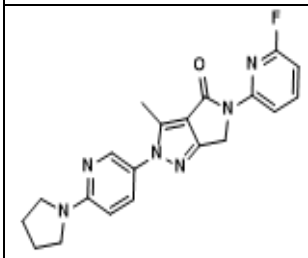

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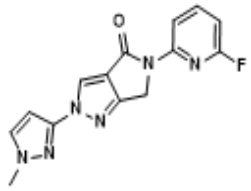

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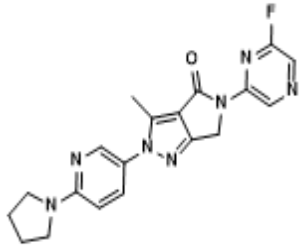

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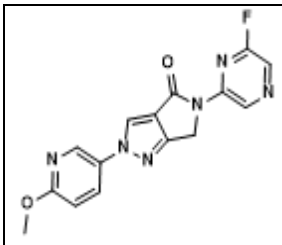

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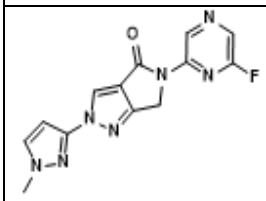

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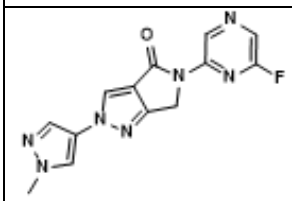

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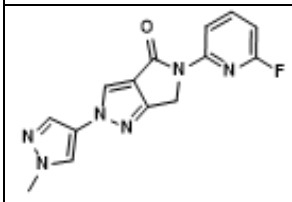

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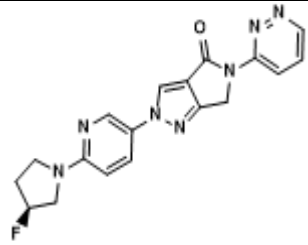

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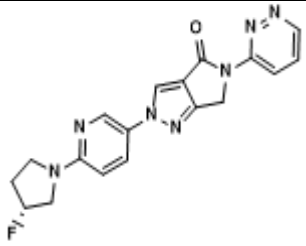

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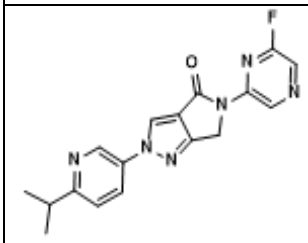

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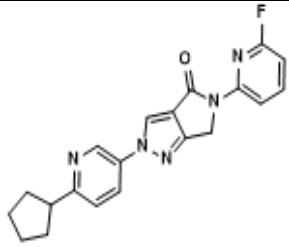

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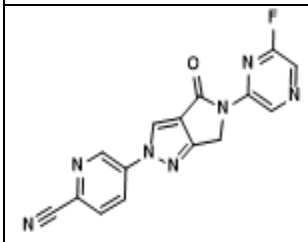

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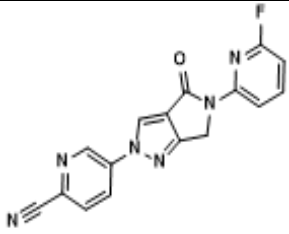

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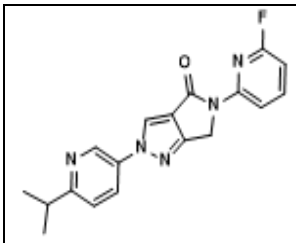

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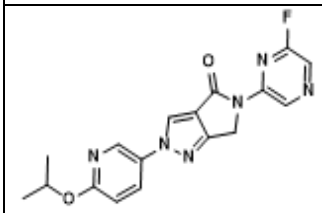

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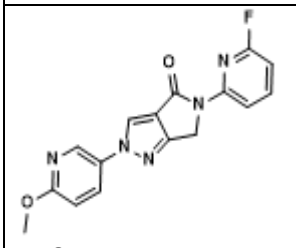

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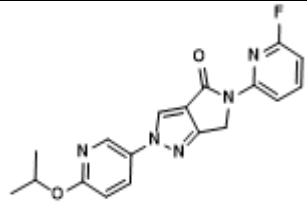

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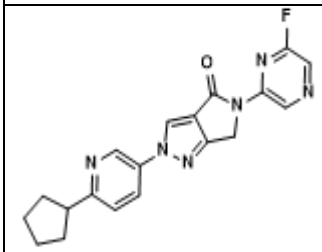

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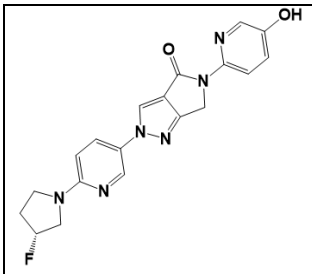

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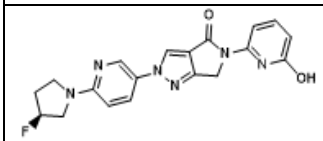

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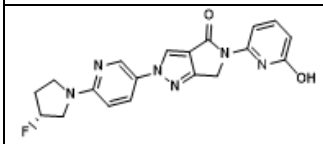

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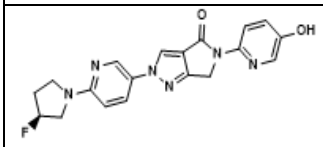

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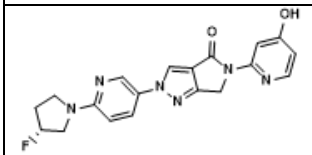

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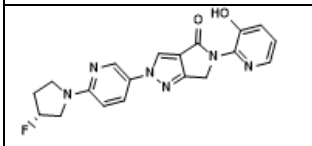

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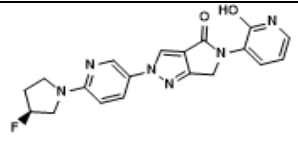

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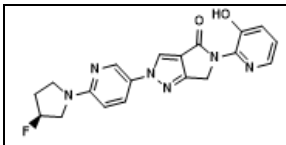

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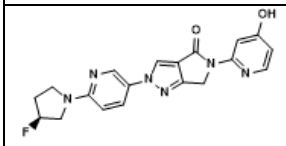

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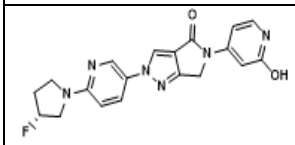

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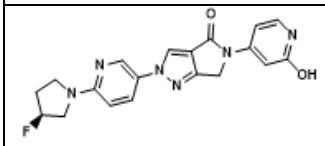

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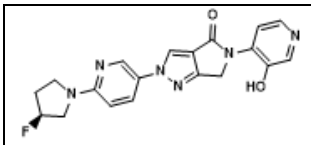

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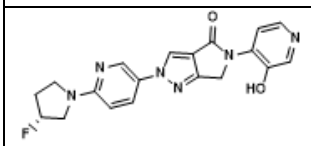

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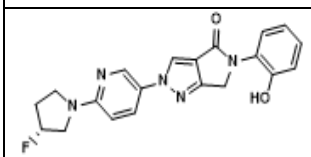

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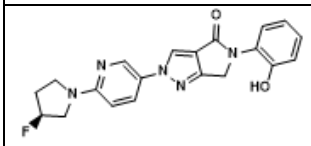

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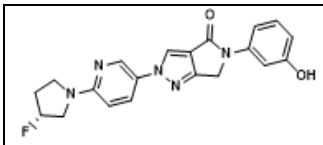

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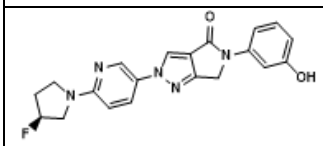

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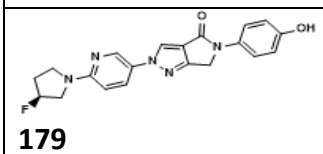

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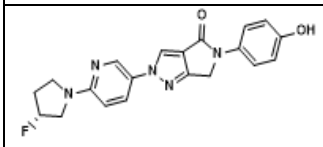

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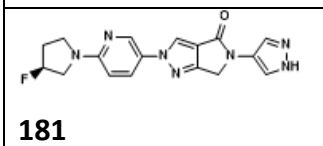
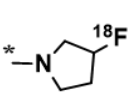
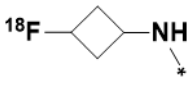
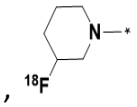
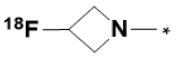
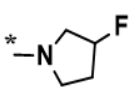
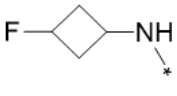
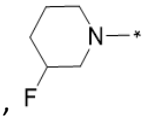


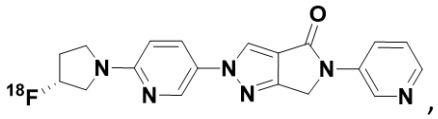
181

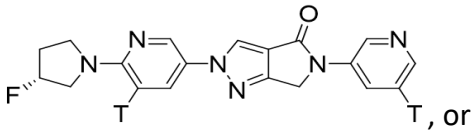
or a detectably labelled compound, stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof.

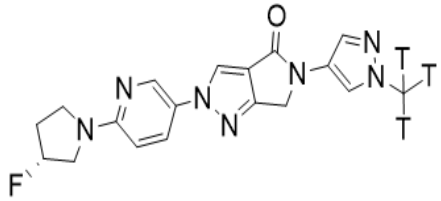
5. The compound of formula (I) according to any one of the preceding claims, wherein the compound is a detectably labelled compound, wherein the detectably labelled compound optionally comprises a detectable label selected from a radioisotope, preferably ^{2}H, ^{3}H or ^{18}F.

6. The compound of formula (I) according to claim 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).

7. The compound according to claim 5 or 6, wherein the detectably labelled compound is

 ,

 , or



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

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

8. The compound according to any one of claims 5 to 7, 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.

9. The compound for use according to claim 8, 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. The compound according to any one of claims 5 to 7, 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.

11. The compound for use according to claim 10, 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.

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

13. An *in vitro* method comprising the steps:

(a) Allowing 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 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;

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.

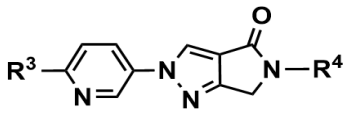
14. The *in vitro* method of claim 13, wherein the step of optionally correlating the presence or absence of the compound bound to the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites with the presence or absence of the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample; 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; and

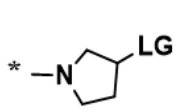
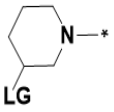
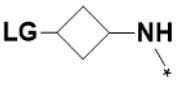
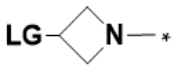
– optionally comparing the amount of the amount of the alpha-synuclein aggregates including, but not limited to, Lewy bodies and/or Lewy neurites in the sample to a normal control value in a healthy control subject.

15. A compound of formula (IV-F)

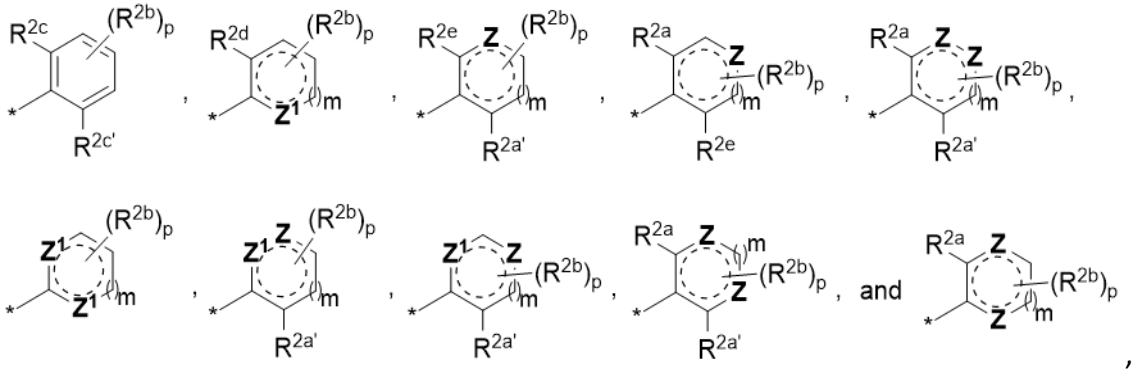


(IV-F)

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

R^3 is selected from  ,  ,  , or  ;

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;

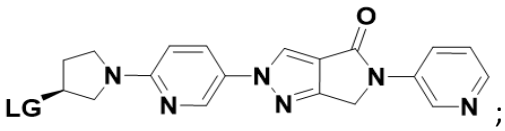
p is 0, 1 or 2;

m is 0 or 1;

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

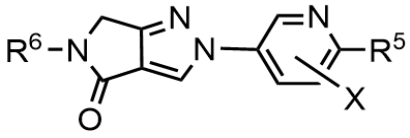
* is the position of bonding; and LG is selected from Bromo, Chloro, Iodo, $C_{1–4}$ alkyl sulfonate and $C_{6–10}$ aryl sulfonate, wherein the $C_{6–10}$ aryl can be optionally substituted by –CH_3 or –NO_2.

16. The compound of formula (IV-F) according to claim 15, which is

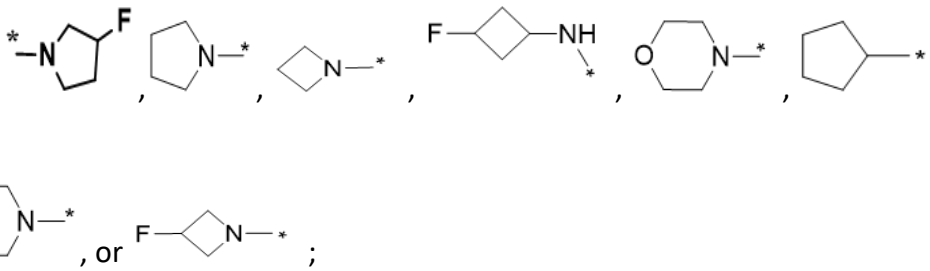


or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein **LG** is mesylate or nosylate.

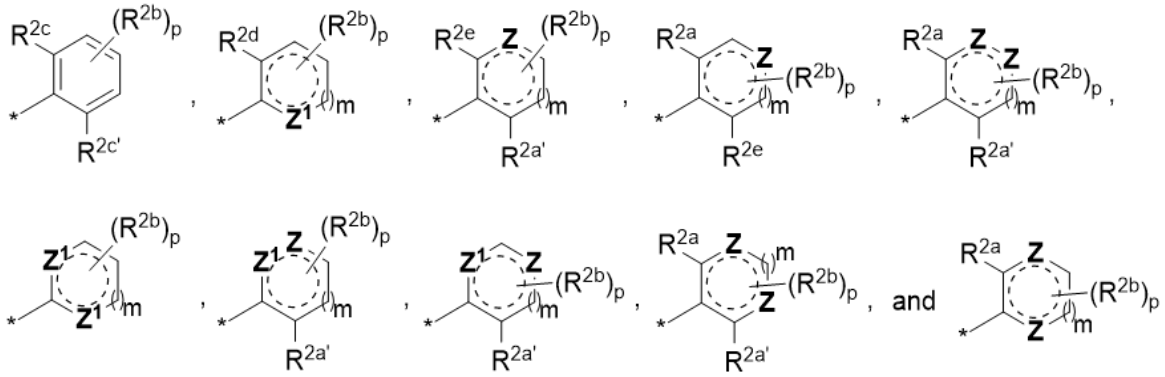
17. A compound of formula (IV-H)


(IV-H)

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

R^5 is selected from 

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, 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;

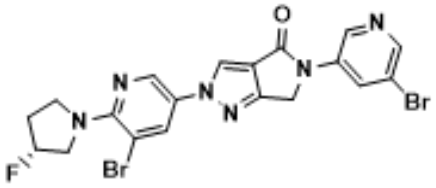
***** is the position of bonding;

Fluoro is ^{19}F;

X is Bromo, Chloro, or Iodo; and

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

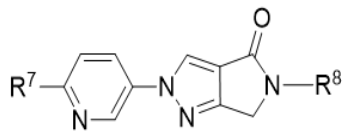
18. The compound of formula (IV-H) according to claim 17, which is



,

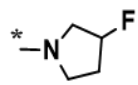
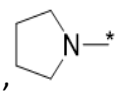
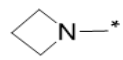
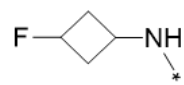
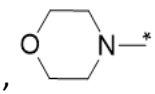
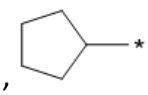
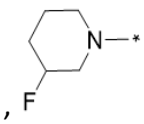
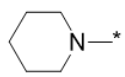
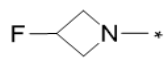
or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

19. A compound of formula (IV-J)

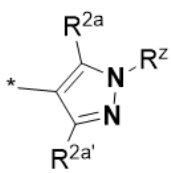
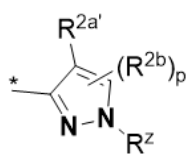
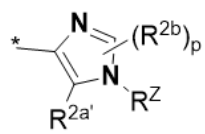


(IV-J),

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

R^7 is selected from  ,  ,  ,  ,  ,  ,  ,  , or  ;

R^8 is selected from the following:

 ,  , and 

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;

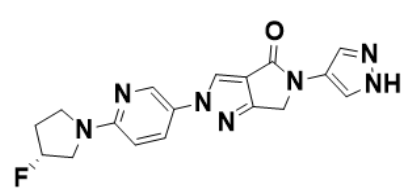
R^z is selected from H, C_1-C_4alkyl or haloC_1-C_4alkyl;

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

Fluoro is ^{19}F; and

***** is the position of bonding.

20. The compound of formula (IV-J) according to claim 19, which is



,

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

21. A method of preparing the compound according to claim 5 or 6 comprising reacting the compound according to any one of claims 15 or 16 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.

22. A method of preparing the compound according to claim 5 or 6, comprising reacting the compound according to claim 17 or 18 with a ^{3}H radiolabeling agent or comprising reacting the compound according to claim 19 or 20 with a CT_3 radiolabeling agent, wherein T is ^{3}H.

23. Use of the compound according to any one of claims 1 to 7, 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.

24. 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 detectably labelled compound as defined in any one of claims 1 to 7, or a stereoisomer, racemic mixture, pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein the detectably labelled compound is radioisotope-labelled.

25. A kit for preparing a radiopharmaceutical preparation, wherein the kit comprises a sealed vial containing at least one compound as defined in any claims 15 to 20.