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(54) Title: SMALL MOLECULE LRRK2 AND ERK5 INHIBITORS

(57) Abstract: Small molecule LRRK2 and ERK5 inhibitors are provided, as well as methods for their use in treating or preventing cancer and/or neurodegenerative disorders.



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Small Molecule LRRK2 and ERK5 Inhibitors

CROSS-REFERENCE TO PRIORITY APPLICATION

This application claims priority to U.S. Provisional Application No. 61/779,495, filed March 13, 2013, which is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY FUNDED RESEARCH

This invention was made with government support under Grant No. RC2-NS0169450 awarded by the National Institutes of Health. The government has certain rights in the invention.

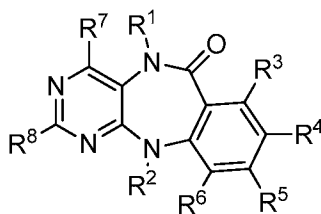
BACKGROUND

Parkinson's disease is a neurodegenerative disorder characterized by death of substantia nigra dopamine neurons, dopamine deficiency within the striatum, and a clinical movement disorder. Most cases of Parkinson's disease are sporadic/idiopathic that may arise from gene-environmental interactions. Among familial forms, mutations in the LRRK2 gene are most common, contributing to over 10% of autosomal dominant familial Parkinson's disease and 3.6% of sporadic cases. The most frequent mutation, G2019S, occurs within the kinase domain of LRRK2. Mutations within the GTPase domain (e.g., R1441C) have also been associated with disease in the human population.

ERK5 is a kinase of the mitogen-activated protein kinase (MAPK) family. ERK5 has been implicated in cell survival, anti-apoptotic signaling, angiogenesis, cell motility, differentiation, and cell proliferation. ERK5 is over-expressed or constitutively active in a number of cancers, including prostate and breast cancers.

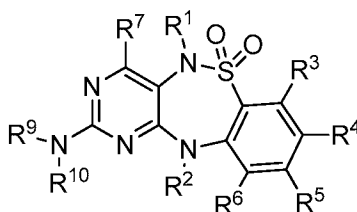
SUMMARY

Provided herein are small molecule LRRK2 and ERK5 inhibitors. Also provided herein are methods for their use in treating or preventing cancer or a neurodegenerative disorder in a subject. A class of compounds described herein includes compounds of the following formula:



and pharmaceutically acceptable salts or prodrugs thereof. In these compounds, R^1 is hydrogen or substituted or unsubstituted alkyl; R^2 is substituted or unsubstituted alkyl; R^3 , R^4 , R^5 , R^6 , and R^7 are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl; and R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

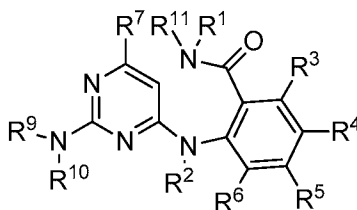
A class of compounds described herein includes compounds of the following formula:



and pharmaceutically acceptable salts or prodrugs thereof. In these compounds, R^1 is hydrogen or substituted or unsubstituted alkyl; R^2 is substituted or unsubstituted alkyl; R^3 , R^4 , R^5 , R^6 , and R^7 are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted

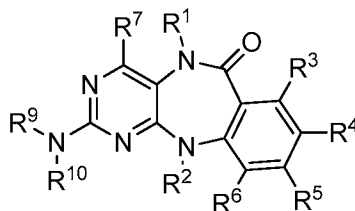
alkoxyl, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl; and R⁹ and R¹⁰ are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

A class of compounds described herein includes compounds of the following formula:



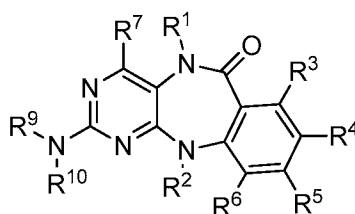
and pharmaceutically acceptable salts or prodrugs thereof. In these compounds, R¹ and R¹¹ are each independently selected from hydrogen or substituted or unsubstituted alkyl; R² is substituted or unsubstituted alkyl; R³, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl; and R⁹ and R¹⁰ are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

A class of compounds described herein includes compounds of the following formula:



and pharmaceutically acceptable salts or prodrugs thereof. In these compounds, R^1 is hydrogen or substituted or unsubstituted alkyl; R^2 is substituted or unsubstituted alkyl; R^3 , R^4 , R^5 , R^6 , and R^7 are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl; and R^9 and R^{10} are each independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, or substituted or unsubstituted heteroalkynyl. In these compounds, R^9 and R^{10} combine to form a substituted or unsubstituted heterocycle or a substituted or unsubstituted heteroaryl.

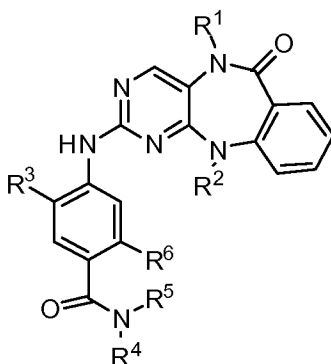
A class of compounds described herein includes compounds of the following formula:



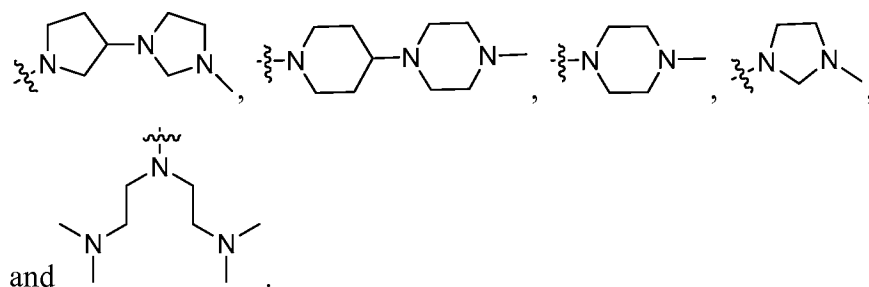
and pharmaceutically acceptable salts or prodrugs thereof. In these compounds, R^1 is hydrogen or substituted or unsubstituted alkyl; R^2 is substituted or unsubstituted alkyl; R^3 , R^4 , R^5 , R^6 , and R^7 are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl; R^9 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, or substituted or unsubstituted heteroalkynyl; and R^{10} is substituted alkyl.

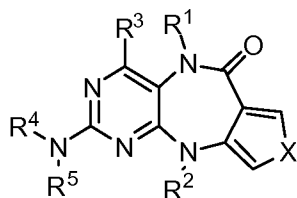
A class of compounds described herein includes compounds of the following formula:



and pharmaceutically acceptable salts or prodrugs thereof. In these compounds, R^1 is hydrogen or substituted or unsubstituted alkyl; R^2 is substituted or unsubstituted alkyl; R^3 and R^6 are each independently selected from halogen, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted amino, or nitro; and R^4 and R^5 are each independently selected from hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl, wherein R^4 and R^5 optionally combine to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. In these compounds, at least one of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 includes a radiolabel selected from the group consisting of ^{11}C and ^{18}F . Optionally, $-\text{NR}^4\text{R}^5$ is selected from the group consisting of:

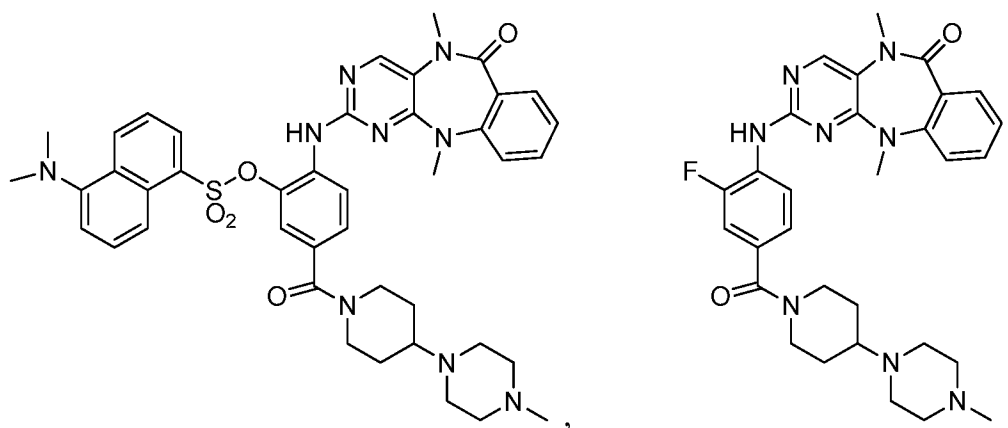


A class of compounds described herein includes compounds of the following formula:



and pharmaceutically acceptable salts or prodrugs thereof. In these compounds, X is O, S, CR⁶R⁷, or NR⁸, wherein R⁶, R⁷, and R⁸ are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R¹, R², and R³ are each independently selected from hydrogen and substituted or unsubstituted alkyl; and R⁴ and R⁵ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

Further described herein are compounds of the following structures:



and pharmaceutically acceptable salts or prodrugs thereof.

Also provided herein are compositions comprising one or more of the compounds described above and a pharmaceutically acceptable carrier.

Further provided herein are methods of treating or preventing a neurodegenerative disorder in a subject. A method of treating or preventing a neurodegenerative disorder in a subject includes administering to the subject an effective amount of a composition as described herein. Optionally, the neurodegenerative disorder is Parkinson's disease. Optionally, the methods of treating or preventing a neurodegenerative disorder in a subject further comprise administering a second therapeutic agent to the subject. The second therapeutic agent can be selected from the group consisting of levadopa, a dopamine agonist, an anticholinergic agent, a monoamine oxidase inhibitor, a COMT inhibitor, amantadine,

rivastigmine, an NMDA antagonist, a cholinesterase inhibitor, riluzole, an anti-psychotic agent, an antidepressant, and tetrabenazine. Optionally, the compound is administered systemically.

Also provided herein are methods of inhibiting LRRK2 in a cell. The methods of inhibiting LRRK2 in a cell include contacting a cell with an effective amount of a compound described herein. Optionally, the LRRK2 is a mutant LRRK2. The mutant LRRK2 can include, for example, a G2019S mutation. The cell can be a neuron. Optionally, the contacting is performed *in vivo*. Optionally, the contacting is performed *in vitro*.

Further provided herein are methods of modulating signaling in a cell as compared to a control. The methods include contacting a cell with an effective amount of a compound described herein. Optionally, the method comprises reducing Akt phosphorylation in a cell. The cell can be a neuron. Optionally, the contacting is performed *in vivo*. Optionally, the contacting is performed *in vitro*.

Further provided herein are methods of imaging an LRRK2 positive cell or population of cells in a subject. The methods include administering to the subject a compound described herein, wherein the compound further comprises a detectable label, and detecting the detectable label in the subject. The detectable label indicates the LRRK2 positive cell or population of cells. Optionally, the LRRK2 positive cell or population of cells is a neuron or neuronal population of cells. The detecting step can comprise PET, SPECT, MRI, or X-ray. Optionally, the detectable label is selected from the group consisting of a radiolabel, fluorescent label, enzymatic label, and biotin. Optionally, the detectable label is a radiolabel that is optionally selected from the group consisting of ^{11}C and ^{18}F .

Also provided herein are methods of treating or preventing cancer in a subject. A method of treating or preventing cancer in a subject includes administering to the subject an effective amount of a composition as described herein. Optionally, the cancer is breast cancer or prostate cancer. Optionally, the methods of treating or preventing cancer in a subject further comprise administering a second therapeutic agent (e.g., a chemotherapeutic agent) to the subject.

Also provided herein are methods of inhibiting ERK5 in a cell. The methods of inhibiting ERK5 in a cell include contacting a cell with an effective amount of a

compound described herein. Optionally, the contacting is performed *in vivo*.

Optionally, the contacting is performed *in vitro*.

The details of one or more embodiments are set forth in the drawings and the description below. Other features, objects, and advantages will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

Fig. 1 contains graphs demonstrating the percentage of kinase activity after treatment with **Fluorophore** or **Fluoro**, relative to DMSO-treated controls, for wild-type LRRK2 (Figure 1A and Figure 1C) and G2019S mutant LRRK2 (Figure 1B and Figure 1D).

Fig. 2 is a picture of a Western blot showing the effects of **Fluorophore**, **Fluoro**, IN-1, SK-15, and AN-1 on the phosphorylation of LRRK2 at T2035.

Fig. 3 (Panels A and B) contains pictures of Western blots using MN9D cell lines stably transfected with a plasmid construct that overexpresses human LRRK2 wild-type (Panel A) or mutant (G2019S) (Panel B) grown in the absence (-) and presence (+) of doxorubicin (DOX). Panel C shows the effects of GST-LRRK2 or GST alone mixed with recombinant his-Akt1 and subjected to pull-down assay by incubation with glutathione agarose beads. Panel D shows recombinant human his-Akt-1 incubated with recombinant GST-LRRK2 in the presence of 5 μ M ATP and using antibodies against LRRK2, p-Akt1 at Ser 473 and total Akt1. Panel E shows the effects of IN-1, **Fluorophore**, and **Fluoro** on the MN9D G2019S cells.

Fig. 4 demonstrates the effects of **Fluorophore**, **Fluoro**, and IN-1 on primary neurons and in the brain. Panel A contains a picture of a Western blot showing the effects of the compounds on rat primary neurons. Panel B contains a picture of a Western blot showing the time course (1 hour, 2 hours, 4 hours, and 8 hours) of Akt-phosphorylation for rat primary neurons treated with IN-1. Panel C contains a picture of a Western blot showing the effects of the compounds on brain tissues after administering the compounds by intraperitoneal injection to wild-type mice. Panel D contains a graph showing the ratios of p-Akt over total Akt in the brains of animals after treatment with the LRRK2 inhibitors.

Fig. 5 contains mass spectrometry spectra of an untreated brain issue (Panel A), brain tissue treated with **Fluoro** (Panel B), and **Fluoro** alone (Panel C).

Fig. 6 contains the results of a neurite length functional assay in MN9 cells with inducible LRRK2G2019S, in the presence (Dox+) and absence (Dox-) of doxycycline.

Fig. 7 shows images acquired of neurites in MN9D cells with inducible LRRK2G2019S. Panel A represents the control. Panel B represents cells treated with IN-1. Panel C represents cells treated with **Fluorophore**. Panel D represents cells treated with **Fluoro**. The top panels depict cells having doxycycline added to the cells, while the bottom panels show the cells without added doxycycline.

Fig. 8, Panel A, shows MN9D-LRRK2G2019S cells with and without doxycycline induction. Panel B shows the neurite length of MN9D-LRRK2G2019S cells treated with DMSO (control) and with **Fluoro**.

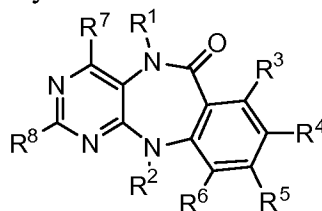
Fig. 9 contains a graph demonstrating the percentage of cell death after treating with **Fluoro**, relative to DMSO-treated controls, for ERK5.

DETAILED DESCRIPTION

Described herein are compounds for use as small molecule inhibitors of LRRK2 and ERK5. Also provided herein are methods for their use in treating or preventing neurodegenerative disorders (e.g., Parkinson's disease). The methods of preventing or treating neurodegenerative disorders described herein include administering to the subject an LRRK2 or ERK5 inhibitor. Such inhibitors are administered in an effective amount to prevent or treat one or more symptoms of Parkinson's disease. Further provided herein are methods for using the compounds in treating or preventing cancer (e.g., prostate cancer and breast cancer). The methods of preventing or treating cancer described herein include administering to the subject an ERK5 inhibitor. Such inhibitors are administered in an effective amount to prevent or treat cancer.

I. Compounds

A class of LRRK2 and ERK5 inhibitors useful in the methods described herein includes compounds represented by **Formula I**:



I

or a pharmaceutically acceptable salt or prodrug thereof.

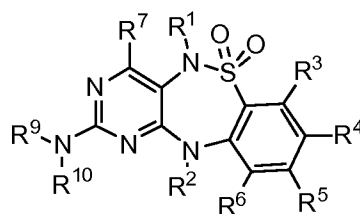
In **Formula I**, R¹ is hydrogen or substituted or unsubstituted alkyl.

Also, in **Formula I**, R² is substituted or unsubstituted alkyl.

Additionally, in **Formula I**, R³, R⁴, R⁵, R⁶, and R⁷ are each independently
 5 selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted
 or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or
 unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or
 unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or
 unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted
 10 heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy,
 substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl.

Further, in **Formula I**, R⁸ is substituted or unsubstituted alkyl, substituted or
 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or
 unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or
 15 unsubstituted heteroalkynyl, substituted or unsubstituted aryl, or substituted or
 unsubstituted heteroaryl.

A class of LRRK2 and ERK5 inhibitors useful in the methods described herein
 includes compounds represented by **Formula II**:



or a pharmaceutically acceptable salt or prodrug thereof.

25 In **Formula II**, R¹ is hydrogen or substituted or unsubstituted alkyl.

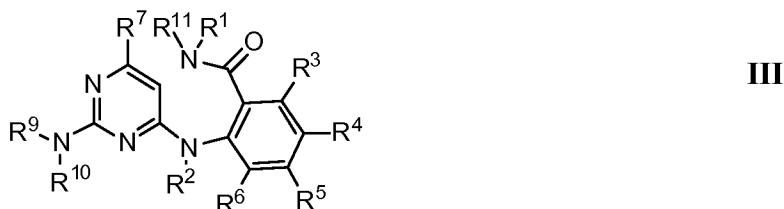
Also, in **Formula II**, R² is substituted or unsubstituted alkyl.

Additionally, in **Formula II**, R³, R⁴, R⁵, R⁶, and R⁷ are each independently
 selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted
 or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or
 30 unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or
 unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or
 unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted

heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl.

Further, in **Formula II**, R⁹ and R¹⁰ are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

A class of LRRK2 and ERK5 inhibitors useful in the methods described herein includes compounds represented by **Formula III**:



or a pharmaceutically acceptable salt or prodrug thereof.

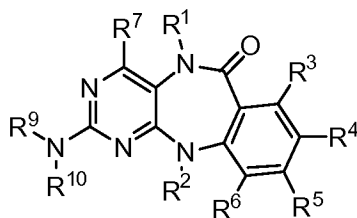
In **Formula III**, R¹ and R¹¹ are each independently selected from hydrogen or substituted or unsubstituted alkyl.

Additionally, in **Formula III**, R² is substituted or unsubstituted alkyl.

Also, in **Formula III**, R³, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl.

Further, in **Formula III**, R⁹ and R¹⁰ are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

A class of LRRK2 and ERK5 inhibitors useful in the methods described herein includes compounds represented by **Formula IV**:



IV

or a pharmaceutically acceptable salt or prodrug thereof.

In **Formula IV**, R¹ is hydrogen or substituted or unsubstituted alkyl.

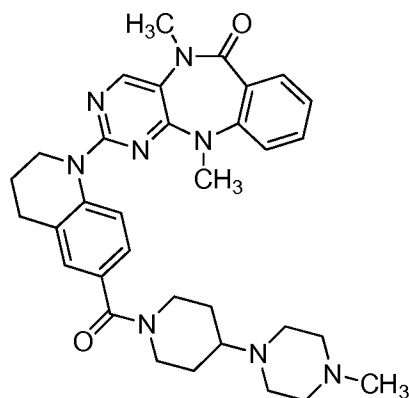
Additionally in **Formula IV**, R² is substituted or unsubstituted alkyl.

Also, in **Formula IV**, R³, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxyl, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl.

Further, in **Formula IV**, R⁹ and R¹⁰ are each independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, or substituted or unsubstituted heteroalkynyl.

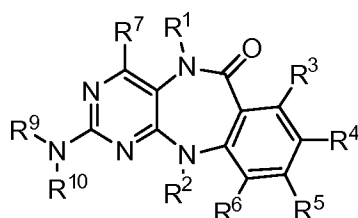
In **Formula IV**, R⁹ and R¹⁰ combine to form a substituted or unsubstituted heterocycle or a substituted or unsubstituted heteroaryl. Optionally, R⁹ and R¹⁰ combine to form substituted or unsubstituted pyridinyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted pyrimidyl, substituted or unsubstituted pyrazyl, substituted or unsubstituted triazinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyrazolyl, or substituted or unsubstituted imidazolyl.

An example of **Formula IV** includes the following compound:



Compound IV-1

A class of LRRK2 and ERK5 inhibitors useful in the methods described herein includes compounds represented by **Formula V**:



V

or a pharmaceutically acceptable salt or prodrug thereof.

In **Formula V**, R¹ is hydrogen or substituted or unsubstituted alkyl.

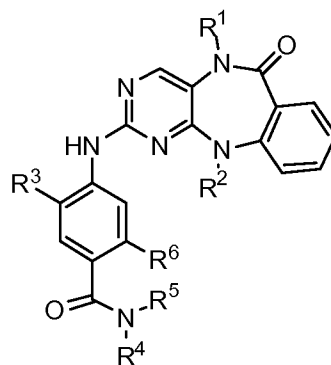
Also, in **Formula V**, R² is substituted or unsubstituted alkyl.

Additionally, in **Formula V**, R³, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxyl, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl.

Further, in **Formula V**, R⁹ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, or substituted or unsubstituted heteroalkynyl.

Additionally, in **Formula V**, R¹⁰ is substituted alkyl. In some embodiments, R¹⁰ is not hydrogen or unsubstituted alkyl.

A class of LRRK2 and ERK5 inhibitors useful in the methods described herein includes compounds represented by **Formula VI**:



VI

or a pharmaceutically acceptable salt of prodrug thereof.

In **Formula VI**, R^1 is hydrogen or substituted or unsubstituted alkyl. Optionally, R^1 is hydrogen or methyl.

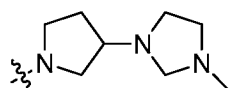
Also, in **Formula VI**, R^2 is substituted or unsubstituted alkyl. Optionally, R^2 is methyl, ethyl, propyl, or butyl. Optionally, R^2 is substituted with a halogen (e.g., -F).

Additionally, in **Formula VI**, R^3 and R^6 are each independently selected from halogen, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted amino, or nitro. Optionally, R^3 is -F, -Cl, -Br, -OH, -OMe, -OCH₂CH₂F, -CH₃, -CH₂CH₂F, or -NO₂.

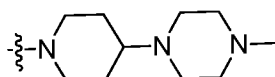
Further, in **Formula VI**, R^4 and R^5 are each independently selected from hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. R^4 and R^5 optionally combine to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

In **Formula VI**, at least one of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 includes a radiolabel selected from the group consisting of ¹¹C and ¹⁸F.

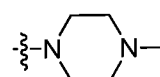
In **Formula VI**, -NR⁴R⁵ combine to form one of the following structures represented by **Structure A**, **Structure B**, **Structure C**, **Structure D**, **Structure E**, **Structure F**, **Structure G**, **Structure H**, **Structure I**, and **Structure J**. In **Structures A**, **B**, **C**, **D**, **E**, **F**, **G**, **H**, **I**, and **J**, signifies the attachment of -NR⁴R⁵ to the adjacent carbonyl in **Formula VI**.



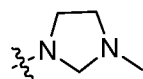
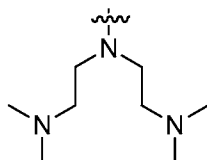
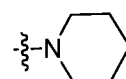
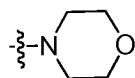
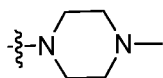
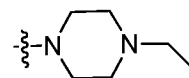
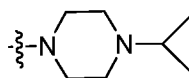
Structure A



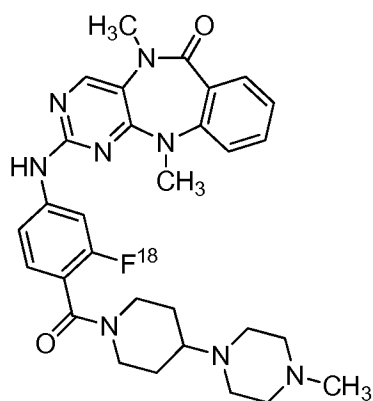
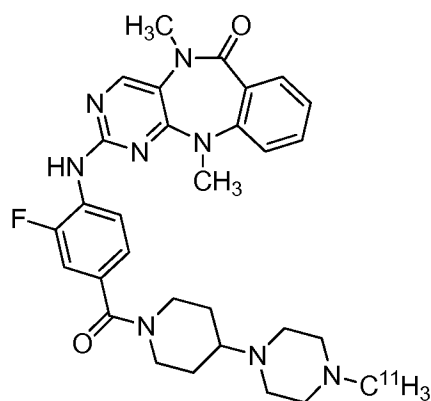
Structure B



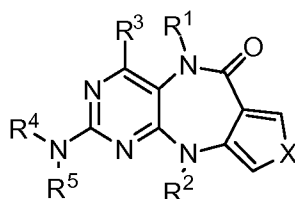
Structure C

**Structure D****Structure E****Structure F****Structure G****Structure H****Structure I****Structure J**

Examples of **Formula VI** include the following compounds:

**Compound VI-1****Compound VI-2**

A class of LRRK2 and ERK5 inhibitors useful in the methods described herein includes compounds represented by **Formula VII**:

**VII**

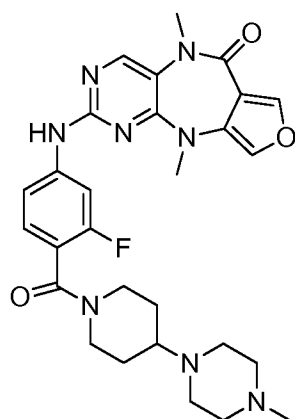
or a pharmaceutically acceptable salt or prodrug thereof.

In **Formula VII**, X is O, S, CR⁶R⁷, or NR⁸, wherein R⁶, R⁷, and R⁸ are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. Optionally, X is NH or NCH₃.

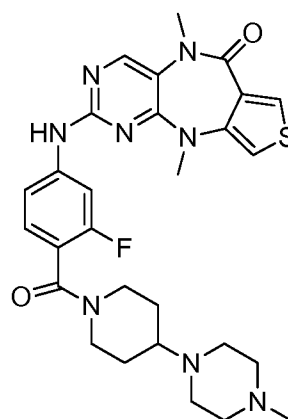
Also, in **Formula VII**, R^1 , R^2 , and R^3 are each independently selected from hydrogen and substituted or unsubstituted alkyl.

Further, in **Formula VII**, R^4 and R^5 are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or
5 unsubstituted heteroaryl. Optionally, R^4 and R^5 are not simultaneously hydrogen.

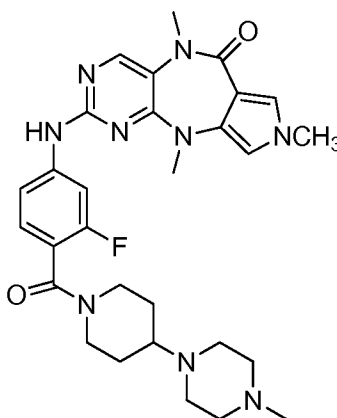
Examples of **Formula VII** include the following compounds:



Compound VII-1

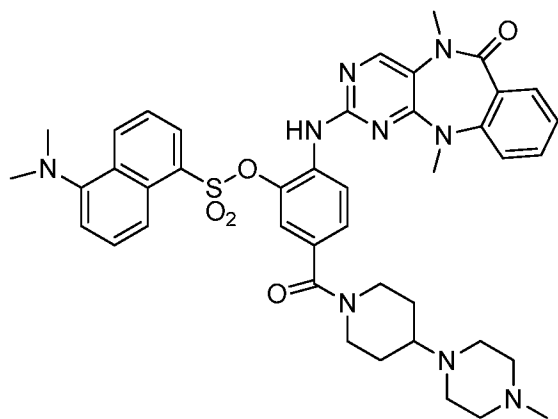
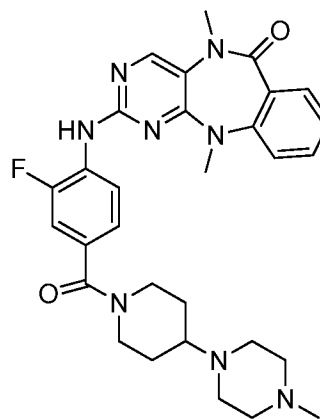


Compound VII-2



Compound VII-3

Further LRRK2 and ERK5 inhibitors useful in the methods described herein include **Fluorophore** and **Fluoro**:

**Fluorophore****Fluoro**

As used herein, the terms alkyl, alkenyl, and alkynyl include straight- and branched-chain monovalent substituents. Examples include methyl, ethyl, isobutyl, 3-butynyl, and the like. Ranges of these groups useful with the compounds and methods described herein include C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, and C₂-C₂₀ alkynyl. Additional ranges of these groups useful with the compounds and methods described herein include C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₄ alkyl, C₂-C₄ alkenyl, and C₂-C₄ alkynyl.

Heteroalkyl, heteroalkenyl, and heteroalkynyl are defined similarly as alkyl, alkenyl, and alkynyl, but can contain O, S, or N heteroatoms or combinations thereof within the backbone. Ranges of these groups useful with the compounds and methods described herein include C₁-C₂₀ heteroalkyl, C₂-C₂₀ heteroalkenyl, and C₂-C₂₀ heteroalkynyl. Additional ranges of these groups useful with the compounds and methods described herein include C₁-C₁₂ heteroalkyl, C₂-C₁₂ heteroalkenyl, C₂-C₁₂ heteroalkynyl, C₁-C₆ heteroalkyl, C₂-C₆ heteroalkenyl, C₂-C₆ heteroalkynyl, C₁-C₄ heteroalkyl, C₂-C₄ heteroalkenyl, and C₂-C₄ heteroalkynyl.

The terms cycloalkyl, cycloalkenyl, and cycloalkynyl include cyclic alkyl groups having a single cyclic ring or multiple condensed rings. Examples include cyclohexyl, cyclopentylethyl, and adamantanyl. Ranges of these groups useful with the compounds and methods described herein include C₃-C₂₀ cycloalkyl, C₃-C₂₀ cycloalkenyl, and C₃-C₂₀ cycloalkynyl. Additional ranges of these groups useful with the compounds and methods described herein include C₅-C₁₂ cycloalkyl, C₅-C₁₂ cycloalkenyl, C₅-C₁₂ cycloalkynyl, C₅-C₆ cycloalkyl, C₅-C₆ cycloalkenyl, and C₅-C₆ cycloalkynyl.

The terms heterocycloalkyl, heterocycloalkenyl, and heterocycloalkynyl are defined similarly as cycloalkyl, cycloalkenyl, and cycloalkynyl, but can contain O, S, or N heteroatoms or combinations thereof within the cyclic backbone. Ranges of these groups useful with the compounds and methods described herein include C₃-C₂₀ heterocycloalkyl, C₃-C₂₀ heterocycloalkenyl, and C₃-C₂₀ heterocycloalkynyl. Additional ranges of these groups useful with the compounds and methods described herein include C₅-C₁₂ heterocycloalkyl, C₅-C₁₂ heterocycloalkenyl, C₅-C₁₂ heterocycloalkynyl, C₅-C₆ heterocycloalkyl, C₅-C₆ heterocycloalkenyl, and C₅-C₆ heterocycloalkynyl.

Aryl molecules include, for example, cyclic hydrocarbons that incorporate one or more planar sets of, typically, six carbon atoms that are connected by delocalized electrons numbering the same as if they consisted of alternating single and double covalent bonds. An example of an aryl molecule is benzene. Heteroaryl molecules include substitutions along their main cyclic chain of atoms such as O, N, or S. When heteroatoms are introduced, a set of five atoms, e.g., four carbon and a heteroatom, can create an aromatic system. Examples of heteroaryl molecules include furan, pyrrole, thiophene, imadazole, oxazole, pyridine, and pyrazine. Aryl and heteroaryl molecules can also include additional fused rings, for example, benzofuran, indole, benzothiophene, naphthalene, anthracene, and quinoline. The aryl and heteroaryl molecules can be attached at any position on the ring, unless otherwise noted.

The alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, cycloalkyl, cycloalkenyl, cycloalkynyl, heterocycloalkyl, heterocycloalkenyl, or heterocycloalkynyl molecules used herein can be substituted or unsubstituted. As used herein, the term substituted includes the addition of an alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, cycloalkyl, cycloalkenyl, cycloalkynyl, heterocycloalkyl, heterocycloalkenyl, or heterocycloalkynyl group to a position attached to the main chain of the alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, cycloalkyl, cycloalkenyl, cycloalkynyl, heterocycloalkyl, heterocycloalkenyl, or heterocycloalkynyl, e.g., the replacement of a hydrogen by one of these molecules. Examples of substitution groups include, but are not limited to, hydroxyl, halogen (e.g., F, Br, Cl, or I), and carboxyl groups. Conversely, as used herein, the term unsubstituted indicates the alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl,

heteroalkynyl, heteroaryl, cycloalkyl, cycloalkenyl, cycloalkynyl, heterocycloalkyl, heterocycloalkenyl, or heterocycloalkynyl has a full complement of hydrogens, i.e., commensurate with its saturation level, with no substitutions, e.g., linear decane ($-(CH_2)_9-CH_3$).

5

II. Pharmaceutical Formulations

The compounds described herein or derivatives thereof can be provided in a pharmaceutical composition. Depending on the intended mode of administration, the pharmaceutical composition can be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, or suspensions, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include a therapeutically effective amount of the compound described herein or derivatives thereof in combination with a pharmaceutically acceptable carrier and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, or diluents. By pharmaceutically acceptable is meant a material that is not biologically or otherwise undesirable, which can be administered to an individual along with the selected compound without causing unacceptable biological effects or interacting in a deleterious manner with the other components of the pharmaceutical composition in which it is contained.

As used herein, the term carrier encompasses any excipient, diluent, filler, salt, buffer, stabilizer, solubilizer, lipid, stabilizer, or other material well known in the art for use in pharmaceutical formulations. The choice of a carrier for use in a composition will depend upon the intended route of administration for the composition. The preparation of pharmaceutically acceptable carriers and formulations containing these materials is described in, e.g., Remington's Pharmaceutical Sciences, 21st Edition, ed. University of the Sciences in Philadelphia, Lippincott, Williams & Wilkins, Philadelphia Pa., 2005. Examples of physiologically acceptable carriers include buffers, such as phosphate buffers, citrate buffer, and buffers with other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers, such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates, including glucose,

mannose, or dextrans; chelating agents, such as EDTA; sugar alcohols, such as mannitol or sorbitol; salt-forming counterions, such as sodium; and/or nonionic surfactants, such as TWEEN[®] (ICI, Inc.; Bridgewater, New Jersey), polyethylene glycol (PEG), and PLURONICS[™] (BASF; Florham Park, NJ).

5 Compositions containing the compound described herein or derivatives thereof suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include 10 water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

15 These compositions may also contain adjuvants, such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be promoted by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. Isotonic agents, for example, sugars, sodium chloride, and the like may also be included. Prolonged absorption of the 20 injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration of the compounds described herein or derivatives thereof include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds described herein or derivatives thereof is admixed 25 with at least one inert customary excipient (or carrier), such as sodium citrate or dicalcium phosphate, or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, 30 agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example, paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (h)

adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

5 Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

 Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others known in the art. They may contain opacifying agents and can also be of such composition that
10 they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned
15 excipients.

 Liquid dosage forms for oral administration of the compounds described herein or derivatives thereof include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as
20 water or other solvents, solubilizing agents, and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan, or
25 mixtures of these substances, and the like.

 Besides such inert diluents, the composition can also include additional agents, such as wetting, emulsifying, suspending, sweetening, flavoring, or perfuming agents.

 Suspensions, in addition to the active compounds, may contain additional agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and
30 sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

 Compositions of the compounds described herein or derivatives thereof for rectal administrations are optionally suppositories, which can be prepared by mixing

the compounds with suitable non-irritating excipients or carriers, such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and, therefore, melt in the rectum or vaginal cavity and release the active component.

5 Dosage forms for topical administration of the compounds described herein or derivatives thereof include ointments, powders, sprays, and inhalants. The compounds described herein or derivatives thereof are admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, ointments, powders, and
10 solutions are also contemplated as being within the scope of the compositions.

The compositions can include one or more of the compounds described herein and a pharmaceutically acceptable carrier. As used herein, the term pharmaceutically acceptable salt refers to those salts of the compound described herein or derivatives thereof that are, within the scope of sound medical judgment, suitable for use in
15 contact with the tissues of subjects without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds described herein. The term salts refers to the relatively non-toxic, inorganic and organic acid addition salts of the compounds described herein. These
20 salts can be prepared *in situ* during the isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate,
25 tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, methane sulphonate, and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to
30 ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See S.M. Barge et al., *J. Pharm. Sci.* (1977) 66, 1, which is incorporated herein by reference in its entirety, at least, for compositions taught therein.)

Administration of the compounds and compositions described herein or pharmaceutically acceptable salts thereof can be carried out using therapeutically effective amounts of the compounds and compositions described herein or pharmaceutically acceptable salts thereof as described herein for periods of time effective to treat a disorder. The effective amount of the compounds and compositions described herein or pharmaceutically acceptable salts thereof as described herein may be determined by one of ordinary skill in the art and includes exemplary dosage amounts for a mammal of from about 0.5 to about 200mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. Alternatively, the dosage amount can be from about 0.5 to about 150mg/kg of body weight of active compound per day, about 0.5 to 100mg/kg of body weight of active compound per day, about 0.5 to about 75mg/kg of body weight of active compound per day, about 0.5 to about 50mg/kg of body weight of active compound per day, about 0.5 to about 25mg/kg of body weight of active compound per day, about 1 to about 20mg/kg of body weight of active compound per day, about 1 to about 10mg/kg of body weight of active compound per day, about 20mg/kg of body weight of active compound per day, about 10mg/kg of body weight of active compound per day, or about 5mg/kg of body weight of active compound per day. Those of skill in the art will understand that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition.

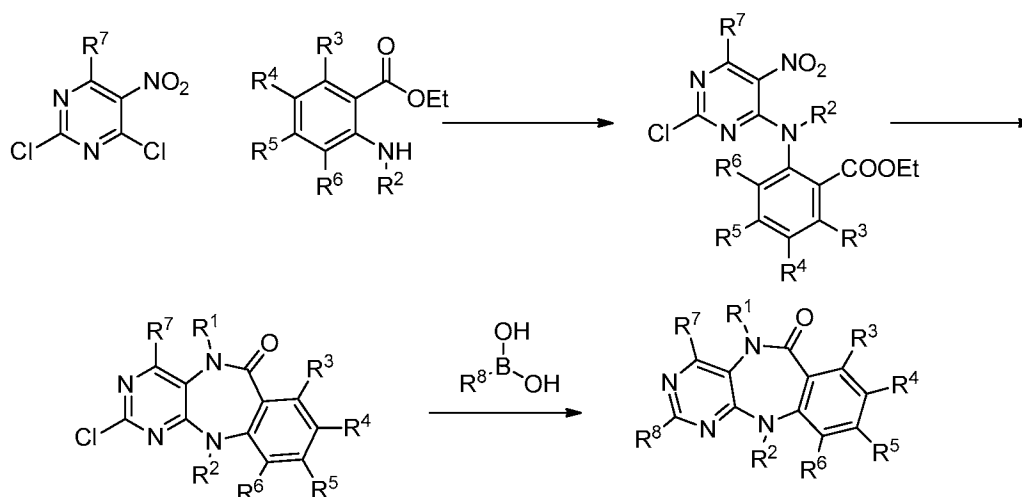
III. Methods of Making the Compounds

The compounds described herein can be prepared in a variety of ways known to one skilled in the art of organic synthesis or variations thereon as appreciated by those skilled in the art. The compounds described herein can be prepared from readily available starting materials. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by one skilled in the art.

Variations on **Formulas I-VII, Fluorophore**, and **Fluoro** include the addition, subtraction, or movement of the various constituents as described for each compound. Similarly, when one or more chiral centers are present in a molecule, the chirality of the molecule can be changed. Additionally, compound synthesis can involve the protection and deprotection of various chemical groups. The use of protection and deprotection, and the selection of appropriate protecting groups can be determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Wuts and Greene, *Protective Groups in Organic Synthesis*, 4th Ed., Wiley & Sons, 2006, which is incorporated herein by reference in its entirety.

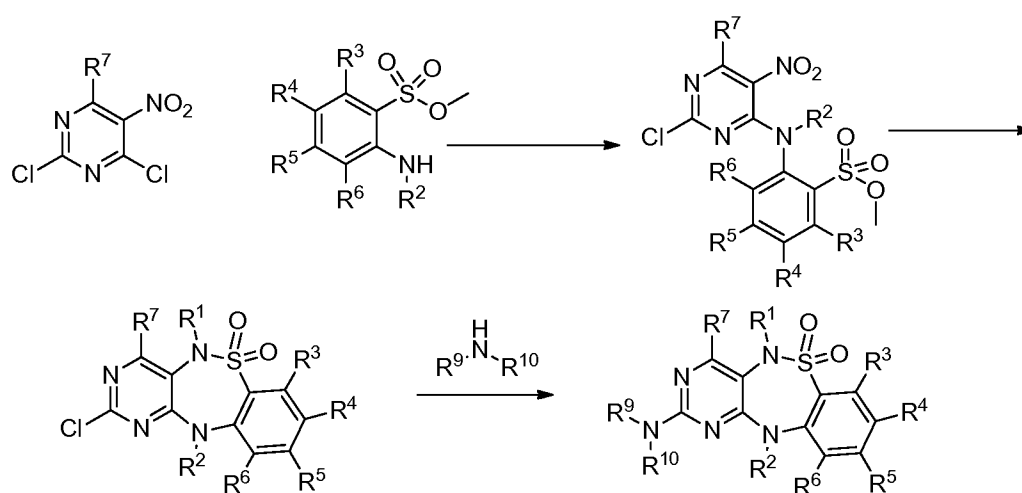
Reactions to produce the compounds described herein can be carried out in solvents, which can be selected by one of skill in the art of organic synthesis. Solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products under the conditions at which the reactions are carried out, i.e., temperature and pressure. Reactions can be carried out in one solvent or a mixture of more than one solvent. Product or intermediate formation can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^1H or ^{13}C) infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

The compounds described by **Formula I** can be made, for example, using reactions known to those of skill in the art according to the method shown in **Scheme 1**.

Scheme 1:

The compounds described by **Formula II** can be made, for example, using reactions known to those of skill in the art according to the method shown in **Scheme**

5

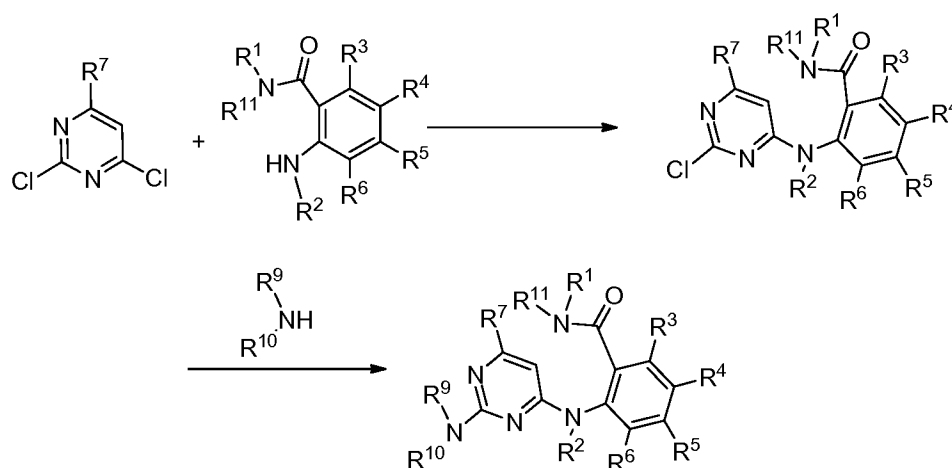
2.**Scheme 2:**

The compounds described by **Formula III** can be made, for example, using reactions known to those of skill in the art according to the method shown in **Scheme**

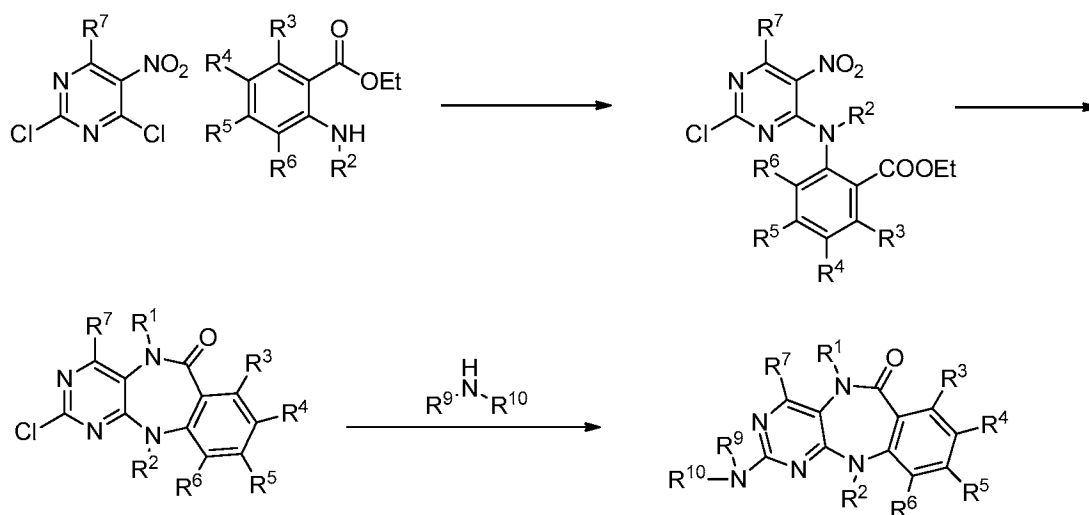
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3:

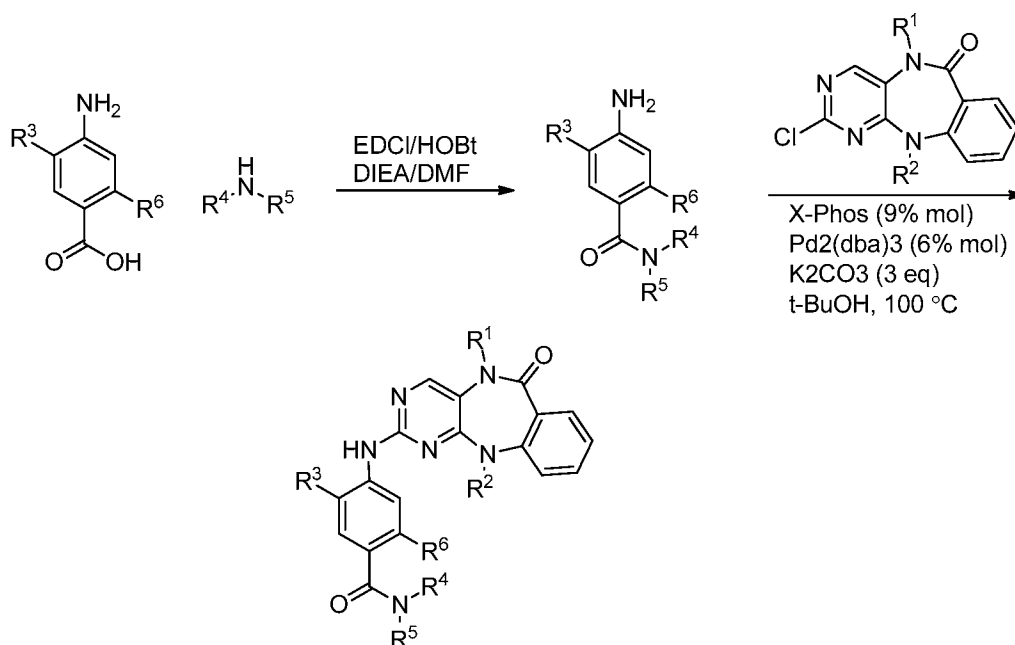
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Scheme 3:

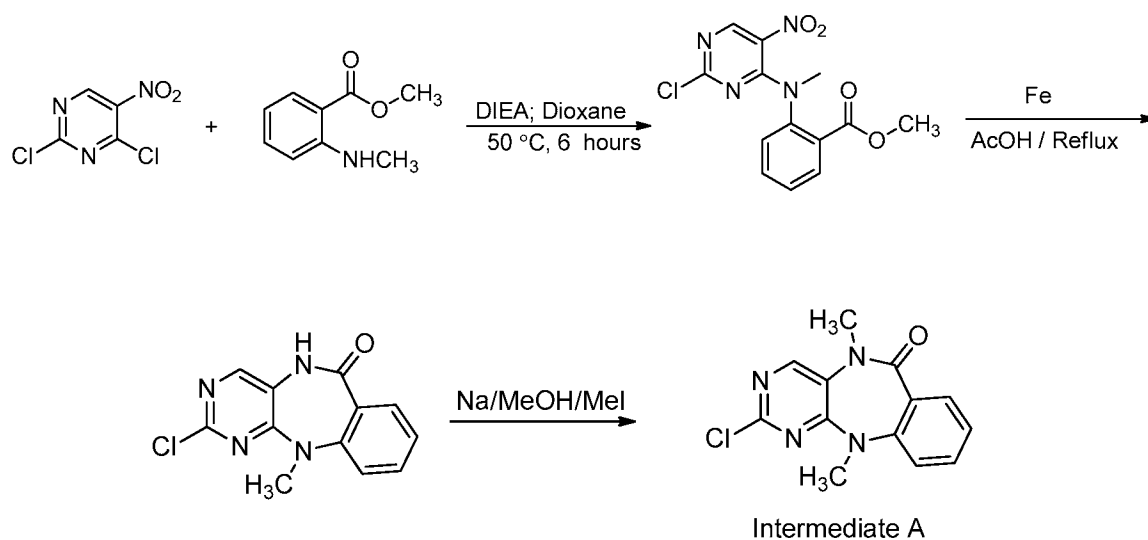
The compounds described by **Formula IV** and **Formula V** can be made, for example, using reactions known to those of skill in the art according to the method shown in **Scheme 4**.

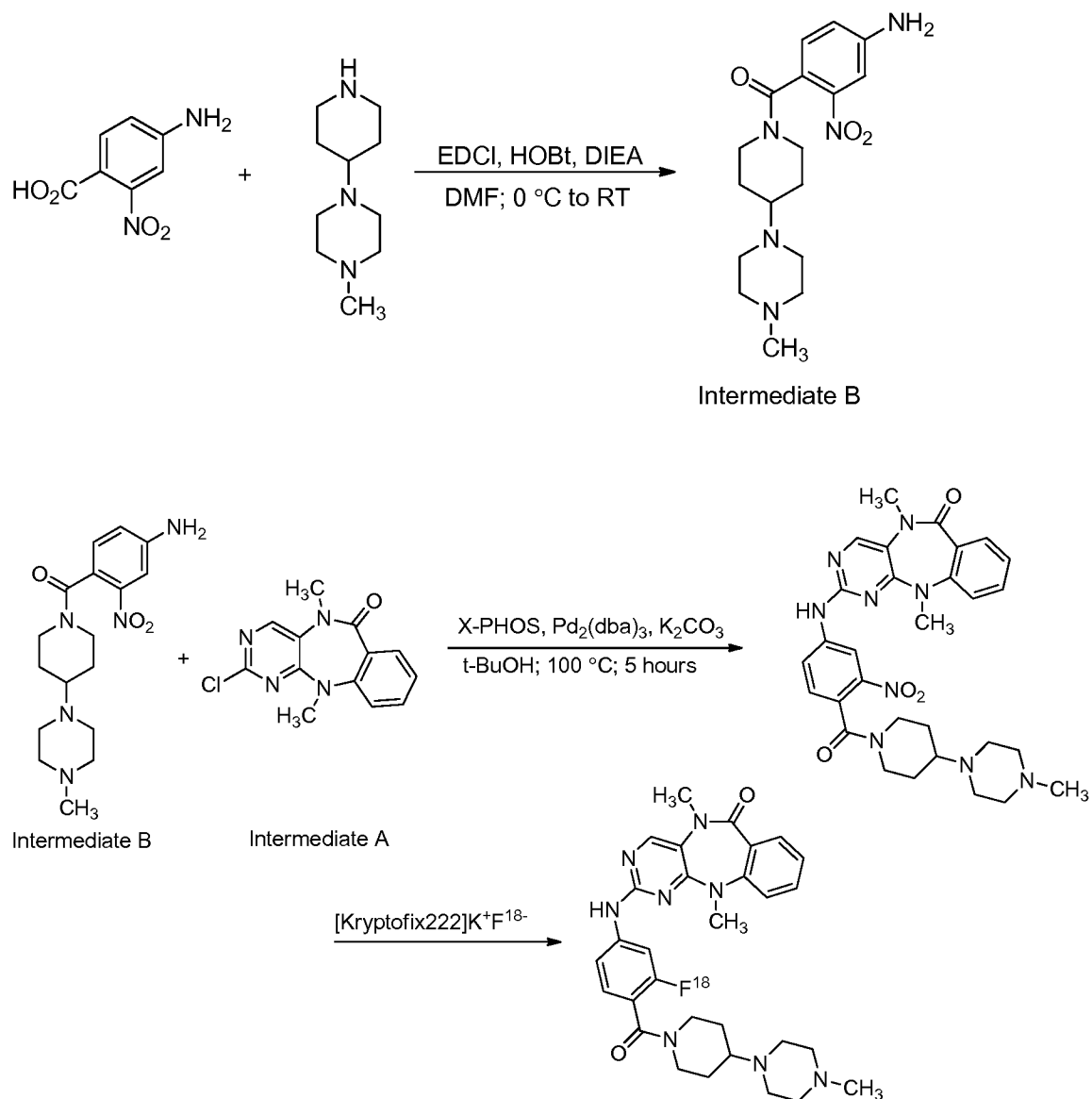
Scheme 4:

The compounds described by **Formula VI**, **Fluorophore**, and **Fluoro** can be made, for example, using reactions shown in **Scheme 5**.

Scheme 5:

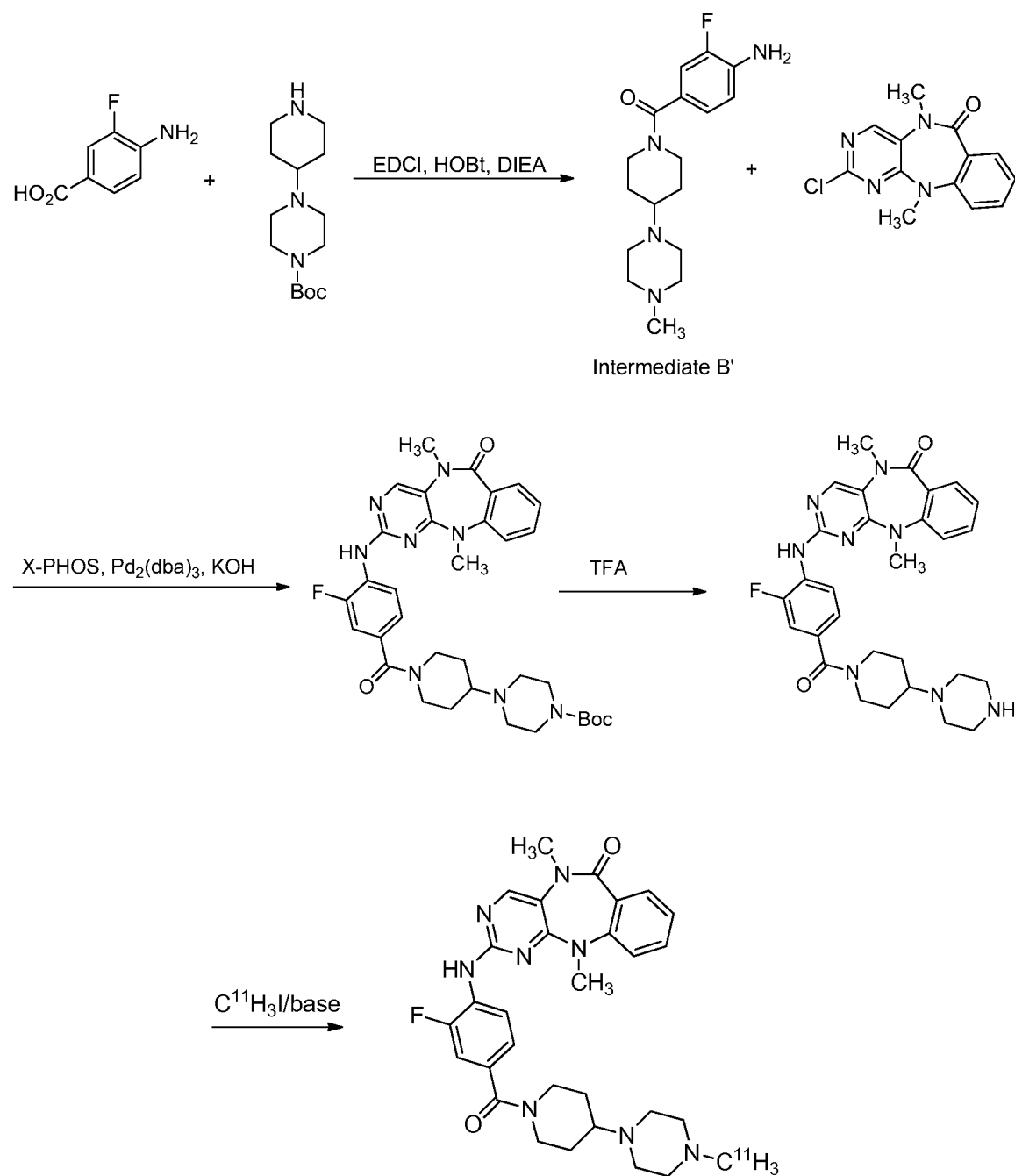
Compound VI-1 can be made, for example, according to the procedure shown in **Scheme 6**.

5 **Scheme 6:**



5 **Compound VI-2** can be made, for example, according to the procedure shown in **Scheme 7**.

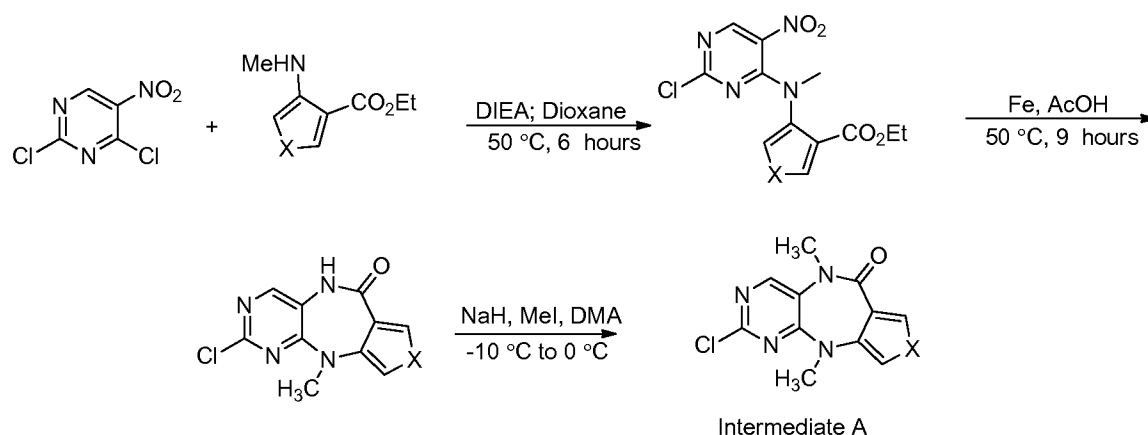
Scheme 7:



5

The compounds described by **Formula VII** can be made, for example, using the method shown in **Scheme 8**.

10

Scheme 8:

Intermediate A can then be coupled with an amine, such as Intermediate B
 5 shown in **Scheme 6** or Intermediate B' shown in **Scheme 7**.

IV. Methods of Use

Provided herein are methods to treat, prevent, or ameliorate cancer or a
 neurodegenerative disorder in a subject. The methods include administering to a
 subject an effective amount of one or more of the compounds or compositions
 10 described herein, or a pharmaceutically acceptable salt or prodrug thereof. The
 expression effective amount, when used to describe an amount of compound in a
 method, refers to the amount of a compound that achieves the desired
 pharmacological effect or other effect. Optionally, the compound can be administered
 systemically. The compounds and compositions described herein or pharmaceutically
 15 acceptable salts thereof are useful for treating cancer or neurodegenerative disorders
 in humans, including, without limitation, pediatric and geriatric populations, and in
 animals, e.g., veterinary applications.

Optionally, the cancer is breast cancer or prostate cancer. Optionally, the
 cancer is bladder cancer, brain cancer, colorectal cancer, cervical cancer,
 20 gastrointestinal cancer, genitourinary cancer, head and neck cancer, lung cancer,
 ovarian cancer, pancreatic cancer, renal cancer, skin cancer, or testicular cancer.

Optionally, the neurodegenerative disorder is Parkinson's disease. Optionally,
 the neurodegenerative disorder is Alexander disease, Alper's disease, Alzheimer
 disease, amyotrophic lateral sclerosis, ataxia telangiectasia, Batten disease (also
 25 known as Spielmeyer-Vogt-Sjogren-Batten disease), Canavan disease, Cockayne
 syndrome, Corticobasal degeneration, Creutzfeldt-Jakob disease, Huntington disease,

Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, Spinocerebellar ataxia type 3, multiple sclerosis, multiple system atrophy, Pelizaeus-Merzbacher disease, Pick's disease, Primary lateral sclerosis, Refsum's disease, Sandhoff disease, Schilder's disease, Spielmeyer-Vogt-Sjogren-Batten disease (also
5 known as Batten disease), Spinocerebellar ataxia (multiple types with varying characteristics), Spinal muscular atrophy, Steele-Richardson-Olszewski disease, Tay-Sachs, Transmissible spongiform encephalopathies (TSE), and Tabes dorsalis.

The methods of treating or preventing cancer or a neurodegenerative disorder in a subject can further comprise administering to the subject one or more additional
10 agents. The one or more additional agents and the compounds described herein or pharmaceutically acceptable salts or prodrugs thereof can be administered in any order, including concomitant, simultaneous, or sequential administration. Sequential administration can be temporally spaced order of up to several days apart. The methods can also include more than a single administration of the one or more
15 additional agents and/or the compounds described herein or pharmaceutically acceptable salts or prodrugs thereof. The administration of the one or more additional agents and the compounds described herein or pharmaceutically acceptable salts or prodrugs thereof can be by the same or different routes and concurrently or sequentially.

20 Therapeutic agents include, but are not limited to, chemotherapeutic agents. A chemotherapeutic agent is a compound or composition effective in inhibiting or arresting the growth of an abnormally growing cell. Thus, such an agent may be used therapeutically to treat cancer as well as other diseases marked by abnormal cell growth. Illustrative examples of chemotherapeutic compounds include, but are not
25 limited to, bexarotene, gefitinib, erlotinib, gemcitabine, paclitaxel, docetaxel, topotecan, irinotecan, temozolomide, carmustine, vinorelbine, capecitabine, leucovorin, oxaliplatin, bevacizumab, cetuximab, panitumumab, bortezomib, oblimersen, hexamethylmelamine, ifosfamide, CPT-11, deflunomide, cycloheximide, dicarbazine, asparaginase, mitotant, vinblastine sulfate, carboplatin, colchicine,
30 etoposide, melphalan, 6-mercaptopurine, teniposide, vinblastine, antibiotic derivatives (e.g. anthracyclines such as doxorubicin, liposomal doxorubicin, and diethylstilbestrol doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil (FU), 5-FU, methotrexate, floxuridine,

interferon alpha-2B, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cisplatin, vincristine and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephallen, chlorambucil, mechlorethamine (nitrogen mustard) and thiotepa); and steroids (e.g., bethamethasone sodium phosphate).

Therapeutic agents further include, but are not limited to, levadopa, a dopamine agonist, an anticholinergic agent, a monoamine oxidase inhibitor, a COMT inhibitor, amantadine, rivastigmine, an NMDA antagonist, a cholinesterase inhibitor, riluzole, an anti-psychotic agent, an antidepressant, and tetrabenazine.

Any of the aforementioned therapeutic agents can be used in any combination with the compositions described herein. Combinations are administered either concomitantly (e.g., as an admixture), separately but simultaneously (e.g., via separate intravenous lines into the same subject), or sequentially (e.g., one of the compounds or agents is given first followed by the second). Thus, the term combination is used to refer to concomitant, simultaneous, or sequential administration of two or more agents.

The methods and compounds as described herein are useful for both prophylactic and therapeutic treatment. For prophylactic use, a therapeutically effective amount of the compounds and compositions or pharmaceutically acceptable salts thereof as described herein are administered to a subject prior to onset (e.g., before obvious signs of cancer or a neurodegenerative disorder), during early onset (e.g., upon initial signs and symptoms of cancer or a neurodegenerative disorder), or after the development of cancer or a neurodegenerative disorder. Prophylactic administration can occur for several days to years prior to the manifestation of symptoms of cancer or a neurodegenerative disorder. Therapeutic treatment involves administering to a subject a therapeutically effective amount of the compounds and compositions or pharmaceutically acceptable salts thereof as described herein after cancer or a neurodegenerative disorder is diagnosed.

The methods and compounds described herein are also useful in inhibiting LRRK2 in a cell. Optionally, LRRK2 can be a mutant LRRK2. The mutant LRRK2 can optionally include a G2019S mutation. The methods and compounds described herein are further useful in modulating signaling in a cell as compared to a control.

5 Optionally, the method includes reducing Akt phosphorylation in a cell. The methods of inhibiting LRRK2 in a cell or modulating signaling in a cell as compared to a control include contacting a cell with an effective amount of one or more compounds as described herein. Optionally, the cell is a neuron. Optionally, the contacting is performed *in vivo*. Optionally, the contacting is performed *in vitro*.

10 The methods and compounds described herein are also useful in inhibiting ERK5 in a cell. ERK5 is a kinase of the mitogen-activated protein kinase (MAPK) family. ERK5 has been implicated in cell survival, anti-apoptotic signaling, angiogenesis, cell motility, differentiation and cell proliferation. ERK5 is over-expressed or constitutively active in a number of cancers including prostate and breast
15 cancers. The compounds described herein, e.g., **Fluoro**, are highly specific inhibitors to ERK5 and inhibit ERK5 phosphorylation activity in low nanomolar concentration. As an inhibitor of ERK5, **Fluoro** can down regulate cell growth, cell survival, and apoptosis, which are the hallmarks of many cancer treatments. Inhibition of ERK5 signal transduction pathway is important in many diseases, including oncology and
20 neurology and the inhibition can be achieved with **Fluoro** compound as a specific ERK5 inhibitor. ERK5's role is also implicated in, but not limited to, vascularization, cell growth, apoptosis, and cell cycle modulation. The methods of inhibiting ERK5 in a cell or modulating signaling in a cell as compared to a control include contacting a cell with an effective amount of one or more compounds as described herein.
25 Optionally, the contacting is performed *in vivo*. Optionally, the contacting is performed *in vitro*.

The methods herein for prophylactic and therapeutic treatment optionally comprise selecting a subject with or at risk of developing a neurodegenerative disorder. A skilled artisan can make such a determination using, for example, a
30 variety of prognostic and diagnostic methods, including, for example, a personal or family history of the disease or condition, clinical tests (e.g., imaging, biopsy, genetic tests), and the like.

Further described herein are methods of imaging an LRRK2 positive cell or population of cells in a subject. The methods of imaging include administering to the subject a compound described herein that further includes a detectable label and detecting the detectable label in the subject. The detectable label indicates the LRRK2 positive cell or population of cells. Optionally, the LRRK2 positive cell or population of cells is a neuron or neuronal population of cells. The detecting step can include imaging methods such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), or X-ray. The detectable label on the compound can optionally be a radiolabel, fluorescent label, enzymatic label, and biotin. Optionally, the detectable label is a radiolabel selected from ^{11}C and ^{18}F . Such imaging methods are useful for assessing the extent of disease and/or the target of the therapeutic agent.

V. Kits

Also provided herein are kits for treating or preventing cancer and/or neurodegenerative disorders in a subject. A kit can include any of the compounds or compositions described herein. For example, a kit can include a compound of **Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula VII, Fluorophore, Fluoro**, or combinations thereof. A kit can further include one or more additional agents, such as a chemotherapeutic agent (e.g., gemcitabine, paclitaxel, or tamoxifen), levodopa, a dopamine agonist, an anticholinergic agent, a monoamine oxidase inhibitor, a COMT inhibitor, amantadine, rivastigmine, an NMDA antagonist, a cholinesterase inhibitor, riluzole, an anti-psychotic agent, an antidepressant, and/or tetrabenazine. A kit can include an intraperitoneal formulation or an oral formulation of any of the compounds or compositions described herein. A kit can additionally include directions for use of the kit (e.g., instructions for treating a subject), a container, a means for administering the compounds or compositions (e.g., syringe, etc.), and/or a carrier.

As used herein the terms treatment, treat, or treating refer to a method of reducing or delaying one or more symptoms of cancer or a neurodegenerative disorder. Thus in the disclosed method, treatment can refer to a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction in the severity of one or more symptoms of the disease or condition. For example, a method for treating a disease is considered to be a treatment if there is a 10% reduction in one or more symptoms or

signs of cancer or a neurodegenerative disease in a subject as compared to a control. As used herein, control refers to the untreated condition. Thus the reduction can be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or any percent reduction in between 10% and 100% as compared to native or control levels. It is understood that treatment does not necessarily refer to a cure or complete ablation of the disease, condition, or symptoms of the disease or condition.

As used herein, the terms prevent, preventing, and prevention of a disease or disorder refer to an action, for example, administration of a composition or therapeutic agent, that occurs before or at about the same time a subject begins to show one or more symptoms of the disease or disorder, which inhibits or delays onset or severity of one or more symptoms of the disease or disorder. For example, the method is considered to be a prevention if there is a reduction or delay in onset, incidence, severity, or recurrence of cancer or neurodegeneration, or one or more symptoms of cancer (e.g., tumor growth) or neurodegeneration (e.g., tremor, weakness, memory loss, rigidity, spasticity, atrophy, dementia) in a subject susceptible to cancer or neurodegeneration compared to control subjects susceptible to cancer or neurodegeneration that did not receive a compound as described herein. The reduction or delay in onset, incidence, severity, or recurrence of cancer or neurodegeneration can be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or any percent reduction in between 10% and 100% as compared to native or control levels.

As used herein, references to decreasing, reducing, or inhibiting include a change of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater as compared to a control level. Such terms can include, but do not necessarily include, complete elimination.

As used herein, subject means both mammals and non-mammals. Mammals include, for example, humans; non-human primates, e.g., apes and monkeys; cattle; horses; sheep; rats; mice; pigs; and goats. Non-mammals include, for example, fish and birds.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application.

The examples below are intended to further illustrate certain aspects of the methods and compositions described herein, and are not intended to limit the scope of the claims.

EXAMPLES

Example 1:

Wild-type LRRK2 and G2019S mutant LRRK2 (LRRK2 G2019S) were assayed using 10 μ M Nicktide in the presence of 100 μ M ATP with increasing concentrations of **Fluorophore** and **Fluoro**. The results, presented as percentage of kinase activity relative to the DMSO-treated control, are provided in Figure 1. As shown, the IC₅₀ values of **Fluorophore** and **Fluoro** were 46 nM and 34 nM, respectively, for wild-type LRRK2 (see Panel A). For LRRK2 G2019S, the IC₅₀ values of **Fluorophore** and **Fluoro** were 11 nM and 16 nM, respectively (see Panel B). For comparison purposes, two inactive compounds (AN-1 and SK-15) were tested, along with known compound IN-1 (wild-type LRRK2 kinase activity: IC₅₀ of 13 nM and LRRK2 G2019S kinase activity: IC₅₀ of 6 nM; see Deng et al., *Nature Chemical Biology*, 2011, 203). The data for wild-type LRRK2 and LRRK2 G2019S are shown in Panels C and D, respectively. These data demonstrate that **Fluorophore** and **Fluoro** retain low nanomolar potency against LRRK2 and LRRK2 G2019S.

Example 2:

LRRK2 fusion protein (40 ng) was incubated with 1 μ M of **Fluorophore**, **Fluoro**, IN-1, SK-15, and AN-1 in the absence (-) or presence (+) of ATP overnight and fractionated on 4 to 20% gel. The membrane was probed with anti-LRRK2 antibody. **Fluorophore**, **Fluoro**, and IN-1 inhibited phosphorylation of LRRK2 at T2035, whereas the two inactive compounds SK-15 and AN-1 failed to inhibit phosphorylation. These data demonstrate that **Fluorophore** and **Fluoro** inhibit autophosphorylation of LRRK2 *in vitro*.

Example 3:

Dopaminergic MN9D parental cells were stably transfected with a plasmid construct that overexpresses human LRRK2 wild-type (WT) or mutant (G2019S) under the control of a tetracycline inducible promoter. These constructs also express enhanced green fluorescent protein (eGFP) using an internal ribosome entry sequence (IRES). MN9D parental cells (CTL), MN9D wild-type (Figure 3, panel A), and MN9D G2019S (Figure 3, panel B) were grown in the absence (-) and presence (+) of

doxorubicin (DOX). Cell lysates were prepared and the expression of LRRK2 (Figure 3, panel A and B; top) and eGFP (Figure 3, panel A and B; bottom) was determined. LRRK2 and eGFP were detected exclusively in the MN9D wild-type (indicated as * in Figure 3, panels A and B) and MN9D G2019S (indicated as ** in Figure 3, panels A and B) following DOX treatment.

GST-LRRK2 or GST alone was mixed with the recombinant his-Akt1 and subjected to pull-down assay by incubation with glutathione agarose beads. The beads-bound proteins were subjected to Western blot analysis using antibodies against Akt1 and GST. The GST-pull-down assay confirmed the direct interaction between LRRK2 and Akt1 (Figure 3, panel C).

Recombinant human his-Akt-1 was incubated with recombinant GST-LRRK2 in the presence of 5 μ M ATP. The blot was probed using antibodies against LRRK2, p-Akt1 at Ser 473, and total Akt1. The intensity of p-Akt was increased with co-incubation with LRRK2 in the presence of ATP (Figure 3, panel D).

Induced MN9D G2019S cells were treated with 500 μ M each of IN-1, **Fluorophore**, and **Fluoro** for two hours. Cell lysates were prepared and Western blotted for LRRK2, total Akt, phosphor-Akt (Ser 473) and β -actin (Figure 3, panel E). These data demonstrate that Akt phosphorylation, but not total Akt, is reduced with IN-1, **Fluorophore**, and **Fluoro**.

Example 4:

Rat primary neurons at 8 DIV were treated with 500 nM of IN-1, **Fluorophore**, or **Fluoro** for two hours. Neurons were lysed directly in SDS-PAGE sample buffer and analyzed by immunoblotting with p-Akt (ser473) and Akt antibodies. Beta actin was used as the loading control. Figure 4, Panel A, demonstrates that the compounds reduce phosphorylated Akt in primary neurons.

Rat primary neurons at 7 DIV were treated with 500 nM of IN-1 and analyzed as described above after 1 hour, 2 hours, 4 hours, and 8 hours. Figure 4, Panel B, demonstrates that the time course of Akt-phosphorylation decreases following treatment with the compounds.

Figure 4, Panel C, demonstrates that LRRK2 inhibitors IN-1, **Fluorophore**, and **Fluoro** reduce phosphorylation of Akt *in vivo*. Inhibitors IN-1, **Fluorophore**, and **Fluoro** (50 mg/kg each) were administered by intraperitoneal injection to wild-type mice (n=3 per group). Brain tissue was collected two hours after compound

injection and analyzed for phosphorylation of Akt protein. Cortical extracts (200 mg) were fractionated on 4 to 20% Tris-Glycine gels and analyzed by immunoblotting with phospho-Akt, pan-Akt, and beta-actin antibodies. The data show that the systemic administration of **Fluorophore** and **Fluoro** reduce Akt phosphorylation in the neurons and in the brain.

Figure 4, Panel D, displays the ratios of p-Akt over total Akt. **Fluoro** produced a significant ($p < 0.05$) decline in phospho-Akt in brains of animals.

Example 5:

Three animals in each group were injected (i.p.) with 50 mg/kg **Fluoro** (558 kD mw). After three hours of treatment, the animals were sacrificed and whole brain was collected. Cortex (10 mg) was used for metabolite studies. Metabolite extraction was performed by homogenizing brain tissue in extraction buffer (50% methanol). The samples were centrifuged at 14K for 10 minutes at 4 °C, and the supernatant was mixed with equal volume of acetonitrile. The samples were incubated at -20 °C for two hours, centrifuged, and the supernatant was dried under vacuum. The samples were resuspended in buffer containing 98% water and 2% acetonitrile and analyzed using ultra-performance liquid chromatography – time of flight mass spectrometry in electro-spray positive ionization mode over a 12 minute gradient. The results are shown in Figure 5. Panel A shows the mass spectrometry spectrum for untreated brain tissue. Panel B shows the mass spectrometry spectrum for **Fluoro** treated brain tissue. Panel C shows the mass spectrometry spectrum for **Fluoro** alone.

Example 6:

MN9D cells stably transfected with G2019S were used to demonstrate that induction of LRRK2 attenuates neurite outgrowth. MN9D-LRRK2G2019S cells and MN9D cells harboring inducible eGFP alone were plated on polyethyleneimine (PEI) coated 12-mm diameter coverslips in a 24-well plate at 1×10^5 cells per well density and differentiated for 6 days with sodium butyrate. On day 6, doxycycline (0.2mg/mL) (Dox) was added and incubated for 2 days to induce LRRK2 and GFP expression. On day 8, cells were fixed with 4% PFA/4% sucrose/1xPBS and immunocytochemistry (ICC) was carried out. Cells were labeled with rabbit polyclonal anti-beta tubulin antibody (1/2,000; Covance; Princeton, NJ) followed by secondary antibody, Alexa-594 goat antirabbit IgG antibody (1/200; Molecular Probe/Life; Carlsbad, CA), and 4',6-diamidino-2-phenylindole (DAPI; 300nM).

Images were acquired (>40 images of beta-tubulin labeled (594nm) cells) per treatment group by an individual blinded to treatment group. The longest neurite extension per cell was measured using NIH ImageJ program. The neurite length from each group was analyzed for difference in mean length. See Figure 6. The Mann-Whitney U post-hoc test was used. No differences in neurite outgrowth were observed between Dox-treated (Dox+) MN9DeGFP cells and Dox-untreated (Dox-) MN9DeGFP cells. In contrast, Dox treated MN9DG2019S cells had marked and significant (<0.0001) reduction of neurite length compared with uninduced cells where LRRK2G2019S levels are not induced.

Example 7:

MN9D-LRRK2G2019S cells were plated on PEI coated 12-mm diameter coverslips in 24-well plate at 1×10^5 cells per well density and differentiated for 6 days with sodium butyrate and treated with IN-1, **Fluorophore**, and **Fluoro**. On day 6, doxycycline (0.2mg/mL) was added and incubated for 2 days to induce LRRK2 and GFP expression. On day 8, cells were fixed with 4% PFA/4% sucrose/1xPBS and immunocytochemistry (ICC) was carried out. Cells were labeled with rabbit polyclonal anti-beta tubulin antibody (1/2,000; Covance) followed by secondary antibody, Alexa-594 goat anti-rabbit IgG antibody (1/200; Molecular Probe/Life technology), and DAPI [300nM]. Images were acquired (>40 images of beta-tubulin labeled (594nm) cells) per treatment group by an individual blinded to treatment group (see Figure 7). Neurite extension was attenuated in MN9D-LRRK2G2019S cells induced with DOX and neurite extension was phenotypically rescued in cultures treated with **Fluoro** (Figure 7, Panel D, top).

Example 8:

Fluoro reverses neurite shortening in MN9D-LRRK2G2019S cells. MN9DG2019 and MN9D parental cells were differentiated by 2mM Sodium Butyrate for 6 days. See Figure 8, Panel A. Then LRRK2G2019S basal (leak through) expression was augmented by 0.25 µg/ml Doxycycline (DOX) for 2 days. MN9DLRR2G2019S cells without DOX induction have leaky LRRK2 expression.

LRRK2 inhibitor **Fluoro** was added for 24 hours followed by immunocytochemistry (ICC) with beta tubulin antibody. Images were acquired (>40 images of betatubulin labeled cells) per treatment group by an individual blinded to treatment group. The longest neurite extension per cell was measured using NIH

ImageJ program. Neurite length from each group was analyzed for difference in mean length using the Mann-Whitney U post-hoc test. *, $p < 0.05$. **Fluoro** was able to increase neurite length only with moderate levels of LRRK2G2019S (Figure 8, Panel B).

5 **Example 9:**

In vivo functional studies of **Fluoro** are performed according to the following method using LRRK2 knockout rats (LEH- *Lrrk2*^{tm1sage}, SAGE labs) and hBAC0LRRK2G2019S rats from Oxford Parkinson's Disease Centre (OPDC). hBAC transgenic rats carry either wild-type or the G2019S or R1441C mutant forms of the LRRK2 genomic locus tagged with a fluorescent marker. The rat model is used to determine **Fluoro** effects on LRRK2 kinase activity, Akt phosphorylation in brain tissues. In these studies, 8-week old compound BAC rats are dosed at 100 mg/kg (formulated with Captisol, Cydex Pharmaceuticals) with **Fluoro**. At times (zero, 60 m, and 120 m) after administration, rats are euthanized for analyses. Half of each group is processed for tissue analyses (perfused), the other half for protein western blot analyses. Separately, peripheral blood mononuclear cells (PBMCs) are collected, which are rich in LRRK2 to examine Akt phosphorylation status following systemic administration.

15 **Example 10:**

20 The avidity and selectivity of radiolabeled **Fluoro** and other compounds described herein on LRRK2 kinase is determined. The radiotracers sensitivity and specificity is evaluated *in vivo* in rats expressing the human LRRK2 kinase as described in Example 9. Compound BAC transgenic rats are dosed at 100 mg/kg with a carbon-11 labeled **Fluoro** or fluorine-18 labeled **Fluoro**. The rats are anesthetized 60 minutes later and a catheter is inserted in the tail vein. The vital signs of the animals are monitored. Data acquisition is commenced just prior to injection of 100-200 μ Ci of labeled tracer (larger amounts of tracer may be needed for brain imaging). Scanning is performed over a time period appropriate to the half-life of the radionuclide and the physiological function being measured. Typical imaging sessions for carbon-11 labeled tracer include 60-120 minutes of dynamic data collection and for fluorine-18 labeled tracers include 60 minute dynamic scans followed by a break with subsequent imaging at several time points up to 6 hours after injection. The first scanning session with each new compound is reviewed to evaluate the *in vivo* time

course of the distribution to enhance and optimize the image acquisition sequence. One week later after complete wash-out of [^{18}F]-**Fluoro**, the rats are re-imaged using [^{18}F]-FDG to determine whether the dysregulated kinase G2019S is metabolically more active than wild type LRRK2.

5 A non-radioactive challenge dose (**Fluoro** or the non-radioactive version of the study compounds) is given to the rats to define the specificity of the radiotracers. This drug is given before, with, or after radiotracer administration. Typical blocking doses are 10-30 mg/kg. Adjustments to the dose are made based on the imaging data.

Based on the imaging data, those compounds showing uptake and retention of the tracer in the LRRK2 expressing regions undergo biodistribution studies. Fluorine-18 or carbon-11 tracer (100-200 μCi) is administered by tail vein injection. At two 10 time points, typically 0.75 and 1.5 h for carbon-11 and 1 and 3 hours for fluorine-18, the rats are euthanized. These times may be modified in accordance with the imaging data. Blood and organs are harvested, weighed, and counted. The % injected dose per 15 gram of tissue is calculated. The brain is sectioned and counted.

Example 11:

Assays were conducted in rat liver microsomes to detect **Fluoro** metabolites in rat liver microsomes. **Fluoro** (10 μM) was incubated with rat liver microsomes (1 mg/mL) for 15 minutes, 30 minutes, 45 minutes, and 60 minutes at 37 °C. The assays 20 were performed in the presence of NADPH (2 nM) or in the absence of NADPH. **Fluoro** was stable in the microsomes after incubating for 60 minutes, as shown in Table 1. After 60 minutes, trace amounts of oxidation and de-methylation metabolites were present.

Table 1

Incubation Time (minutes)	Fluoro (%) with NADPH	Fluoro (%) without NADPH
0	100.00	100.00
15	94.12	92.35
30	91.23	90.68
45	86.15	92.06
60	79.00	83.92

Example 12:

SAHA and **Fluoro** were tested for ERK5 kinase activity in cancer cell lines. A cytotoxicity assay was performed using neuroendocrine carcinomas of the cervix

was performed. The cells were treated with increasing concentrations of SAHA and **Fluoro** and the percentage of cells that died after exposure to the compounds was measured. DMSO served as the control. The ERK5 inhibition data for the compounds are shown in Figure 9.

5 **Example 13:**

Fluoro (at 1 μ M and at 10 μ M) was tested for activity against several protein kinases. The results are shown below in **Table 2**:

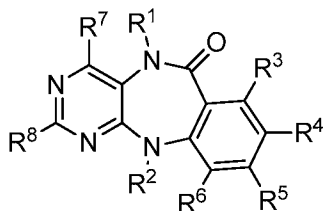
Table 2

No.	Kinase	%Ctr at 1 uM	%Ctr at 10 uM
0	LRRK2	12	4.8
	LRRK2 {G2019S}	4	7.1
1	AURKA	11	0.15
2	DCAMKL1	20	9.4
3	DCAMKL2	3.3	1.1
4	ERK5	0.2	0.25
5	MKNK2	21	0.55
6	PIK3CG	21	0.6
7	PLK4	6.2	0.1
8	TNK1	6.6	0
9	TYK2	22	1.6

10 The compounds and methods of the appended claims are not limited in scope by the specific compounds and methods described herein, which are intended as illustrations of a few aspects of the claims and any compounds and methods that are functionally equivalent are within the scope of this disclosure. Various modifications of the compounds and methods in addition to those shown and described herein are
 15 intended to fall within the scope of the appended claims. Further, while only certain representative compounds, methods, and aspects of these compounds and methods are specifically described, other compounds and methods and combinations of various features of the compounds and methods are intended to fall within the scope of the appended claims, even if not specifically recited. Thus, a combination of steps,
 20 elements, components, or constituents may be explicitly mentioned herein; however, all other combinations of steps, elements, components, and constituents are included, even though not explicitly stated.

WHAT IS CLAIMED IS:

1. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

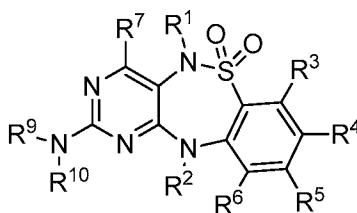
R^1 is hydrogen or substituted or unsubstituted alkyl;

R^2 is substituted or unsubstituted alkyl;

R^3 , R^4 , R^5 , R^6 , and R^7 are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl; and

R^8 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

2. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is hydrogen or substituted or unsubstituted alkyl;

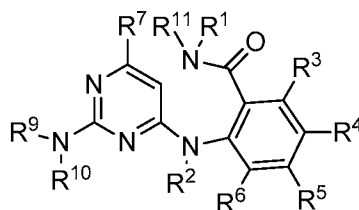
R^2 is substituted or unsubstituted alkyl;

R^3 , R^4 , R^5 , R^6 , and R^7 are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl,

substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl; and

R^9 and R^{10} are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

3. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 and R^{11} are each independently selected from hydrogen or substituted or unsubstituted alkyl;

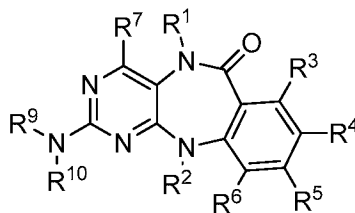
R^2 is substituted or unsubstituted alkyl;

R^3 , R^4 , R^5 , R^6 , and R^7 are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl; and

R^9 and R^{10} are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

4. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is hydrogen or substituted or unsubstituted alkyl;

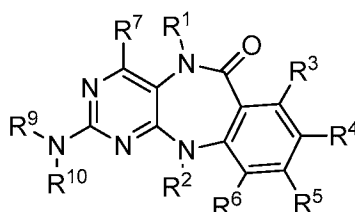
R^2 is substituted or unsubstituted alkyl;

R^3 , R^4 , R^5 , R^6 , and R^7 are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl; and

R^9 and R^{10} are each independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, or substituted or unsubstituted heteroalkynyl,

wherein R^9 and R^{10} combine to form a substituted or unsubstituted heterocycle or a substituted or unsubstituted heteroaryl.

5. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is hydrogen or substituted or unsubstituted alkyl;

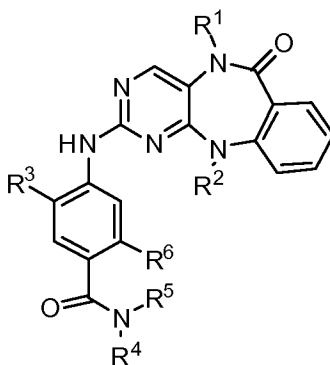
R^2 is substituted or unsubstituted alkyl;

R^3 , R^4 , R^5 , R^6 , and R^7 are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, trifluoromethyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted carbonyl, or substituted or unsubstituted carboxyl;

R^9 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, or substituted or unsubstituted heteroalkynyl; and

R^{10} is substituted alkyl.

6. A compound of the following structure:



or a pharmaceutically acceptable salt of prodrug thereof, wherein:

R^1 is hydrogen or substituted or unsubstituted alkyl;

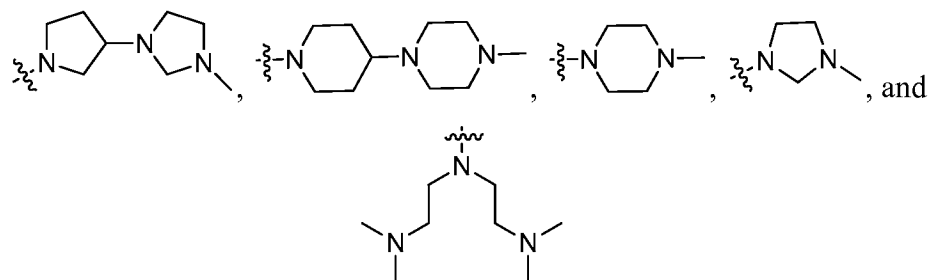
R^2 is substituted or unsubstituted alkyl;

R^3 and R^6 are each independently selected from halogen, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted amino, or nitro; and

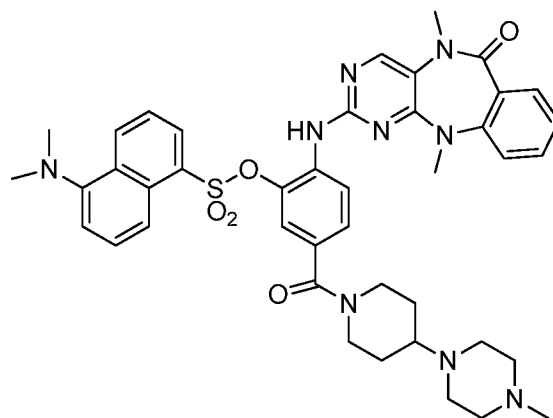
R^4 and R^5 are each independently selected from hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl, wherein R^4 and R^5 optionally combine to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl,

wherein at least one of R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 includes a radiolabel selected from the group consisting of ^{11}C and ^{18}F .

7. The compound of claim 6, wherein $-\text{NR}^4\text{R}^5$ is selected from the group consisting of:

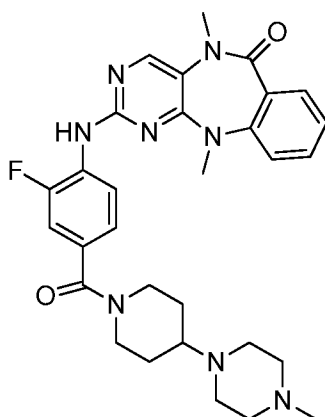


8. A compound of the following structure:



or a pharmaceutically acceptable salt or prodrug thereof.

9. A compound of the following structure:

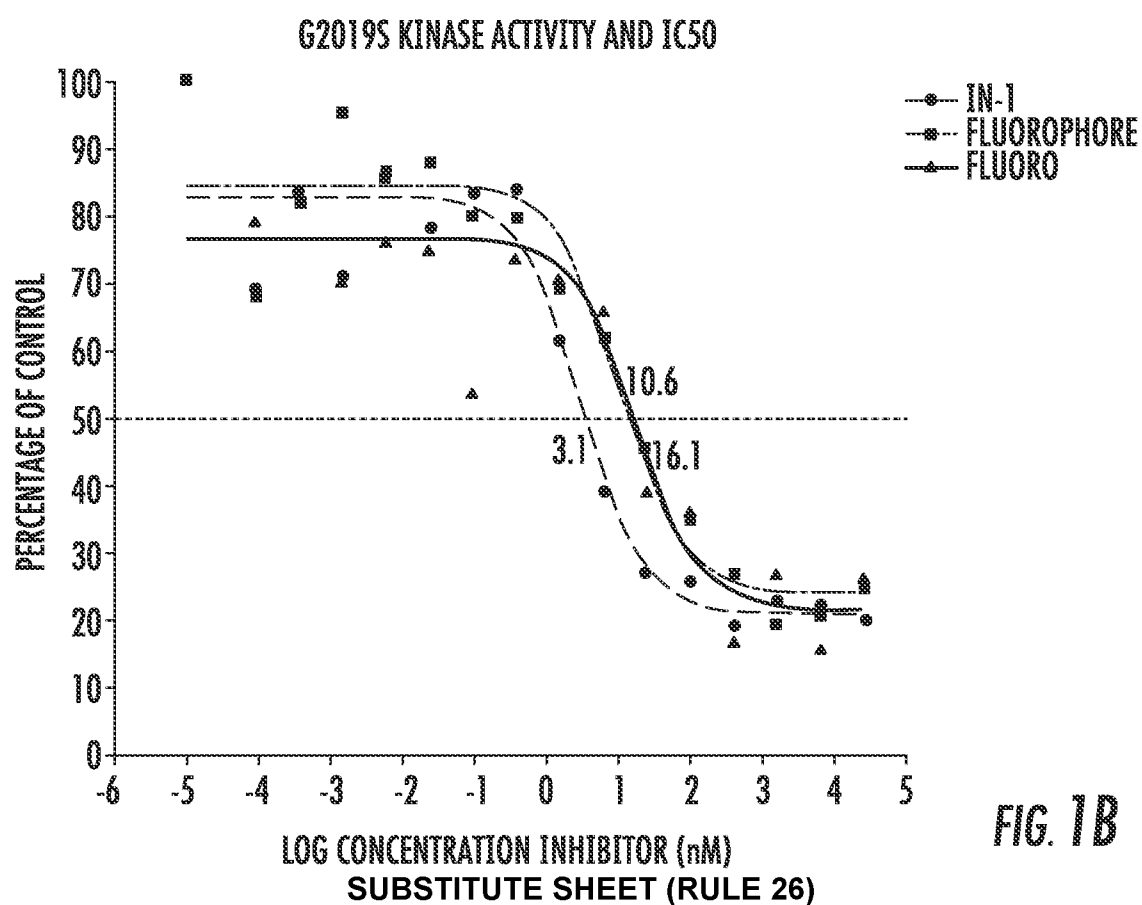
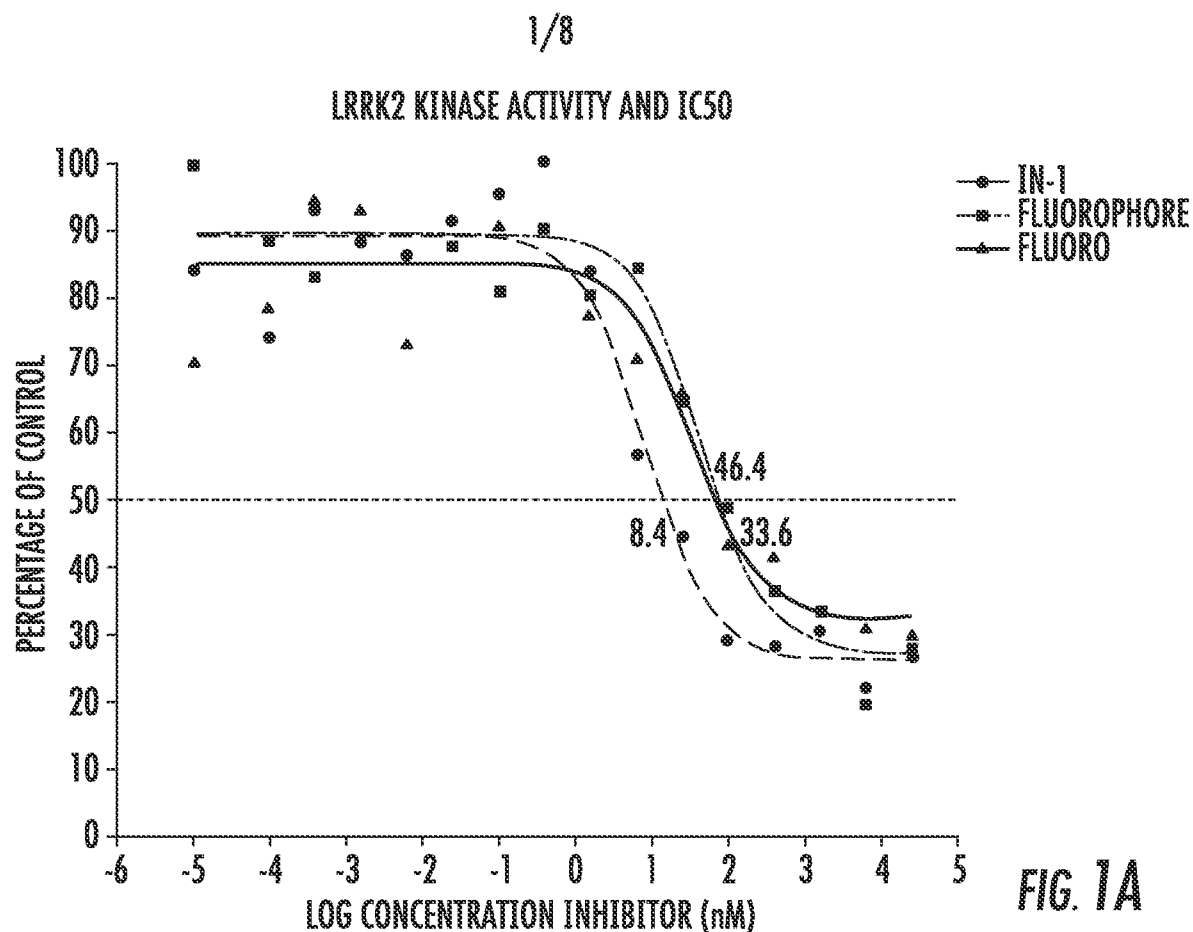


or a pharmaceutically acceptable salt or prodrug thereof.

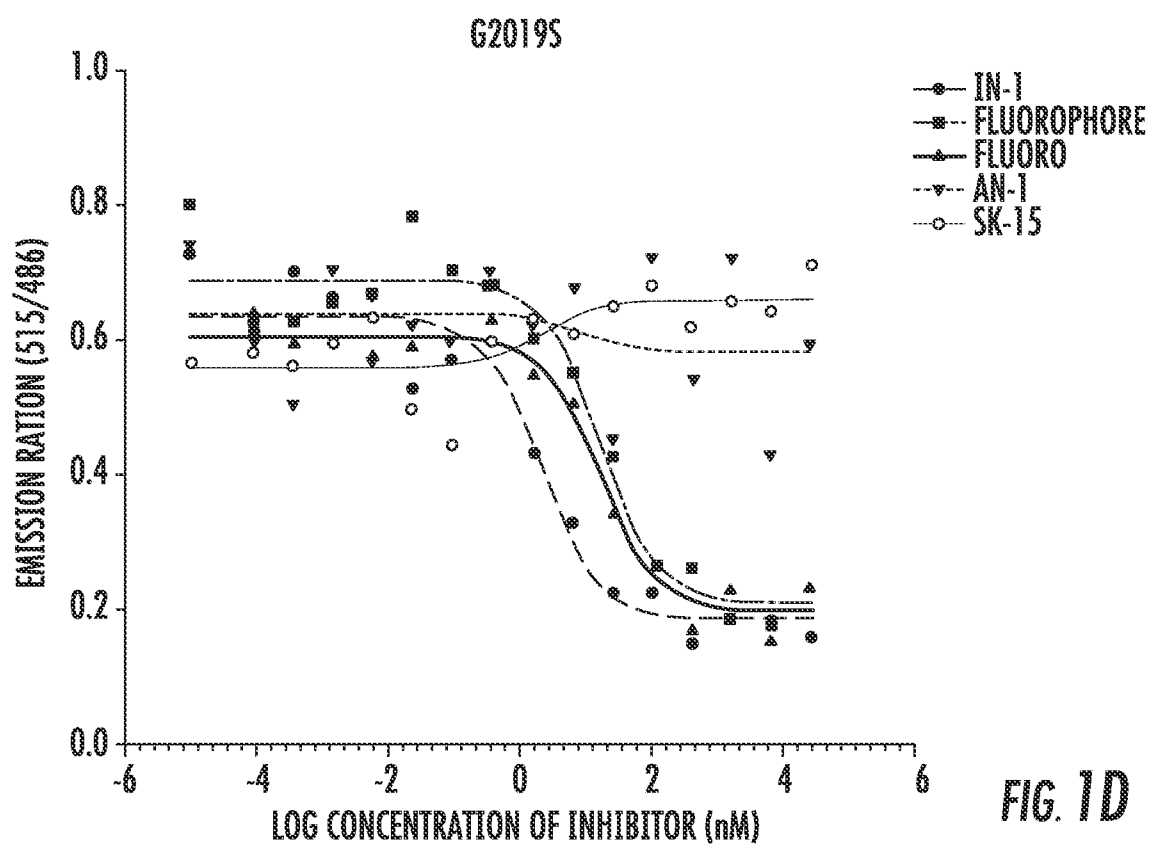
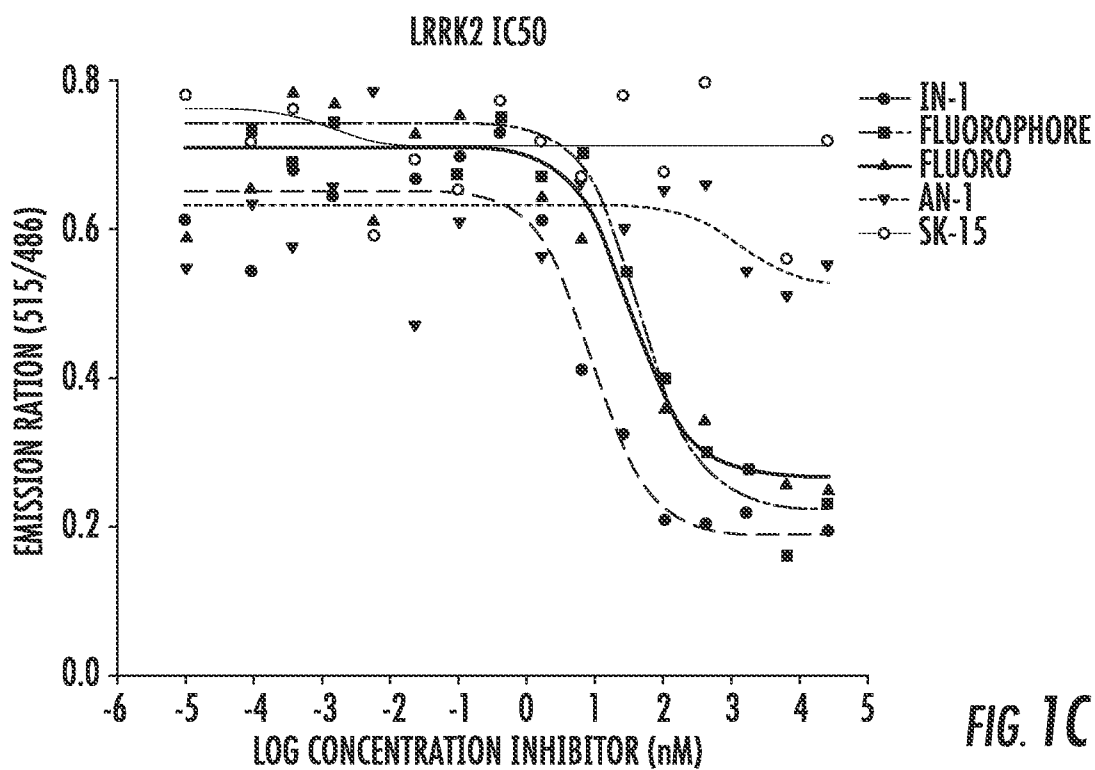
10. A composition comprising one or more of the compounds of claims 1-9 and a pharmaceutically acceptable carrier.
11. A method of treating or preventing a neurodegenerative disorder in a subject, comprising:
 - administering to the subject an effective amount of a composition according to claim 10.
12. The method of claim 11, wherein the neurodegenerative disorder is Parkinson's disease.
13. The method of claim 11 or 12, further comprising administering a second therapeutic agent to the subject.
14. The method of claim 13, wherein the second therapeutic agent is selected from the group consisting of levodopa, a dopamine agonist, an anticholinergic agent, a monoamine oxidase inhibitor, a COMT inhibitor, amantadine, rivastigmine, an NMDA antagonist, a cholinesterase inhibitor, riluzole, an anti-psychotic agent, an antidepressant, and tetrabenazine.
15. The method of any of claims 11-14, wherein the compound is administered systemically.
16. A method of inhibiting LRRK2 in a cell, comprising:
 - contacting a cell with an effective amount of a compound according to any of claims 1-9.
17. A method of modulating signaling in a cell as compared to a control, comprising:
 - contacting a cell with an effective amount of a compound according to any of claims 1-9.
18. The method of claim 17, wherein the method comprises reducing Akt phosphorylation in a cell.
19. The method of any of claims 16-18, wherein the cell is a neuron.

20. The method of any of claims 16-18, wherein the contacting is performed *in vivo*.
21. The method of any of claims 16-18, wherein the contacting is performed *in vitro*.
22. A method of imaging an LRRK2 positive cell or population of cells in a subject, comprising:
 - (a) administering to the subject a compound according to any of claims 1-9, wherein the compound further comprises a detectable label; and
 - (b) detecting the detectable label in the subject, wherein the detectable label indicates the LRRK2 positive cell or population of cells.
23. The method of claim 22, wherein the LRRK2 positive cell or population of cells is a neuron or neuronal population of cells.
24. The method of claim 22 or 23, wherein the detecting step comprises PET, SPECT, MRI, or X-ray.
25. The method of any of claims 22-24, wherein the detectable label is selected from the group consisting of a radiolabel, fluorescent label, enzymatic label, and biotin.
26. The method of any of claims 22-25, wherein the detectable label is a radiolabel.
27. The method of claim 26, wherein the radiolabel is selected from the group consisting of ^{11}C and ^{18}F .
28. A method of treating or preventing cancer in a subject, comprising:
 - administering to the subject an effective amount of a composition according to claim 10.
29. The method of claim 28, wherein the cancer is breast cancer.
30. The method of claim 28, wherein the cancer is prostate cancer.

31. The method of any of claims 28-30, further comprising administering a second therapeutic agent to the subject.
32. The method of claim 31, wherein the second therapeutic agent is a chemotherapeutic agent.
33. A method of inhibiting ERK5 in a cell, comprising:
contacting a cell with an effective amount of a compound according to any of claims 1-9.
34. The method of claim 33, wherein the contacting is performed *in vivo*.
35. The method of claim 33, wherein the contacting is performed *in vitro*.



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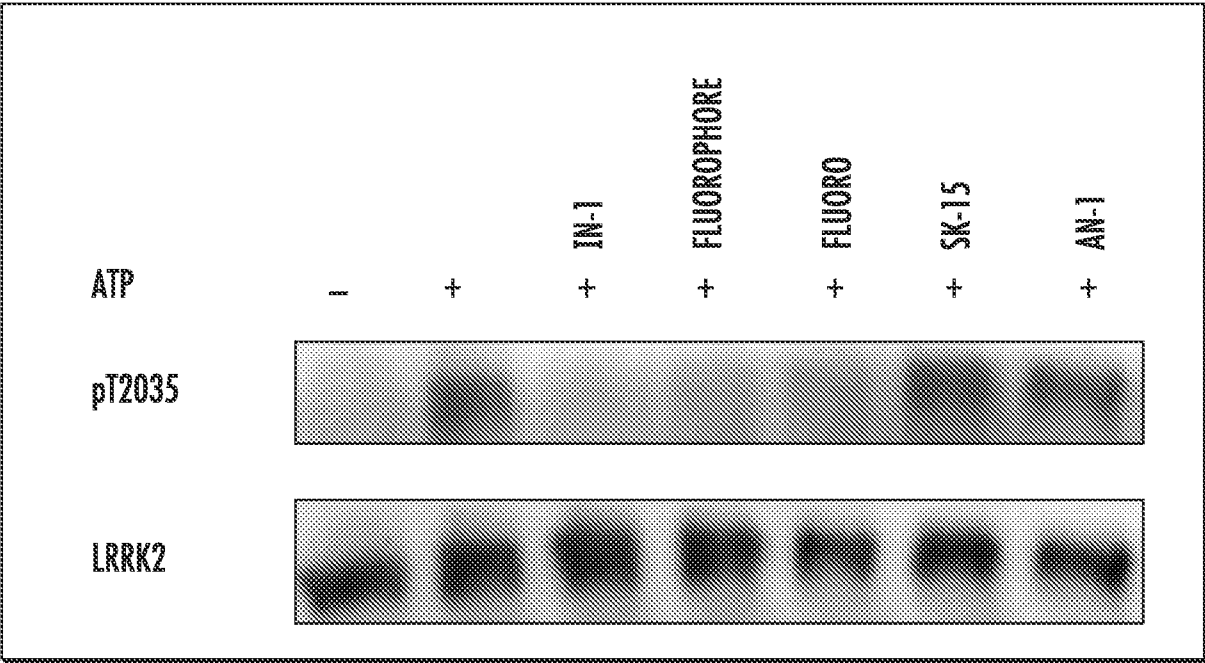
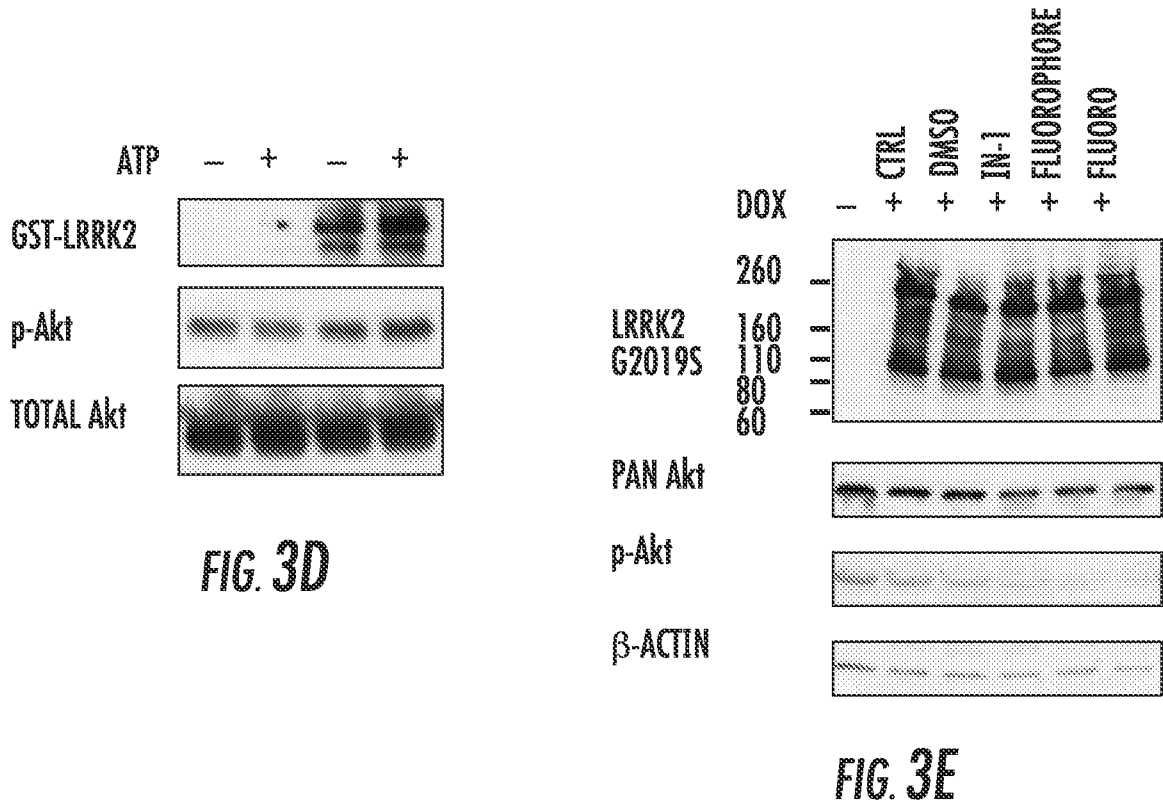
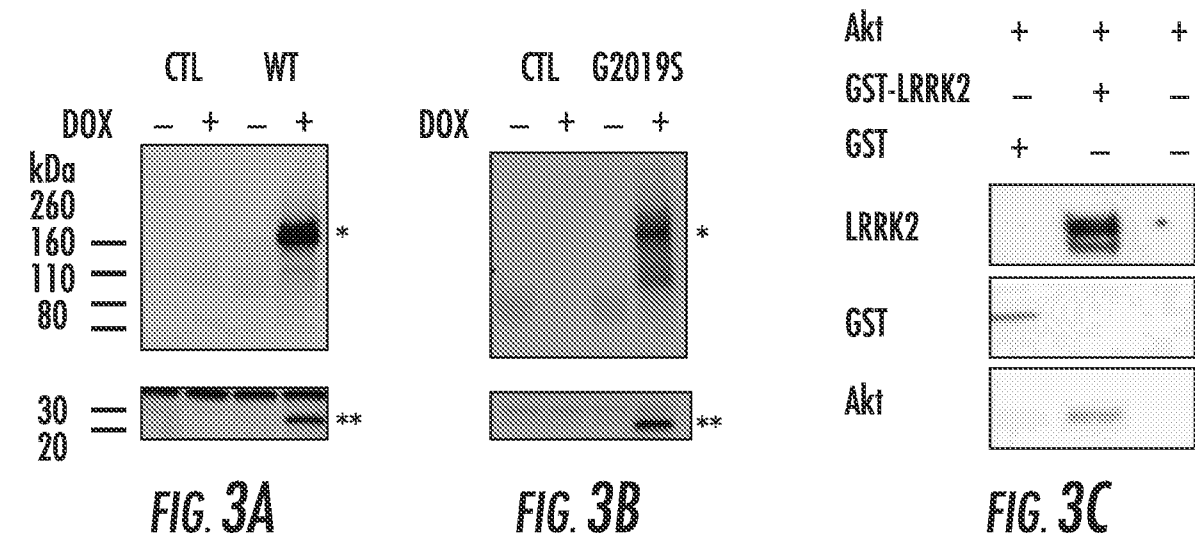


FIG. 2



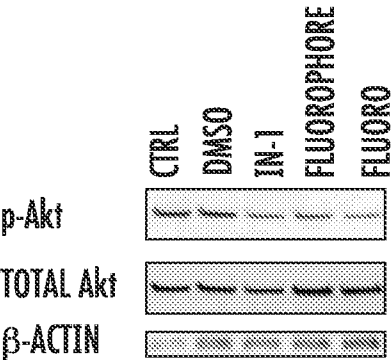


FIG. 4A

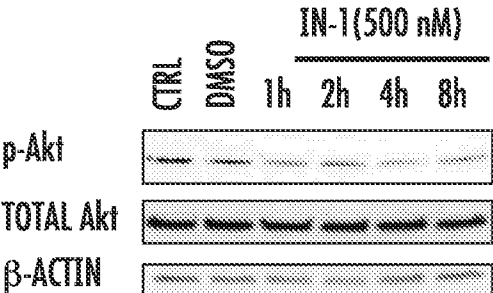


FIG. 4B

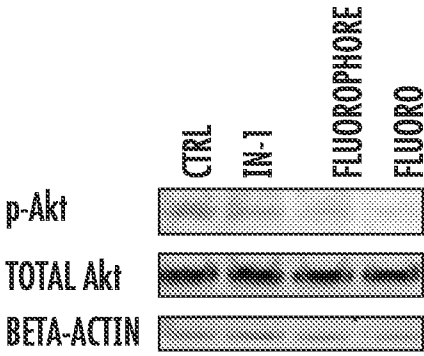


FIG. 4C

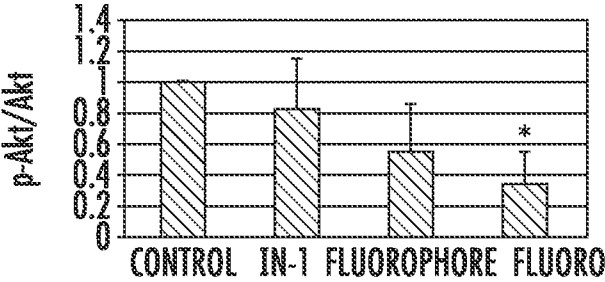


FIG. 4D

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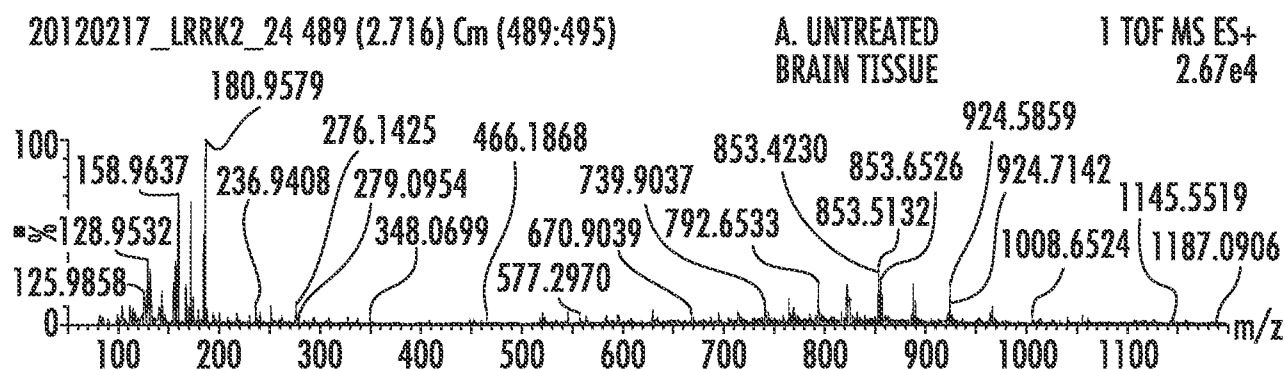


FIG. 5A

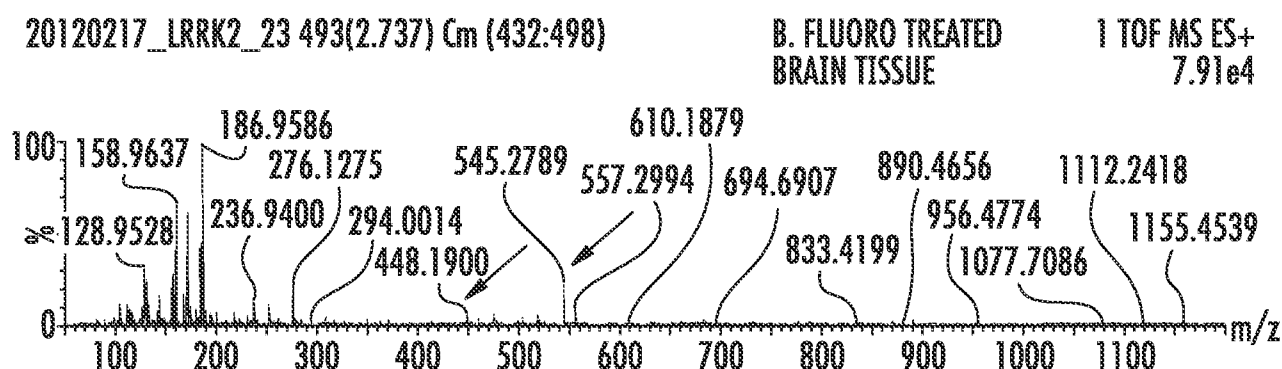


FIG. 5B

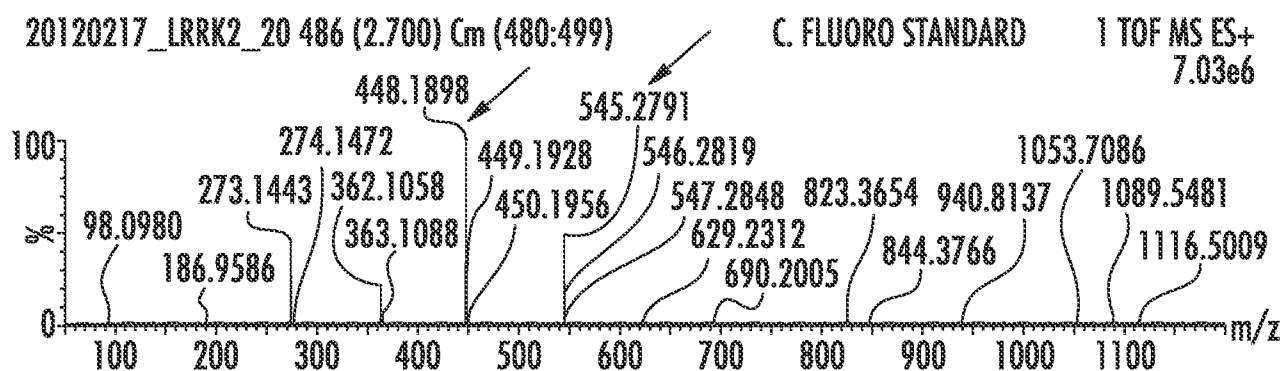


FIG. 5C

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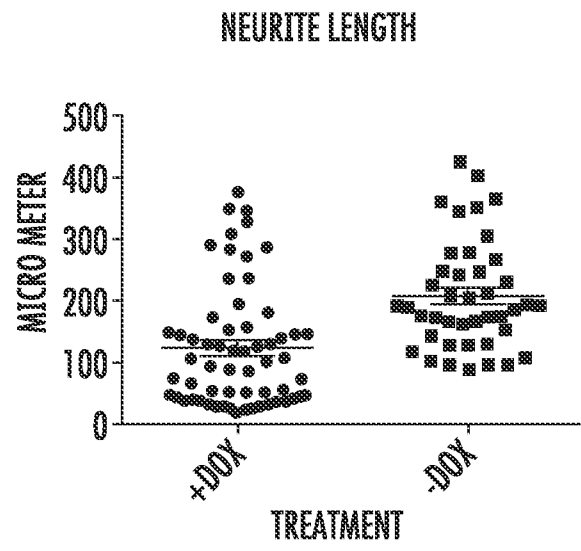


FIG. 6

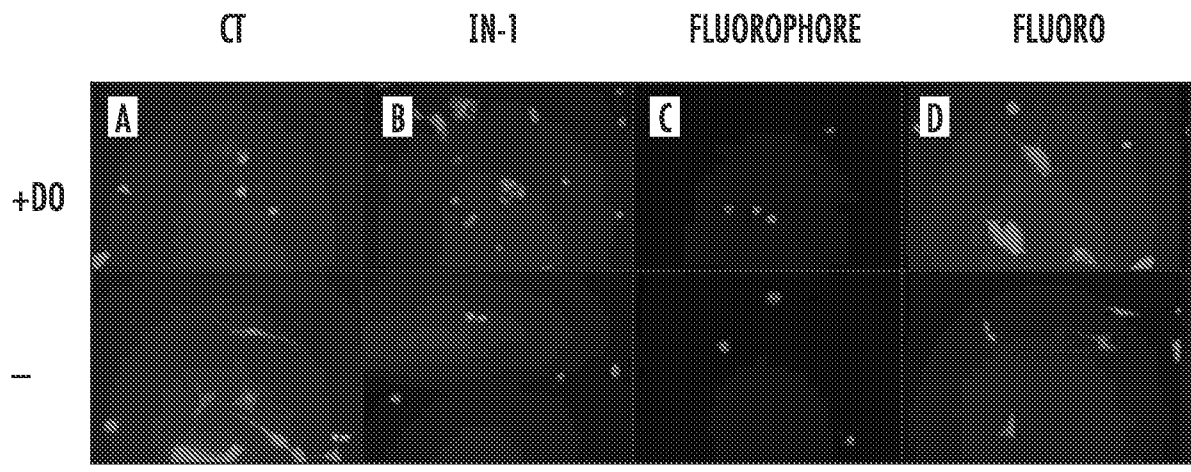


FIG. 7

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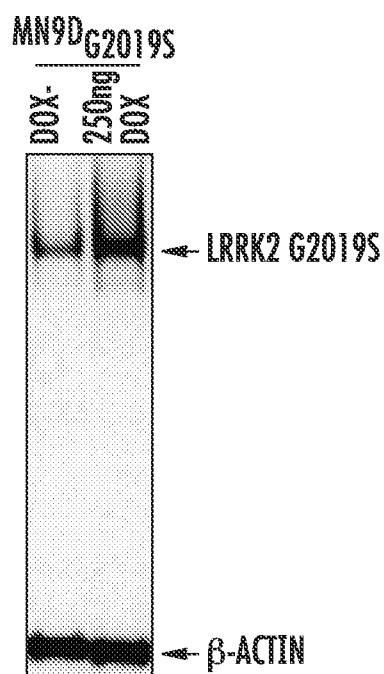


FIG. 8A

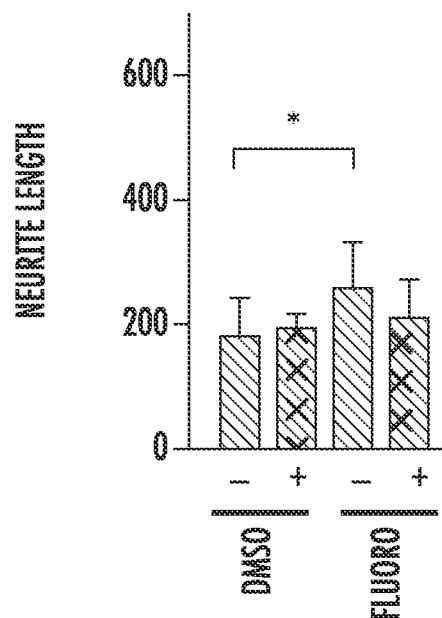


FIG. 8B

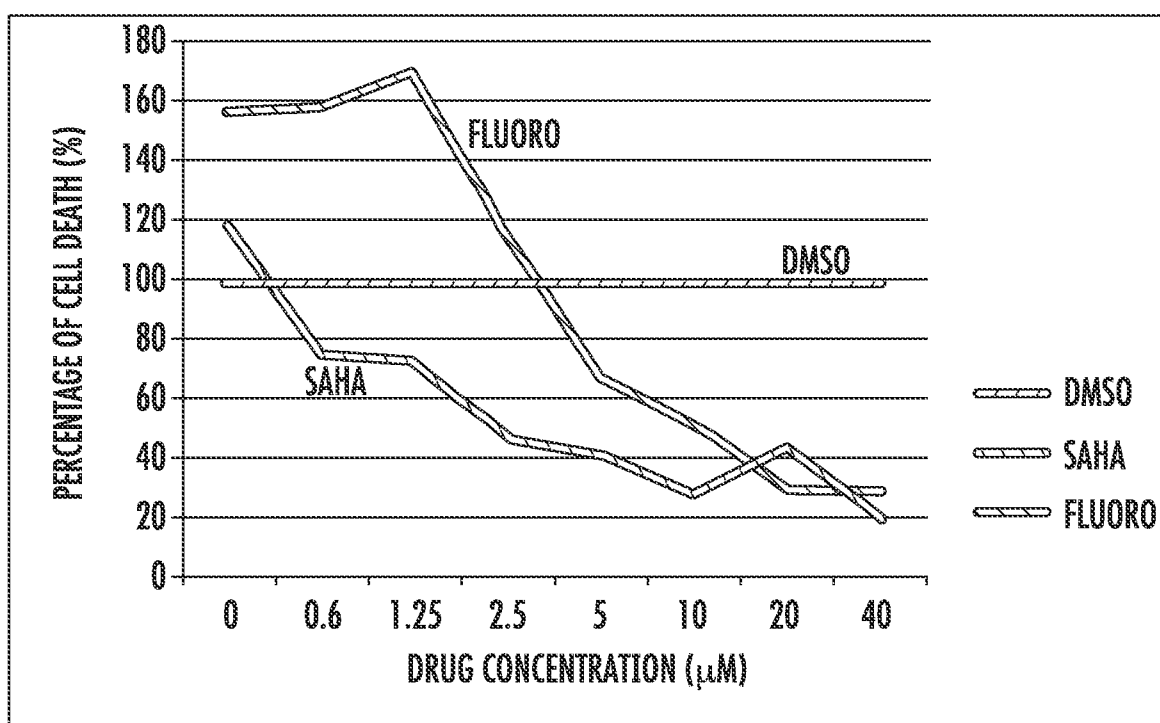


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/026583**A. CLASSIFICATION OF SUBJECT MATTER****C07D 487/04(2006.01)i, C07D 513/04(2006.01)i, C07D 403/14(2006.01)i, C07D 401/14(2006.01)i, C07D 403/04(2006.01)i, A61K 31/5517(2006.01)i, A61P 35/00(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 487/04; C07D 513/04; A61K 31/554; C07D 487/12; C07D 403/14; C07D 401/14; C07D 403/04; A61K 31/5517; A61P 35/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: LRRK2 and ERK5 inhibitors, cancer, neurodegenerative disorders

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 102690278 A (CHANGCHUN DISCOVERY SCIENCES, LTD.) 26 September 2012 See abstract, claims and the entire document.	1,6-10
A	WO 2010-080712 A2 (DANA FARBER CANCER INSTITUTE et al.) 15 July 2010 See abstract, claims and the entire document.	1,6-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 July 2014 (15.07.2014)

Date of mailing of the international search report

15 July 2014 (15.07.2014)

Name and mailing address of the ISA/KR

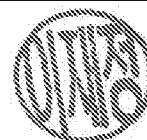
International Application Division
Korean Intellectual Property Office
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Republic of Korea

Facsimile No. +82-42-472-7140

Authorized officer

LEE, Jae Jeong

Telephone No. +82-42-481-3488



Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11-35
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 11-35 pertain to methods for treatment of the human body, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. ☒ Claims Nos.: 27
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 27 is a dependent claim of a multiple dependent claim.
3. ☒ Claims Nos.: 15, 19-21, 24-26
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- I. Claims 1, 6-9, 10(partial) directed to compounds and a composition represented by Formula I (see page 9 in description) and Formula VI (see page 14 in description).
- II. Claims 2, 10(partial) directed to compounds and a composition represented by Formula II (see page 10 in description).
- III. Claims 3, 10(partial) directed to compounds and a composition represented by Formula III (see page 11 in description).
- IV. Claims 4, 5, 10(partial) directed to compounds and a composition represented by Formula IV (see page 12-13 in description).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1, 6-9, 10(partial)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2014/026583

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN102690278 A	26/09/2012	None	
WO 2010-080712 A2	15/07/2010	CA 2748181 A1	15/07/2010
		EP 2379559 A2	26/10/2011
		EP 2379559 A4	16/05/2012
		JP 2012-514601 A	28/06/2012
		US 2012-0040961 A1	16/02/2012
		WO 2010-080712 A3	11/11/2010