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(54) Title: COMPOSITIONS AND METHODS USING THE SAME FOR TREATMENT OF NEURODEGENERATIVE AND MITOCHONDRIAL DISEASE

(57) Abstract: The present disclosure is directed, in part, to compounds, or pharmaceutically acceptable salts thereof, for the treatment and/or prevention of neurodegenerative disease, mitchonodrial disease, fibrosis, and/or cardiomyopathy.

COMPOSITIONS AND METHODS USING THE SAME FOR TREATMENT OF NEURODEGENERATIVE AND MITOCHONDRIAL DISEASE

Related Applications

[01] This application claims the benefit of priority to U.S. provisional application No. 62/522,840, filed June 21, 2017, the entire contents of which are incorporated herein.

Field Of The Disclosure

[02] The present disclosure is directed, in part, to compounds, or pharmaceutically acceptable salts thereof, for modulating the activity of PINK1 and/or methods for treating and /or preventing neurodegenerative disease, mitochondrial disease, fibrosis, and/or cardiomyopathy.

Background

[03] Studies have correlated mitochondrial function with the disease of cardiomyopathy and for neuron health and survival. Specifically, aberrant mitochondrial quality control has been demonstrated to be an important factor in the development of neurodegenerative diseases and cardiomyopathy. See e.g., Schapira, A.H. Mitochondrial disease. Lancet 379, 1825-1834, (2012) and Chen, Y. and Dorn, G. PINK1-Phosphorylated Mitofusin-2 Is a Parkin Receptor for Culling Damaged Mitochondria. Science 340, 471-475, (2013). The mitochondrial kinase PTEN Induced Kinase 1 (PINK1) plays an important role in the mitochondrial quality control processes by responding to damage at the level of individual mitochondria. The PINK1 pathway has also been linked to the induction of mitochondrial biogenesis, and, critically, the reduction of mitochondrially induced apoptosis.See e.g., Narendra, D. P. et al. PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. PLoS Biol 8, e1000298 (2010), Wang, X., (2011). et al. PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. Cell 147, 893-906, (2011), and Shin, J. H. et al. PARIS (ZNF746) repression of PGC-1alpha contributes to neurodegeneration in Parkinson's disease. Cell 144, 689-702, (2011).

[04] Parkinson's Disease (PD) is one of the most common neurodegenerative disorders, however no disease modifying therapies are currently approved to treat PD. Both environmental and genetic factors lead to progressive apoptosis of dopaminergic neurons, lowered dopamine levels and ultimately PD. PINK1 kinase activity appears to mediate its neuroprotective activity. The regulation of mitochondrial movement, distribution and

clearance is a key part of neuronal oxidative stress response. Disruptions to these regulatory pathways have been shown to contribute to chronic neurodegenerative disease. See Schapira and Chen cited above.

[05] Cardiomyopathy refers to a disease of cardiac muscle tissue, and it is estimated that cardiomyopathy accounts for 5–10% of the 5–6 million patients already diagnosed with heart failure in the United States. Based on etiology and pathophysiology, the World Health Organization created a classification of cardiomyopathy types which includes dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and unclassified cardiomyopathy. See e.g., Richardson P, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. Circulation 1996; 93:841. PINK1 kinase activity appears to mediate its cardioprotective activity. The regulation of mitochondrial movement, distribution and clearance is a part of cardiac cell oxidative stress response. Disruptions to these regulatory pathways have been shown to contribute to cardiomyopathy. See Schapira and Chen cited above.

[06] Neural pathologies frequently result from dysfunctional mitochondria, and Leigh syndrome (LS) is a common clinical phenotype (1). LS, or subacute necrotizing encephalopathy, is a progressive neurodegenerative disorder (2) affecting 1 in 40,000 live births (3). LS is regarded as the most common infantile mitochondrial disorder, and most patients exhibit symptoms before 1 mo of age. See e.g., Wang, X., (2011) et al. PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility Cell 147, 893-906, (2011) and Richardson P, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. Circulation 1996; 93:841. Several cases of adult-onset LS have also been reported recently. See e.g., Longo, D, et al. Harrison's Internal Medicine. 18th ed. (online), Ch. 238 (2011), Petit, A. et al. Wild-type PINK1 prevents basal and induced neuronal apoptosis, a protective effect abrogated by Parkinson disease-related mutations. J Biol Chem 280, 34025-34032 (2005), Koh, H. & Chung, J. PINK1 as a molecular checkpoint in the maintenance of mitochondrial function and integrity, Mol Cells 34, 7-13, (2012), Martins-Branco, D. et al. Ubiquitin proteasome system in Parkinson's disease: a keeper or a witness? Exp Neurol 238, 89-99, (2012), and Geisler, S. et al. The PINK1/Parkin-mediated mitophagy is compromised by PD-associated mutations. Autophagy 6, 871-878, (2010). In vivo imaging techniques such as MRI reveal bilateral hyperintense lesions in the basal ganglia, thalamus, substantia nigra, brainstem, cerebellar white matter and

cortex, cerebral white matter, or spinal cord of LS patients. See e.g., Longo cited above and Shin, J. H. et al. PARIS (ZNF746) repression of PGC-1alpha contributes to neurodegeneration in Parkinson's disease. Cell 144, 689-702, (2011), Henchcliffe, C. & Beal, M. F. Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. Nat Clin Pract Neurol 4, 600-609 (2008), Pridgeon, J. W., Olzmann, J. A., Chin, L. S. & Li, L. PINK1 Protects against Oxidative Stress by Phosphorylating Mitochondrial Chaperone TRAP1. PLoS Biol 5, e172 (2007), and Haque, M. E. et al. Cytoplasmic Pink1 activity protects neurons from dopaminergic neurotoxin MPTP. Proc Natl Acad Sci U S A 105, 1716-1721 (2008). The lesions usually correlate with gliosis, demyelination, capillary proliferation, and/or necrosis See Geisler, S. et al. The PINK1/Parkin-mediated mitophagy is compromised by PD-associated mutations. Autophagy 6, 871-878, (2010) and Gautier, C. A., Kitada, T. & Shen, J. Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. Proc Natl Acad Sci U S A 105, 11364-11369 (2008). Behavioral symptoms of LS patients can include (with a wide variety of clinical presentation) developmental retardation, hypotonia, ataxia, spasticity, dystonia, weakness, optic atrophy, defects in eye or eyelid movement, hearing impairment, breathing abnormalities, dysarthria, swallowing difficulties, failure to thrive, and gastrointestinal problems. See e.g., Wang and Richardson cited above, and Samaranch, L. et al. PINK1-linked parkinsonism is associated with Lewy body pathology. Brain 133, 1128-1142, (2010) and Merrick, K. A. et al. Switching Cdk2 on or off with small molecules to reveal requirements in human cell proliferation. Mol Cell 42, 624-636, (2011). The cause of death in most LS cases is unclear, and the lack of a genetic model to study the disease progression and cause of death has impeded the development of adequate treatment. Prognosis for LS (and most diseases resulting from mitochondrial dysfunction) is very poor; there is no cure and treatment is often ineffective.

Summary

[07] Previously, we disclosed effective modulators of PINK1 and their implications in the treatment of related conditions such as neurodegenerative disease, mitochondrial disease, fibrosis, and cardiomyopathy. See e.g., WO 2015/123365 and WO 2014/124458, both incorporated herein by reference. Here, it has now been found that substitution of both R_3 and R_5 with alkyl groups (e.g., methyl groups) leads to a substantial increase in potency. See e.g., **Fig. 5**, where a direct comparison is made between compounds bearing methyl substitutions at R_3 and R_5 and those which do not. For example, the only difference between MTX-115D

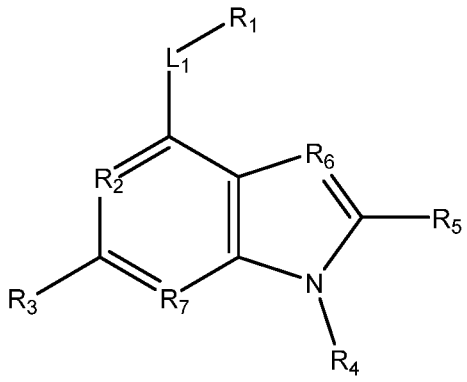
and MTX-63H is the replacement of hydrogen for methyl at R^3. Yet, this addition led to almost a 40% increase in activity. A similar trend is seen for MTK-115 when compared with the mono-methyl MTK-54 and hydrogen bearing kinetin analogues. See **Fig. 5**.

[08] Improvements in toxicity were also identified using the inventive compounds. **Fig. 6**, for example, shows a substantial decrease in toxicity between the R^3/R^5 methyl substituted MTK-115 and mono-substituted MTK-64 derivative.

[09] Improvements in oral PK were also found as the corresponding R^3/R^5 methyl substituted MTK-115A analogue of MTK-63A provided a substantial increase in AUC. See e.g., **Fig. 7**.

[010] Improvements in brain plasma indicating blood brain barrier crossover was seen when inventive compounds were used instead of the R^3/R^5 substituted counterparts. See e.g., **Fig. 8**. Further improvements are disclosed below.

[011] In some embodiments, the present disclosure provides a compound having Formula VIII:



VIII

or pharmaceutically acceptable salt thereof, wherein

L_1 is selected from the group consisting of: a bond, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon; an amine, an aminohydrocarbon, an aminoalkyl, an aminoalkene, and $–NH-CH_2-$;

R_7 is selected from the group consisting of: a saturated or unsaturated C or N, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon, and a substituted or unsubstituted aminohydrocarbon;

R_1 is selected from the group consisting of: a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a

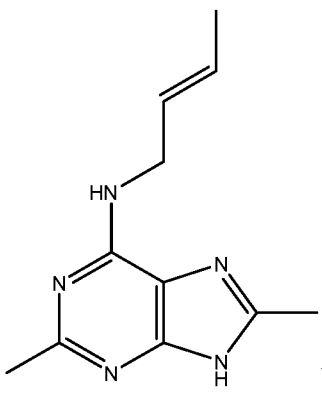
substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted alkene, a substituted or unsubstituted heteroalkene, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl;

R_2 and R_6 are independently selected from the group consisting of: a substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, -CH-, O, S and N;

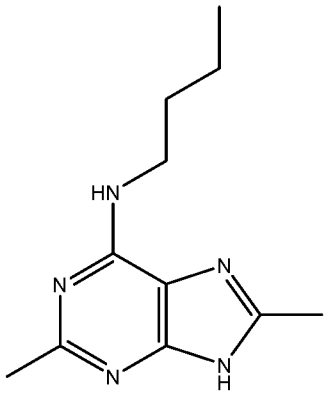
R_4 is selected from the group consisting of a hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkyne, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkyne, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl; and

R_3 and R_5 are independently selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl.

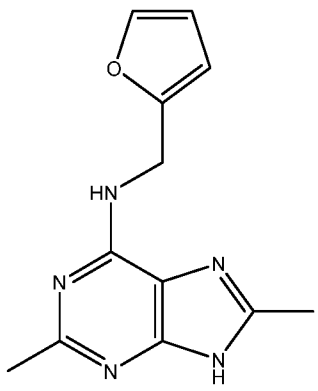
[012] In some embodiments, the composition comprises at least one or a combination of the compounds, or their respective pharmaceutically acceptable salts thereof, chosen from:

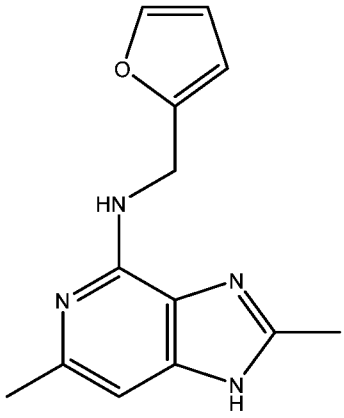
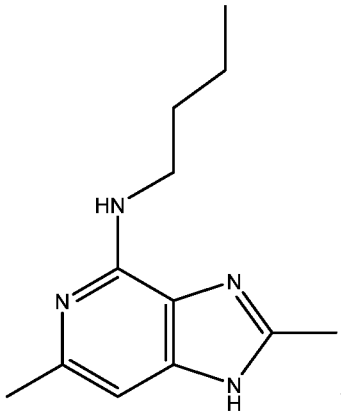


VIIIa,



VIIIb,



VIIIc,  , and  VIIId.

[013] In some embodiments, a composition comprising a compound or pharmaceutically acceptable salt thereof that is described herein, or an isomer thereof, is provided. In some embodiments, the compositions disclosed herein comprise one or more active agents other than the compound having Formula VIII.

[014] In some embodiments, a pharmaceutical composition comprising a compound that is described herein, a pharmaceutically acceptable salt thereof, or an isomer thereof, is provided along with a pharmaceutically acceptable carrier.

[015] In some embodiments, a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof that is described herein is provided wherein one or more of the compounds disclosed herein is excluded. In some embodiments, a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof that is described herein is provided wherein compounds of Formula VIII as disclosed herein are excluded.

[016] In some embodiments, the disclosure relates to methods of treating and/or preventing neurodegenerative disease, mitochondrial disease, fibrosis, and/or cardiomyopathy in a subject in need thereof comprising administering to the subject one or more compounds, or a pharmaceutically acceptable salt thereof described herein or a pharmaceutical composition comprising one or more compounds described herein, or pharmaceutically acceptable salt thereof.

[017] In some embodiments, a method of treating and/or preventing Parkinson's disease with a compound described herein or salt thereof is provided. In some embodiments, a method of preventing early onset of Parkinson's disease with a compound described herein or salt thereof is provided. In some embodiments, a method of reducing the number or severity of symptoms of Parkinson's disease with a compound described herein or salt thereof is provided.

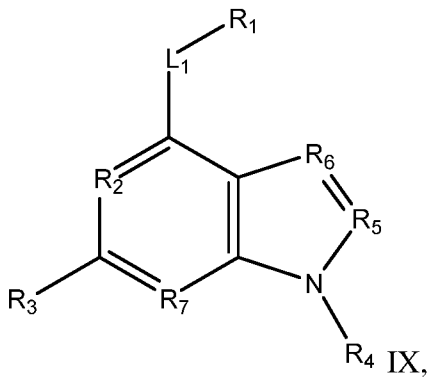
[018] In some embodiments, a method of treating and/or preventing mitochondrial disease with a compound described herein or salt thereof is provided. In some embodiments, a method of preventing early onset of mitochondrial disease with a compound described herein or salt thereof is provided. In some embodiments, a method of reducing the number or severity of symptoms of mitochondrial disease with a compound described herein or salt thereof is provided.

[019] In some embodiments, a method of treating and/or preventing Leigh's Disease with a compound described herein or salt thereof is provided. In some embodiments, a method of preventing early onset of Leigh's Disease with a compound described herein or salt thereof is provided. In some embodiments, a method of reducing the number or severity of symptoms of Leigh's Disease with a compound described herein or salt thereof is provided.

[020] In some embodiments, a method of treating and/or preventing cardiomyopathy with a compound described herein or salt thereof is provided. In some embodiments, a method of preventing early onset of cardiomyopathy with a compound described herein or salt thereof is provided. In some embodiments, a method of reducing the number or severity of symptoms of cardiomyopathy with a compound described herein or salt thereof is provided.

[021] In some embodiments, a method of treating and/or preventing Chronic Kidney Disease with a compound described herein or salt thereof is provided. In some embodiments, a method of treating and/or preventing renal fibrosis with a compound described herein or salt thereof is provided. In some embodiments, a method of treating and/or preventing fatty liver diseases (e.g., non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, etc.) with a compound described herein or salt thereof is provided. In some embodiments, a method of treating and/or preventing Duchenne's Muscular Dystrophy with a compound described herein or salt thereof is provided. In some embodiments, a method of treating and/or preventing reperfusion injury (including post infarction, stroke, etc) with a compound described herein or salt thereof is provided.

[022] In some embodiments, a method of treating and/or preventing fibrosis with a compound described herein or salt thereof is provided. In some embodiments, a method of preventing early onset of fibrosis with a compound described herein or salt thereof is provided. In some embodiments, a method of reducing the number or severity of symptoms of fibrosis with a compound described herein or salt thereof is provided. In some embodiments, the compound to treat and/or prevent fibrosis has the following formula:



IX,

or pharmaceutically acceptable salt thereof, wherein

L_1 is selected from the group consisting of: a bond, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon; an amine, an aminohydrocarbon, an aminoalkyl, an aminoalkene, and –NH-CH_2-;

R_7 is selected from the group consisting of: a saturated or unsaturated C or N, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon, and a substituted or unsubstituted aminohydrocarbon;

R_1 is selected from the group consisting of: a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted alkene, a substituted or unsubstituted heteroalkene, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl;

R_2 and R_6 are independently selected from the group consisting of: a substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, -CH-, O, S and N;

R_4 is selected from the group consisting of a hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkyne, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkyne, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl; and

R_3 and R_5 are independently selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted alkene, a substituted or unsubstituted heteroalkene, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a

substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl; or a pharmaceutically acceptable salt thereof.

[023] Methods of making a compound or composition described herein are also provided.

[024] The dislcosure also relates to methods of increasing the level of activity of PINK1 in a cell by contacting the cell with a neo-substrate of PINK1, wherein the neo-substrate of PINK1 is a compound of any of the disclosed compounds herein. In some embodiments, the cell is a cell of a subject. In some embodiments, the step of contacting is performed *in vivo* or within the subject. In some embodiments, the step of contacting is performed *in vitro* or outside of the body of a subject.

Brief Description Of The Drawings

[025] **Fig. 1** is a graph showing results from the viral model of Idiopathic Pulmonary Fibrosis. Whole lung samples were assayed via Quantitative PCR to determine transcription levels of fibrosis-associated genes TGF-beta, TNF-alpha, collagen 1, and Fibronectin.

[026] **Fig. 2** is a graph showing results from the viral model of Idiopathic Pulmonary Fibrosis. After sacrifice, lung and spleen were removed from animals and samples assayed for viral load markers.

[027] **Fig. 3** is a graph showing results from the viral model of Idiopathic Pulmonary Fibrosis. Bronchoalveolar lavage was performed and macrophage, neutrophil, and lymphocyte cell counts assayed.

[028] **Fig. 4** is a graph quantifying results from the western blot of mutant Huntington phosphorylation at serine 16. Cells were treated with DMSO, experimental compound (concentrations shown in uM), kinetin, or ketoprofen for 12 hrs then lysed and analyzed for combined serine 13 + serine 16 phosphorylation on the huntingtin protein via western blot.

[029] **Fig. 5** illustrates the differences in mitophagy activity between inventive compounds having methyl substitutions at both R^3 and R^5 and direct comparators which do not.

[030] **Fig. 6** illustrates the toxicity differences at 50 μM between inventive compounds having methyl substitutions at both R^3 and R^5 and direct comparators which do not.

[031] **Fig. 7** illustrates the oral PK differences at 5 mg/kg between inventive compounds having methyl substitutions at both R^3 and R^5 and direct comparators which do not.

[032] **Fig. 8** illustrates the plamsa concentration in the brain between inventive compounds having methyl substitutions at both R^3 and R^5 and direct comparators which do not.

Description Of Embodiments

[033] Unless defined otherwise, all technical and scientific terms have the same meaning as is commonly understood by one of ordinary skill in the art to which the embodiments disclosed belongs.

[034] As used herein, the terms “a” or “an” means that “at least one” or “one or more” unless the context clearly indicates otherwise. The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified unless clearly indicated to the contrary. Thus, as a non-limiting example, a reference to "A and/or B," when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A without B (optionally including elements other than B); in another embodiment, to B without A (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

[035] The term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e. "one or the other but not both") when preceded by terms of exclusivity, "either," "one of," "only one of," or "exactly one of."

[036] As used herein, the terms "comprising" (and any form of comprising, such as "comprise", "comprises", and "comprised"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include"), or "containing" (and any form of containing, such as "contains" and "contain"), are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

[037] As used herein, the term “about” means that the numerical value is approximate and small variations would not significantly affect the practice of the disclosed embodiments. Where a numerical limitation is used, unless indicated otherwise by the context, “about” means the numerical value can vary by ±10% and remain within the scope of the disclosed embodiments.

[038] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[039] Where substituent groups are specified by their conventional chemical formulae,

written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[040] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). Alkyl is not cyclized. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds (e.g. alkene, alkyne). Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-). Alkenes are aliphatic unsaturated hydrocarbons of the type C_nH_{2n}. As used herein, "alkenes" is to be understood to include substituted alkenes. Wherever "alkene" is used herein, it is to be understood that the "compound contains one or more carbon-carbon double bonds," or the equivalent, which can be substituted with O, N, S, P, and many other groups.

[041] The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present disclosure. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[042] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. In one aspect, a "heteroalkyl" includes at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, and S, without quaternization. Heteroalkyl is not cyclized. The heteroatom(s) O, N, P, S, and Si may be placed at any interior position of the heteroalkyl group or at the position at

which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $–CH_2-O-Si(CH_3)_3$.

[043] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R'', -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R'' or the like, it will be understood that the terms heteroalkyl and -NR'R'' are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R'' or the like.

[044] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Cycloalkyl and heterocycloalkyl are non-aromatic. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

[045] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[046] The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[047] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and

heteroaryl, respectively. Non-limiting examples of heteroaryl groups include pyridinyl, pyrimidinyl, thiophenyl, thienyl, furanyl, indolyl, benzoxadiazolyl, benzodioxolyl, benzodioxanyl, thianaphthanyl, pyrrolopyridinyl, indazolyl, quinolinyl, quinoxalinyl, pyridopyrazinyl, quinazolinonyl, benzoisoxazolyl, imidazopyridinyl, benzofuranyl, benzothienyl, benzothiophenyl, phenyl, naphthyl, biphenyl, pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, furylthienyl, pyridyl, pyrimidyl, benzothiazolyl, purinyl, benzimidazolyl, isoquinolyl, thiadiazolyl, oxadiazolyl, pyrrolyl, diazolyl, triazolyl, tetrazolyl, benzothiadiazolyl, isothiazolyl, pyrazolopyrimidinyl, pyrrolopyrimidinyl, benzotriazolyl, benzoxazolyl, or quinolyl. The examples above may be substituted or unsubstituted and divalent radicals of each heteroaryl example above are non-limiting examples of heteroarylene.

[048] A "furan group," as used herein, is any five-membered saturated or unsaturated ring with one oxygen atom and four carbon atoms that may each individually be substituted or unsubstituted. Non-limiting examples of furan groups are 2-furyl, 3-furyl, furanyl, furfural, furanose, benzofuranyl, furylthienyl, tetrahydrofuranyl, and 2,5-dihydrofuranyl.

[049] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[050] Each of the above terms (e.g., "alkyl," "heteroalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[051] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -NR'NR"R"', -ONR'R", -NR'C=(O)NR"NR"'R"", -CN, -NO_2, monophosphate (or derivatives thereof), diphosphate (or derivatives thereof), triphosphate (or derivatives thereof), in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R"', and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl

groups. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[052] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, -SiR'R"R'", -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", $-NR"C(O)_2R'$, -NR-C(NR'R"R'")=NR"", -NR-C(NR'R")=NR'", $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, -NR'NR"R'", -ONR'R", -NR'C=(O)NR"NR'"R"", -CN, $-NO_2$, -R', $-N_3$, $-CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, monophosphate (or derivatives thereof), diphosphate (or derivatives thereof), triphosphate (or derivatives thereof), in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R'", and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" groups when more than one of these groups is present.

[053] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In embodiments, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[054] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-(CRR')q-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH_2)r-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, -$S(O)_2$-, -$S(O)_2$NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CRR')s-X'- (C"R"R'")d-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R", and R'" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[055] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include, oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[056] A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_2Cl, -SO_3H, -SO_4H, -SO_2NH_2, -$NHNH_2$, -ONH_2, -NHC=(O)$NHNH_2$, -NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, -$NHSO_2CH_3$, -N_3, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, monophosphate (or derivatives thereof), diphosphate (or derivatives thereof), or triphosphate (or derivatives thereof), and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, monophosphate (or derivatives thereof), diphosphate (or derivatives thereof), or triphosphate (or derivatives thereof), substituted with at least one substituent selected from:

(i) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_2Cl, -SO_3H, -SO_4H, -SO_2NH_2, -$NHNH_2$, -ONH_2, -NHC=(O)$NHNH_2$, -NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, -$NHSO_2CH_3$, -N_3, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, monophosphate (or derivatives thereof), diphosphate (or derivatives thereof), or triphosphate (or derivatives thereof), and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, monophosphate (or derivatives thereof), diphosphate (or derivatives thereof), or triphosphate (or derivatives thereof), substituted with at least one substituent selected from:

(a) oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)\ NH_2$, $-NHSO_2H$, $-NHC{=}\ (O)H$, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, $-NHSO_2CH_3$, $-N_3$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, monophosphate (or derivatives thereof), diphosphate (or derivatives thereof), or triphosphate (or derivatives thereof), and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, monophosphate (or derivatives thereof), diphosphate (or derivatives thereof), or triphosphate (or derivatives thereof), substituted with at least one substituent selected from: oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)\ NH_2$, $-NHSO_2H$, $-NHC{=}\ (O)H$, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, $-NHSO_2CH_3$, $-N_3$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, monophosphate (or derivatives thereof), diphosphate (or derivatives thereof), and triphosphate (or derivatives thereof).

[057] A "size-limited substituent" or " size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[058] A "lower substituent" or " lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a

substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[059] In embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

[060] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_{20} alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[061] In embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered

heteroaryl. In embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_8 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In embodiments, the compound is a chemical species set forth in the Examples section below.

[062] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, e.g., Berge et al., Journal of Pharmaceutical Science 66:1-19 (1977)). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. Other pharmaceutically acceptable carriers known to those of skill in the art are suitable for the present disclosure. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. In other cases, the preparation may be a

lyophilized powder in 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

[063] Thus, the compounds of the present disclosure may exist as salts, such as with pharmaceutically acceptable acids. The present disclosure includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

[064] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[065] In addition to salt forms, the present disclosure provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present disclosure. Additionally, prodrugs can be converted to the compounds of the present disclosure by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present disclosure when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. In embodiments, the prodrug form may include a phosphate derivative or a sugar (e.g. ribose) derivative. For example prodrugs moieties used in HCV nucleoside and nucleotide prodrugs may be added to the compounds described herein or the compounds used in methods described herein. In embodiments, prodrug moieties described in Murakami et al. J. Med Chem., 2011, 54, 5902; Sofia et al., J. Med Chem. 2010, 53, 7202; Lam et al. ACC, 2010, 54, 3187; Chang et al., ACS Med Chem Lett., 2011, 2, 130; Furman et al., Antiviral Res., 2011, 91, 120; Vernachio et al., ACC, 2011, 55, 1843; Zhou et al, AAC, 2011, 44, 76; Reddy et al., BMCL, 2010, 20, 7376; Lam et al., J. Virol., 2011, 85, 12334; Sofia et al., J. Med. Chem., 2012, 55, 2481, Hecker et al., J. Med. Chem., 2008, 51, 2328; or Rautio et al., Nature Rev. Drug. Discov., 2008, 7, 255, all of which are incorporated herein by reference in their entirety for all purposes, may be added to compounds described herein or used in methods described herein.

[066] As used herein, the term "salt" refers to acid or base salts of the compounds used in the methods of the present disclosure. Illustrative examples of acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid

(acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts.

[067] When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, unless specified otherwise, the compounds include one or geometric isomer, e.g., E and/or Z.

[068] Certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure.

[069] The symbol "-" denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[070] Descriptions of compounds of the present disclosure are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[071] The terms "treating" or "treatment" refers to any indicia of success in the treatment of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, electrocardiogram, echocardiography, radio-imaging, nuclear scan, and/or stress testing, neuropsychiatric exams, and/or a psychiatric evaluation. For example, certain methods herein treat a neurodegenerative disease, a mitochondrial disease, fibrosis, or cardiomyopathy. In embodiments, certain methods herein treat Parkinson's disease by decreasing the production of Lewy bodies, decreasing the accumulation of alpha-synuclein, decreasing cell death, decreasing loss of dopamine-generating cells, decreasing loss of cells in the substantia nigra, decreasing loss of dopamine production, decreasing a symptom of Parkinson's disease, decreasing loss of motor function, decreasing shaking or slowing an increase in shaking (tremor), decreasing rigidity or an increase in rigidity, decreasing slowness (bradykinesia) of

movement or a slowing of movement, decreasing sensory symptoms, decreasing insomnia, decreasing sleepiness, increasing mental wellbeing, increasing mental function, slowing the decrease of mental function, decreasing dementia, delaying the onset of dementia, improving cognitive skills, decreasing the loss of cognitive skills, improving memory, decreasing the degradation of memory, or extending survival. In embodiments, certain methods herein treat cardiomyopathy by increasing cardiac performance, improving exercise tolerance, preventing heart failure, increasing blood oxygen content, or improving respiratory function. The term "preventing" and conjugations thereof, include prevention of an injury, pathology, condition, or disease (e.g. preventing the development of one or more symptoms of a neurodegenerative disease such as Parkinson's disease, or of a cardiomyopathy). In one aspect, the terms "prevention" or "preventing" mean a reduction of the risk of acquiring a particular disease, condition, or disorder. In one aspect, the term "treating" means therapeutic treatment, i.e., reversing, alleviating, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein.

[072] An "effective amount" is an amount sufficient to accomplish a stated purpose (e.g. achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, and/or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, Pharmaceutical Dosage Forms (vols. 1-3, 1992); Lloyd, The Art, Science and Technology of Pharmaceutical Compounding (1999); Pickar, Dosage Calculations (1999); and Remington: The Science and Practice of Pharmacy, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[073] The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease, a symptom associated with a cardiomyopathy, neurodegenerative disease, or symptom associated with Parkinson's disease) means that the disease (e.g. cardiomyopathy, neurodegenerative disease or Parkinson's disease) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, a symptom of a disease or condition associated with a reduction in the level of PINK1 activity may be a symptom that results (entirely or partially) from a reduction in the level of PINK1 activity (e.g. loss of function mutation or gene deletion or modulation of PINK1 signal transduction pathway). As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, a disease associated with PINK1, may be treated with an agent (e.g. compound as described herein) effective for increasing the level of activity of PINK1.

[074] "Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects.

[075] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules, or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated, however, that the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture. The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme (e.g. PINK1). In embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway.

[076] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor (e.g. antagonist) interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a signal transduction pathway or signaling pathway. Thus, inhibition includes, at

least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein.

[077] The symbol "〰" denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[078] As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein-activator (e.g. agonist) interaction means positively affecting (e.g. increasing) the activity or function of the protein (e.g. PINK1) relative to the activity or function of the protein in the absence of the activator (e.g. compound described herein). In embodiments, activation refers to an increase in the activity of a signal transduction pathway or signaling pathway (e.g. PINK1 pathway). Thus, activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease (e.g. reduction of the level of PINK1 activity or protein associated with a cardiomyopathy or a neurodegenerative disease such as Parkinson's disease). Activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein (e.g. PINK1) that may modulate the level of another protein or increase cell survival (e.g. increase in PINK1 activity may increase cell survival in cells that may or may not have a reduction in PINK1 activity relative to a non-disease control).

[079] The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule. In embodiments, the modulator is a modulator of PINK1. In embodiments, the modulator is a modulator of PINK1 and is a compound that reduces the severity of one or more symptoms of a disease associated with PINK1 (e.g. reduction of the level of PINK1 activity or protein associated with a cardiomyopathy, neurodegenerative disease such as Parkinson's disease). In embodiments, a modulator is a compound that reduces the severity of one or more symptoms of a cardiomyopathy or neurodegenerative disease that is not caused or characterized by PINK1 (e.g. loss of PINK1 function) but may benefit from modulation of PINK1 activity (e.g. increase in level of PINK1 or PINK1 activity).

[080] "Patient" or "subject in need thereof" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a compound or pharmaceutical composition, as provided herein. Non-limiting examples include humans,

other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In embodiments, a patient is human.

[081] "Disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with a compound, pharmaceutical composition, or method provided herein. In embodiments, the disease is a disease related to (e.g. characterized by) a reduction in the level of PINK1. In embodiments, the disease is a disease characterized by loss of dopamine-producing cells (e.g. Parkinson's disease). In embodiments, the disease is a disease characterized by neurodegeneration. In embodiments, the disease is a disease characterized by neural cell death. In embodiments, the disease is a disease characterized by a reduction in the level of PINK1 activity. In embodiments, the disease is Parkinson's disease. In embodiments, the disease is a neurodegenerative disease. In embodiments, the disease is a cardiomyopathy.

[082] As used herein, the term "cardiomyopathy" refers to a disease condition that adversely affects cardiac cell tissue leading to a measurable deterioration in myocardial function (e.g. systolic function, diastolic function). Dilated cardiomyopathy is characterized by ventricular chamber enlargement with systolic dysfunction and no hypertrophy. Hypertrophic cardiomyopathy, is a genetic disease transmitted as an autosomal dominant trait. Hypertrophic cardiomyopathy is morphologically characterized by a hypertrophied and non-dialated left ventricle. Restrictive cardiomyopathy is characterized by nondialated nonhypertrophied morphology with diminished ventricular volume leading to poor ventricular filling. Arrhythmogenic right ventricular cardiomyopathy is an inheritable heart disease characterized by myocardial electric instability. Unclassified cardiomyopathy is a category for cardiomyopathies that do not match the features of any one of the other types. Unclassified cardiomyopathies may have features of multiple types or, for example, have the features of fibroelastosis, noncompacted myocardium, or systolic dysfunction with minimal dilatation.

[083] As used herein, the term "neurodegenerative disease" refers to a disease or condition in which the function of a subject's nervous system becomes impaired. Examples of neurodegenerative diseases that may be treated with a compound or method described herein include Alexander's disease, Alper's disease, Alzheimer's disease, Amyotrophic lateral sclerosis, Ataxia telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease), Bovine spongiform encephalopathy (BSE), Canavan disease, Cockayne syndrome, Corticobasal degeneration, Creutzfeldt-Jakob disease, epilepsy, Friedreich ataxia, frontotemporal dementia, Gerstmann-Sträussler-Scheinker syndrome, Huntington's disease,

HIV-associated dementia, Kennedy's disease, Krabbe's disease, kuru, Leigh's disease (Leigh syndrome), Lewy body dementia, Machado-Joseph disease (Spinocerebellar ataxia type 3), Multiple sclerosis, Multiple System Atrophy, Narcolepsy, Neuroborreliosis, Parkinson's disease, Pelizaeus-Merzbacher Disease, Pick's disease, Primary lateral sclerosis, Prion diseases, Refsum's disease, Sandhoff's disease, Schilder's disease, Shy-Drager syndrome, Subacute combined degeneration of spinal cord secondary to Pernicious Anaemia, Schizophrenia, Spinocerebellar ataxia (multiple types with varying characteristics), Spinal muscular atrophy, Steele-Richardson-Olszewski disease, Tabes dorsalis, drug-induced Parkinsonism, progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy, Idiopathic Parkinson's disease, Autosomal dominant Parkinson disease, Parkinson disease, familial, type 1 (PARK1), Parkinson disease 3, autosomal dominant Lewy body (PARK3), Parkinson disease 4, autosomal dominant Lewy body (PARK4), Parkinson disease 5 (PARK5), Parkinson disease 6, autosomal recessive early-onset (PARK6), Parkinson disease 2, autosomal recessive juvenile (PARK2), Parkinson disease 7, autosomal recessive early-onset (PARK7), Parkinson disease 8 (PARK8), Parkinson disease 9 (PARK9), Parkinson disease 10 (PARK10), Parkinson disease 11 (PARK11), Parkinson disease 12 (PARK12), Parkinson disease 13 (PARK13), or Mitochondrial Parkinson's disease. In embodiments, dysautonomia is not a neurodegenerative disease.

[084] The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propagated to other signaling pathway components.

[085] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present disclosure without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic

substances and the like that do not deleteriously react with the compounds of the disclosure. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present disclosure.

[086] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[087] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc. By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. cardiomyopathy therapies including, for example, Angiotensin Converting Enzyme Inhibitors (e.g. Enalipril, Lisinopril), Angiotensin Receptor Blockers (e.g. Losartan, Valsartan), Beta Blockers (e.g. Lopressor, Toprol-XL), Digoxin, or Diuretics (e.g. Lasix; or Parkinson's disease therapies including, for example, levodopa, dopamine agonists (e.g. bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine, lisuride), MAO-B inhibitors (e.g. selegiline or rasagiline), amantadine, anticholinergics, antipsychotics (e.g. clozapine), cholinesterase inhibitors, modafinil, or non-steroidal anti-inflammatory drugs.

[088] The compound of the disclosure can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present disclosure can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral

preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present disclosure may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present disclosure can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, J. Biomater Sci. Polym. Ed. 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao Pharm. Res. 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, J. Pharm. Pharmacol. 49:669-674, 1997). In embodiments, the formulations of the compositions of the present disclosure can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present disclosure into the target cells in vivo. (See, e.g., Al-Muhammed, J. Microencapsul. 13:293-306, 1996; Chonn, Curr. Opin. Biotechnol. 6:698-708, 1995; Ostro, Am. J. Hosp. Pharm. 46:1576-1587, 1989). The compositions of the present disclosure can also be delivered as nanoparticles.

[089] Pharmaceutical compositions provided by the present disclosure include compositions wherein the active ingredient (e.g. compounds described herein, including embodiments or examples) is contained in a therapeutically effective amount, i.e., in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, inter alia, on the condition being treated. When administered in methods to treat a disease, such compositions will contain an amount of active ingredient effective to achieve the desired result, e.g., modulating the activity of a target molecule (e.g. PINK1), and/or reducing, eliminating, or slowing the progression of disease symptoms (e.g. symptoms of cardiomyopathy or a neurodegeneration such as symptoms of Parkinson's disease).

Determination of a therapeutically effective amount of a compound of the disclosure is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure herein.

[090] The dosage and frequency (single or multiple doses) administered to a mammal can vary depending upon a variety of factors, for example, whether the mammal suffers from another disease, and its route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated (e.g. symptoms of cardiomyopathy or neurodegeneration such as Parkinson's disease and severity of such symptoms), kind of concurrent treatment, complications from the disease being treated or other health-related problems. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds of Applicants' disclosure. Adjustment and manipulation of established dosages (e.g., frequency and duration) are well within the ability of those skilled in the art.

[091] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[092] As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[093] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present disclosure should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached.

[094] Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This

will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[095] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

[096] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating a disease associated neurodegeneration (e.g. Parkinson's disease such as levodopa, dopamine agonists (e.g. bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine, lisuride), MAO-B inhibitors (e.g. selegiline or rasagiline), amantadine, anticholinergics, antipsychotics (e.g. clozapine), cholinesterase inhibitors, modafinil, or non-steroidal anti-inflammatory drugs), or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[097] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating a cardiomyopathy such as Angiotensin Converting Enzyme Inhibitors (e.g. Enalipril, Lisinopril), Angiotensin Receptor Blockers (e.g. Losartan, Valsartan), Beta Blockers (e.g. Lopressor, Toprol-XL), Digoxin, or Diuretics (e.g. Lasixdisease associated neurodegeneration (e.g. Parkinson's disease such as levodopa, dopamine agonists (e.g. bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine, lisuride), MAO-B inhibitors (e.g. selegiline or rasagiline), amantadine, anticholinergics, antipsychotics (e.g. clozapine), cholinesterase inhibitors, modafinil, or non-steroidal anti-inflammatory drugs), or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[098] In embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In embodiments, the active and/or adjunctive agents may be linked or conjugated to one another. In embodiments, the compounds

described herein may be combined with treatments for neurodegeneration such as surgery. In embodiments, the compounds described herein may be combined with treatments for cardiomyopathy such as surgery.

[099] "PINK1" is used according to its common, ordinary meaning and refers to proteins of the same or similar names and functional fragments and homologs thereof. The term includes and recombinant or naturally occurring form of PINK1 (e.g. "PTEN induced putative kinase 1"; Entrez Gene 65018, OMIM 608309, UniProtKB Q9BXM7, and/or RefSeq (protein) NP_115785.1). The term includes PINK1 and variants thereof that maintain PINK1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity as compared to PINK1).

[0100] The term "neo-substrate" refers to a composition that is structurally similar to a composition that is a substrate for a protein or enzyme during the normal functioning of the protein or enzyme, but that is structurally distinct from the normal substrate of the protein or enzyme. In embodiments, the neo-substrate is a better substrate for the protein or enzyme than the normal substrate (e.g. the reaction kinetics are better (e.g. faster), binding is stronger, turnover rate is higher, reaction is more productive, equilibrium favors product formation). In embodiments, the neo-substrate is a derivative of adenine, adenosine, AMP, ADP, or ATP. In embodiments, the neo-substrate is a substrate for PINK1. In embodiments, the neo-substrate is an N6 substituted adenine, adenosine, AMP, ADP, or ATP.

[0101] The term "derivative" as applied to a phosphate containing, monophosphate, diphosphate, or triphosphate group or moiety refers to a chemical modification of such group wherein the modification may include the addition, removal, or substitution of one or more atoms of the phosphate containing, monophosphate, diphosphate, or triphosphate group or moiety. In embodiments, such a derivative is a prodrug of the phosphate containing, monophosphate, diphosphate, or triphosphate group or moiety, which is converted to the phosphate containing, monophosphate, diphosphate, or triphosphate group or moiety from the derivative following administration to a subject, patient, cell, biological sample, or following contact with a subject, patient, cell, biological sample, or protein (e.g. enzyme). In an embodiment, a triphosphate derivative is a gamma-thio triphosphate. In an embodiment, a derivative is a phosphoramidate. In embodiments, the derivative of a phosphate containing, monophosphate, diphosphate, or triphosphate group or moiety is as described in Murakami et al. J. Med Chem., 2011, 54, 5902; Sofia et al., J. Med Chem. 2010, 53, 7202; Lam et al. ACC, 2010, 54, 3187; Chang et al., ACS Med Chem Lett., 2011, 2, 130; Furman et al., Antiviral Res., 2011, 91, 120; Vernachio et al., ACC, 2011, 55, 1843; Zhou et al, AAC, 2011,

44, 76; Reddy et al., BMCL, 2010, 20, 7376; Lam et al., J. Virol., 2011, 85, 12334; Sofia et al., J. Med. Chem., 2012, 55, 2481, Hecker et al., J. Med. Chem., 2008, 51, 2328; or Rautio et al., Nature Rev. Drug. Discov., 2008, 7, 255, all of which are incorporated herein by reference in their entirety for all purposes.

[0102] The term "mitochondrial dysfunction" is used in accordance with its ordinary meaning and refers to aberrant activity of function of the mitochondria, including for example aberrant respiratory chain activity, reactive oxygen species levels, calcium homeostasis, programmed cell death mediated by the mitochondria, mitochondrial fusion, mitochondrial fission, lipid concentrations in the mitochondrial membrane, and/or mitochondrial permeability transition.

[0103] As used herein, the term "mitochondrial disease" refers to a disease, disorder, or condition in which the function of a subject's mitochondria becomes impaired or dysfunctional. Examples of mitochondrial diseases that may be treated with a compound or method described herein include Alzheimer's disease, amyotrophic lateral sclerosis, Asperger's Disorder, Autistic Disorder, bipolar disorder, cancer, cardiomyopathy, Charcot Marie Tooth disease (CMT, including various subtypes such as CMT type 2b and 2b), Childhood Disintegrative Disorder (CDD), diabetes, diabetic nephropathy, epilepsy, Friedreich's Ataxia (FA), Hereditary motor and sensory neuropathy (HMSN), Huntington's Disease, Keams-Sayre Syndrome (KSS), Leber's Hereditary Optic Neuropathy (LHON, also referred to as Leber's Disease, Leber's Optic Atrophy (LOA), or Leber' s Optic Neuropathy (LON)), Leigh Disease or Leigh Syndrome, macular degeneration, Mitochondrial Myopathy, Lactacidosis, and Stroke (MELAS), mitochondrial neurogastrointestinal encephalomyophathy (MNGIE), motor neuron diseases, Myoclonic Epilepsy With Ragged Red Fibers (MERRF), Neuropathy, ataxia, retinitis pigmentosa, and ptosis (NARP), Parkinson's disease, Peroneal muscular atrophy (PMA), Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), renal tubular acidosis, Rett's Disorder, Schizophrenia, and types of stroke.

[0104] The term "oxidative stress" is used in accordance with its ordinary meaning and refers to aberrant levels of reactive oxygen species.

[0105] As used herein, the term "animal" includes, but is not limited to, humans and non-human vertebrates such as wild, domestic, and farm animals.

[0106] As used herein, the term "antagonize" or "antagonizing" means reducing or completely eliminating an effect, such as an activity of GPR109a.

[0107] As used herein, the phrase "anti-receptor effective amount" of a compound can be measured by the anti-receptor effectiveness of the compound. In some embodiments, an anti-receptor effective amount inhibits an activity of the receptor by at least 10%, by at least 20%, by at least 30%, by at least 40%, by at least 50%, by at least 60%, by at least 70%, by at least 80%, by at least 90%, or by at least 95%. In some embodiments, an "anti-receptor effective amount" is also a "therapeutically effective amount" whereby the compound reduces or eliminates at least one effect of GPR109a. In some embodiments, the effect is the B-arrestin effect. In some embodiments, the effect is the G-protein mediated effect.

[0108] As used herein, the term "carrier" means a diluent, adjuvant, or excipient with which a compound is administered. Pharmaceutical carriers can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical carriers can also be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents can be used.

[0109] As used herein, the terms "comprising" (and any form of comprising, such as "comprise", "comprises", and "comprised"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include"), or "containing" (and any form of containing, such as "contains" and "contain"), are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

[0110] As used herein, the term "contacting" means bringing together of two elements in an *in vitro* system or an *in vivo* system. For example, "contacting" a compound disclosed herein with an individual or patient or cell includes the administration of the compound to an individual or patient, such as a human, as well as, for example, introducing a compound into a sample containing a cellular or purified preparation containing the compounds or pharmaceutical compositions disclosed herein.

[0111] As used herein, the terms "individual", "subject" or "patient," used interchangeably, means any animal, including mammals, such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, such as humans.

[0112] As used herein, the phrase "inhibiting activity," such as enzymatic or receptor activity means reducing by any measurable amount the activity of PINK1.

[0113] As used herein, the phrase "in need thereof" means that the animal or mammal has been identified as having a need for the particular method or treatment. In some embodiments, the identification can be by any means of diagnosis. In any of the methods and

treatments described herein, the animal or mammal can be in need thereof. In some embodiments, the animal or mammal is in an environment or will be traveling to an environment in which a particular disease, disorder, or condition is prevalent.

[0114] As used herein, the phrase "integer from X to Y" means any integer that includes the endpoints. For example, the phrase "integer from 1 to 5" means 1, 2, 3, 4, or 5.

[0115] As used herein, the term "isolated" means that the compounds described herein are separated from other components of either (a) a natural source, such as a plant or cell, or (b) a synthetic organic chemical reaction mixture, such as by conventional techniques.

[0116] As used herein, the term "mammal" means a rodent (i.e., a mouse, a rat, or a guinea pig), a monkey, a cat, a dog, a cow, a horse, a pig, or a human. In some embodiments, the mammal is a human.

[0117] As used herein, the phrase "pharmaceutically acceptable" means those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with tissues of humans and animals. In some embodiments, "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0118] As used herein, the phrase "pharmaceutically acceptable salt(s)," includes, but is not limited to, salts of acidic or basic groups. Compounds that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. Acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions including, but not limited to, sulfuric, thiosulfuric, citric, maleic, acetic, oxalic, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, bisulfite, phosphate, acid phosphate, isonicotinate, borate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, bicarbonate, malonate, mesylate, esylate, napsydisylate, tosylate, besylate, orthophoshate, trifluoroacetate, and pamoate (i.e., 1,1′-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include, but are not limited to, alkali metal or alkaline earth metal salts and,

particularly, calcium, magnesium, ammonium, sodium, lithium, zinc, potassium, and iron salts. The present disclosure also includes quaternary ammonium salts of the compounds described herein, where the compounds have one or more tertiary amine moiety.

[0119] As used herein, the term "prodrug" means a derivative of a known direct acting drug, which derivative has enhanced delivery characteristics and therapeutic value as compared to the drug, and is transformed into the active drug by an enzymatic or chemical process. The compounds described herein also include derivatives referred to as prodrugs, which can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Examples of prodrugs include compounds of the disclosure as described herein that contain one or more molecular moieties appended to a hydroxyl, amino, sulfhydryl, or carboxyl group of the compound, and that when administered to a patient, cleaves in vivo to form the free hydroxyl, amino, sulfhydryl, or carboxyl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the disclosure. Preparation and use of prodrugs is discussed in T. Higuchi et al., "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference in their entireties.

[0120] As used herein, the term "purified" means that when isolated, the isolate contains at least 90%, at least 95%, at least 98%, or at least 99% of a compound described herein by weight of the isolate.

[0121] As used herein, the phrase "solubilizing agent" means agents that result in formation of a micellar solution or a true solution of the drug.

[0122] As used herein, the term "solution/suspension" means a liquid composition wherein a first portion of the active agent is present in solution and a second portion of the active agent is present in particulate form, in suspension in a liquid matrix.

[0123] As used herein, the phrase "substantially isolated" means a compound that is at least partially or substantially separated from the environment in which it is formed or detected.

[0124] As used herein, the phrase "therapeutically effective amount" means the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician. The therapeutic effect is dependent upon the disorder being treated or the biological effect desired. As such, the therapeutic effect can be a

decrease in the severity of symptoms associated with the disorder and/or inhibition (partial or complete) of progression of the disorder, or improved treatment, healing, prevention or elimination of a disorder, or side-effects. The amount needed to elicit the therapeutic response can be determined based on the age, health, size and sex of the subject. Optimal amounts can also be determined based on monitoring of the subject's response to treatment.

[0125] It is further appreciated that certain features described herein, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

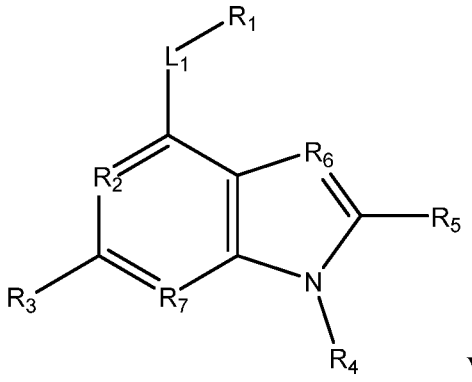
[0126] It should be noted that any embodiment of the invention can optionally exclude one or more embodiment for purposes of claiming the subject matter.

[0127] In some embodiments, the compounds, or salts thereof, are substantially isolated. Partial separation can include, for example, a composition enriched in the compound of the disclosure. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the disclosure, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

[0128] Compounds containing an amine function can also form N-oxides. A reference herein to a compound that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom can be oxidized to form an N-oxide. Examples of N-oxides include N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g., a peroxycarboxylic acid) (see, Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience).

[0129] Embodiments of various compounds and salts thereof are provided. Where a variable is not specifically recited, the variable can be any option described herein, except as otherwise noted or dictated by context.

[0130] In a first embodiment, the disclosure relates to a compound having the following formula or pharmaceutically acceptable salt thereof:



VIII

wherein L_1 is selected from the group consisting of: a bond, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon; an amine, an aminohydrocarbon, an aminoalkyl, an aminoalkene, and –NH-CH_2-;

R_7 is selected from the group consisting of: a saturated or unsaturated C or N, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon, and a substituted or unsubstituted aminohydrocarbon;

R_1 is selected from the group consisting of: a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted alkene, a substituted or unsubstituted heteroalkene, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl;

R_2 and R_6 are independently selected from the group consisting of: a substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, -CH-, O, S and N;

R_4 is selected from the group consisting of a hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkyne, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkyne, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl; and

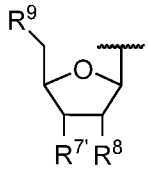
R_3 and R_5 are independently selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted

cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl.

[0131] In a second embodiment, R_7 in the compound of Formula VIII is a saturated or unsaturated C or N, heteromethyl, ethyl, propyl, butylalkene, alkene, or alkyne, wherein the remaining variables are described above for Formula VIII.

[0132] In a third embodiment, L_1 in the compound of Formula VIII is an aminohydrocarbon, an aminoalkyl, or -NH-CH_2-, wherein the remaining variables are described above for Formula VIII or the second embodiment. In some aspects, a compound or composition described herein is free of kinetin.

[0133] In a fourth embodiment, R_1 in the compound of Formula VIII is C_{1-4}alkyl, C_{1-4}alkyne, C_{1-4}alkene, or a 5 or 6 membered cycloalkyl, cycloalkyne, heterocycloalkyl, heterocycloalkyne, aryl, or heteroaryl, or a substituted or unsubstituted furan group, wherein the remaining variables are described above for Formula VIII or the second or third embodiment. Alternatively, R_1 in the compound of Formula VIII is C_3alkyl, C_3alkyne, a 5 membered heteroaryl, -C=C-C, -C-C-C, or a substituted or unsubstituted furan group, wherein the remaining variables are described above for Formula VIII or the second or third embodiment. In another alternative, R_1 in the compound of Formula VIII is or is free of the formula:



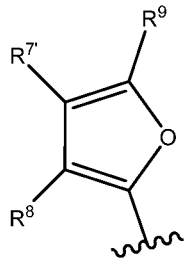
(II),

wherein $R^{7'}$ and R^8 are independently or free of hydrogen, oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_2Cl, -SO_3H, -SO_4H, -SO_2NH_2, -$NHNH_2$, -ONH_2, -NHC(O)$NHNH_2$, -NHC(O) NH_2, -$NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

R^9 is or is free of hydrogen, oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_2Cl, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC(O)$NHNH_2$, –NHC(O)NH_2, -$NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl,

substituted or unsubstituted heteroaryl, substituted or unsubstituted phosphate, substituted or unsubstituted monophosphate, substituted or unsubstituted diphosphate, or substituted or unsubstituted triphosphate, wherein the remaining variables are described above for Formula VIII or the second or third embodiment.

[0134] In a fifth embodiment, R_1 in the compound of Formula VIII is or is free of the formula:



(XI)

wherein $R^{7'}$ and R^8 are independently or free of hydrogen, oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)\ NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

R^9 is or is free of hydrogen, oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted phosphate, substituted or unsubstituted monophosphate, substituted or unsubstituted diphosphate, or substituted or unsubstituted triphosphate, wherein the remaining variables are described above for Formula VIII or the second, third, or fourth embodiment.

[0135] In some embodiments, a halogen in any of the compounds described herein is fluorine. In some embodiments, the compounds described herein are free of a halogen and/or free of anything larger than fluorine.

[0136] In a sixth embodiment, R_2 and R_6 in the compound of Formula VIII are independently selected from -CH-, O, S and N, wherein the remaining variables are described above for Formula VIII or the second, third, fourth, or fifth embodiment. Alternatively, R_2 and R_6 in the

compound of Formula VIII are each N, wherein the remaining variables are described above for Formula VIII or the second, third, fourth, or fifth embodiment.

[0137] In a seventh embodiment, R_4 in the compound of Formula VIII is hydrogen, wherein the remaining variables are described above for Formula VIII or the second, third, fourth, fifth, or sixth embodiment.

[0138] In an eighth embodiment, R_3 and R_5 in the compound of Formula VIII are independently selected from C_{1-8}alkyl, C_{1-8}alkene, C_{1-8}alkyne, C_{1-8}heteroalkyl, and C_{1-8}heteroalkyne, wherein the remaining variables are described above for Formula VIII or the second, third, fourth, fifth, sixth, or seventh embodiment. Alternatively, R_3 and R_5 in the compound of Formula VIII are independently selected from C_{1-4}alkyl, C_{1-4}alkene, and C_{1-4}alkyne, wherein the remaining variables are described above for Formula VIII or the second, third, fourth, fifth, sixth, or seventh embodiment. In another alternative, R_3 and R_5 in the compound of Formula VIII are each methyl, wherein the remaining variables are described above for Formula VIII or the second, third, fourth, fifth, sixth, or seventh embodiment.

[0139] In a ninth embodiment, L_1 in the compound of Formula VIII is an aminohydrocarbon, an aminoalkyl, or -NH-CH_2-;

R_7 is a saturated C or N;

R_1 is selected from the group consisting of: a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted alkene, and a substituted or unsubstituted furan group;

R_2 and R_6 are independently selected from the group consisting of: a substituted or unsubstituted alkyl, a substituted or unsubstituted heteroalkyl, -CH-, O, S and N;

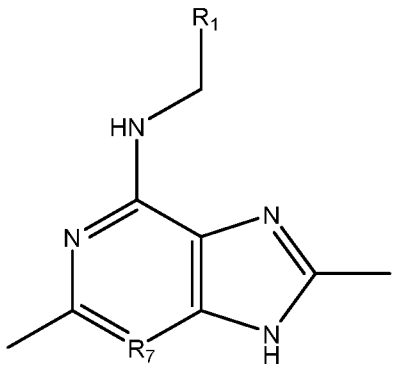
R_4 is selected from the group consisting of: a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted alkene, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl; and

R_3 and R_5 are independently selected from the group consisting of: a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or

unsubstituted aryl, and a substituted or unsubstituted heteroaryl, wherein the remaining variables are described above for Formula VIII.

[0140] In a tenth embodiment, R_1 is a substituted or unsubstituted furan group, wherein the remaining variables are described above for Formula VIII or the ninth embodiment.

[0141] In an eleventh embodiment, the invention relates to a compound having formula:



(X),

or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of: $C_{2\text{-}6}$alkyl, $C_{2\text{-}6}$alkyne, $C_{2\text{-}6}$alkene, a substituted or unsubstituted furan group, and a 5 or 6 membered cycloalkyl, cycloalkene, methylene, ethylene, propylene, butylene, heterocycloalkyl, aryl, thiophene or heteroaryl; and

R_7 is a saturated C or N.

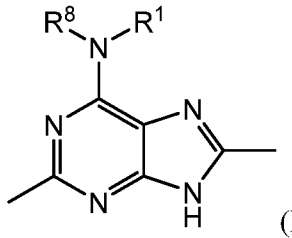
[0142] In a twelfth embodiment, R_1 in the compound of Formula X is $C_{2\text{-}6}$alkyl, cycolopentyl, furan or thiophene group, each group optionally substituted with methyl, ethyl, propyl, methylene, ethylene, propylene, butylene, methoxy, ethoxy, carboxy, carboxymethly, carboxyethyl, hydroxyl, or halogen, wherein the remaining variables are described above for Formula X.

[0143] In one aspect, each of the substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyne, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkyne, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl of any compound described herein is independently selected from the group consisting of:

substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted 2,5-dihydrofuranyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted 2,5-dihydrothienyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted 2,5-dihydro-IH -pyrrolyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclopentenyl, and substituted or unsubstituted 1,3-oxathiolanyl.

[0144] In a thirteenth embodiment, L_1 is -NH-CH_2-; R_7 is a saturated C or N; R_1 is a C_{1-4}alkyl, a C_{1-4}alkene, or a substituted or unsubstituted furan group; R_2 and R_6 are each N; R_4 is H; and R_3 and R_5 are each methyl, wherein the remaining variables are described above for Formula VIII, Formula X or the, wherein the remaining variables are described above for Formula VIII or the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or twelfth embodiment.

[0145] In a fourteenth embodiment, also provided are compounds having the formula XI:

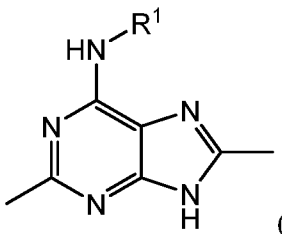

(XI);

or a pharmaceutically acceptable salt thereof, wherein

R^8 is hydrogen or unsubstituted C_1-C_4alkyl; and

R^1 is a (C_1-C_6)alkyl optionally substituted with a substituted or unsubstituted heteroaryl.

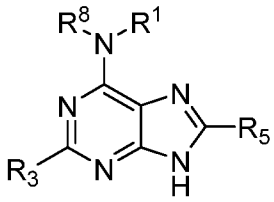
[0146] In a fifteenth embodiment, the compound of formula XI is of the formula XII:


(XII);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for formula XI.

[0147] In a sixteenth embodiment, R^1 in Formula XI or XII is a (C_1-C_6)alkyl optionally substituted with a substituted or unsubstituted pyranyl. Alternatively, R^1 in Formula XI or XII is a (C_1-C_6)alkyl optionally substituted with an unsubstituted pyranyl. In another alternative, R^1 in Formula XI or XII is a (C_1-C_4)alkyl optionally substituted with an unsubstituted pyranyl. In another alternative, R^1 in Formula XI or XII is a (C_1-C_4)alkyl optionally substituted with a thiophene.

[0148] In a seventeenth embodiment, provided is a compound having the formula XX:



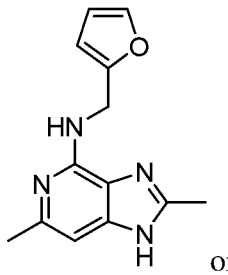
(XX);

or a pharmaceutically acceptable salt thereof, wherein

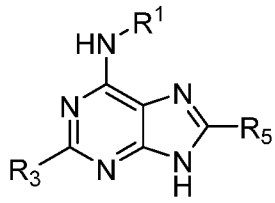
R_3 and R_5 are each unsubstituted $(C_1\text{-}C_4)$alkyl;

R^8 is hydrogen or unsubstituted $(C_1\text{-}C_4)$alkyl; and

R^1 is a $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$alkene, wherein said $(C_1\text{-}C_6)$alkyl is optionally substituted with phenyl, a monocyclic 5-7 membered heterocycloalkyl, or a monocyclic 5-7 membered heteroaryl, each of which are optionally substituted with 1 or 2 $(C_1\text{-}C_4)$alkyl;

provided the compound is not  or a pharmaceutically acceptable salt thereof.

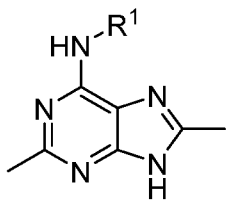
[0149] In an eighteenth embodiment, the compound of Formula XX is of the Formula XX^a:



(XX^a);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula XX.

[0150] In a nineteenth embodiment, the compound of Formula XX is of the Formula XX^b



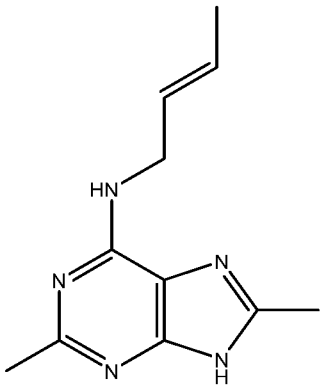
(XX^b);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula XX.

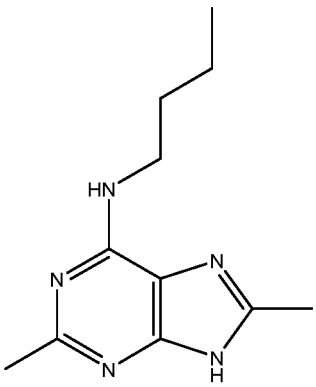
[0151] In a twentieth embodiment, said $(C_1\text{-}C_6)$alkyl for R_1 in the compound of Formula XX, XX^a, or XX^b is optionally substituted with phenyl, furanyl, tetrahydropyranyl, pyridinyl, or pyrizinyl, each of which are optionally substituted with 1 or 2 $(C_1\text{-}C_4)$alkyl, wherein the variables are as described above for Formula XX, XX^a, or XX^b.

[0152] In a twenty-first embodiment, R_1 in the compound of Formula XX, XX^a, or XX^b is a $(C_1\text{-}C_5)$alkyl or $(C_2\text{-}C_4)$alkene, wherein said $(C_1\text{-}C_5)$alkyl for R_1 is optionally substituted with phenyl, furanyl, tetrahydropyranyl, pyridinyl, or pyrizinyl, and wherein said furanyl is optionally substituted with $(C_1\text{-}C_4)$alkyl, wherein the remaining variables are as described above for Formula XX, XX^a, or XX^b.

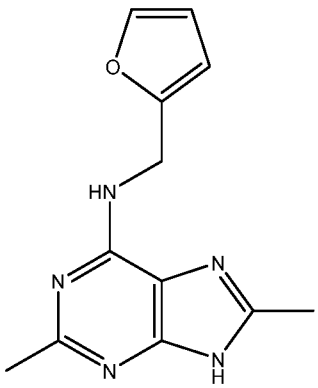
[0153] In some embodiments, the present disclosure provides a compound having the formula of one of the following:



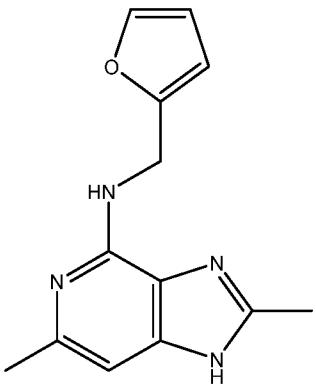
(VIIIa),



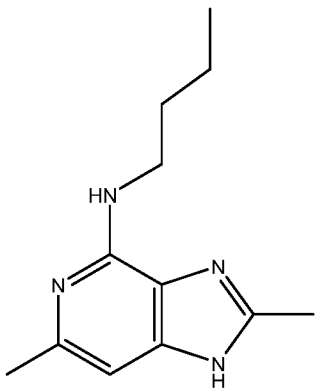
(VIIIb),



(VIIIc),



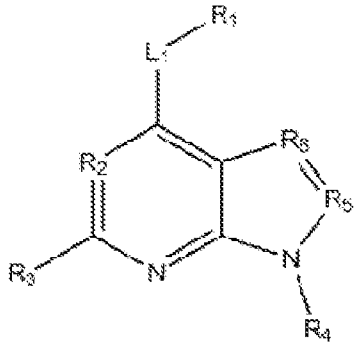
(VIIId), and



(VIIIe), or a pharmaceutically acceptable salt thereof.

[0154] In some embodiments, a composition is provided comprising one or a plurality of compounds described herein. In some embodiments, the composition is substantially free of one or more of the compounds described herein. In some embodiments, the composition further comprises one or more active agents. In some embodiments, a pharmaceutical composition is provided, comprising one or a plurality of compounds described herein and a pharmaceutically acceptable carrier.

[0155] In some embodiments, the disclosure relates to a compound having the following formula or pharmaceutically acceptable salt thereof:

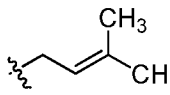


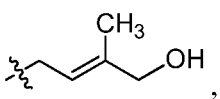
(I)

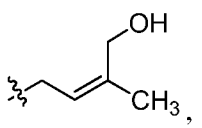
wherein X is independently selected from a -CH, -$CHCH_3$, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

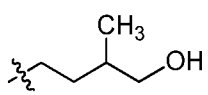
L^1 is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

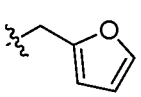
R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and R^4 is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

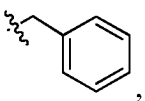
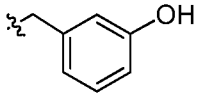
wherein if R^4 is hydrogen, then $-L^1-R^1$ is not hydrogen, 

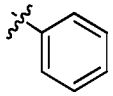
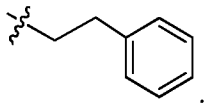
, 

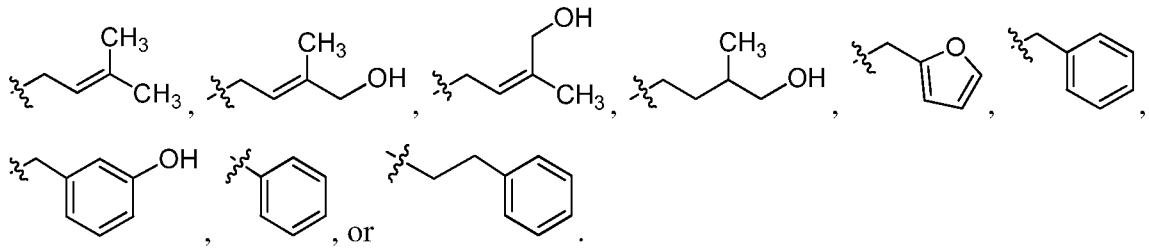
, 

, 

, 

, 
, 

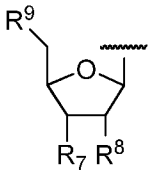
, 
, or  . In some embodiments, X is independently selected from a carbon with a methyl, ethyl, or butyl group. In some embodiments, X is independently selected from



[0156] In some embodiments, X is a methyl group. In some embodiments, X is independently a hydrogen, oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)\ NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, X is independently slected from a substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted 2,5-dihydrofuranyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted 2,5-dihydrothienyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted 2,5-dihydro-1H-pyrrolyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclopentenyl, or substituted or unsubstituted 1,3-oxathiolanyl. In some embodiments, R^4 is independently hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0157] In some embodiments, R^4 is independently substituted with at least one oxo; halogen; -OH; $-CH_2OH$; $-N_3$; or monophosphate, diphosphate, triphosphate, or a derivative thereof.

[0158] In some embodiments, R^4 is or is free of the formula:



(II),

wherein,

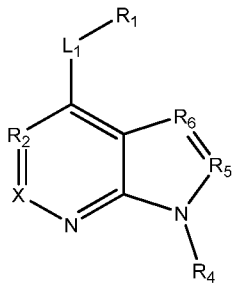
R^7 and R^8 are independently or free of hydrogen, oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)\ NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

R^9 is or is free of hydrogen, oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_2Cl, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –$NHC(O)NHNH_2$, –$NHC(O)NH_2$, -$NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted phosphate, substituted or unsubstituted monophosphate, substituted or unsubstituted diphosphate, or substituted or unsubstituted triphosphate.

[0159] In some embodiments, R^7 and R^8 are independently hydrogen or –OH; and R^9 is a –OH, monophosphate, diphosphate, triphosphate, or a derivative thereof.

[0160] In some embodiments, the compounds of the present disclosure does not comprise kinetin or any molecule comprising the monophosphate, diphosphate, triphosphate, or a derivative thereof based upon its position at the R^4 position.

[0161] In some embodiments, the invention relates to a compound having formula:



wherein X is independently selected from a -CH, -$CHCH_3$, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^1 is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

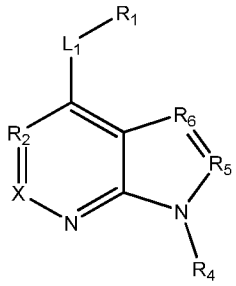
R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and R^4 is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is an amino group;

R^5 is a –$CHCH_3$; and

R^6 is an amino group.

[0162] In some embodiments, the invention relates to a compound having formula:



wherein X is independently selected from a -CH, -$CHCH_3$, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

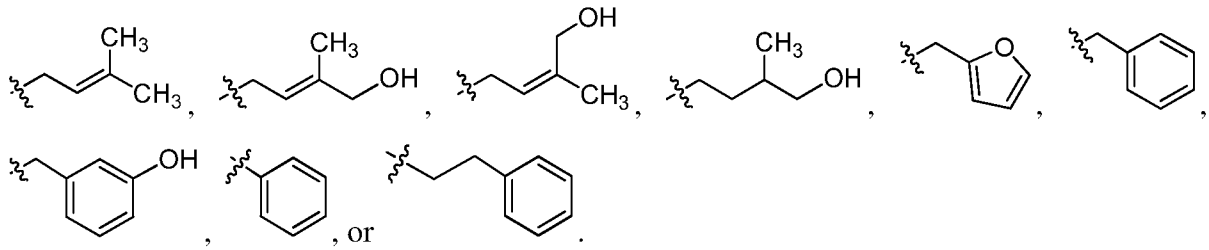
L^1 is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and R^4 is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

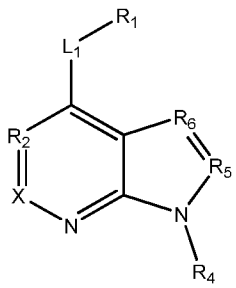
R^2 is an amino group;

R^5 is a saturated carbon atom; and

R^6 is an amino group; and wherein if R^4 is hydrogen, then $-L^1-R^1$ is not hydrogen,



[0163] In some embodiments, the invention relates to a compound having formula:



wherein X is independently selected from a -CH, -$CHCH_3$, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, substituted or unsubstituted

tetrahydrofuranyl, substituted or unsubstituted 2,5-dihydrofuranyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted 2,5-dihydrothienyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted 2,5-dihydro-1H-pyrrolyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclopentenyl, or substituted or unsubstituted 1,3-oxathiolanyl, independently be R^{99}-substituted, where R^{99} is as described herein, including embodiments thereof.

L^1 is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

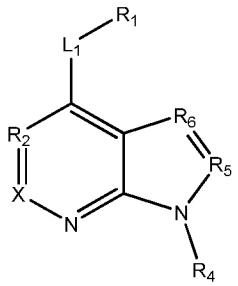
R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and R^4 is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is an amino group;

R^5 is a saturated carbon atom; and

R^6 is an amino group; and wherein the compound is not a compound disclosed in U.S. Patent Application No. 61/763,444, filed February 11, 2013 and to U.S. Patent Application No. 61/845,529, filed July 12, 2103, or any non-provisional application, filed February 11, 2014, claiming priority to thereto.

[0164] In some embodiments, the invention relates to a compound having formula:



wherein X is independently selected from a -CH, -CHCH3, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted 2,5-dihydrofuranyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted 2,5-dihydrothienyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted 2,5-dihydro-1H-pyrrolyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclopentenyl, or

substituted or unsubstituted 1,3-oxathiolanyl, independently be R^{99}-substituted, where R^{99} is as described herein, including embodiments thereof.

L^1 is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

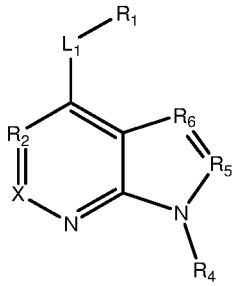
R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and R^4 is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is an N;

R^5 is an N; and

R^6 is a saturated carbon atom.

[0165] In some embodiments, the invention relates to a compound having formula:

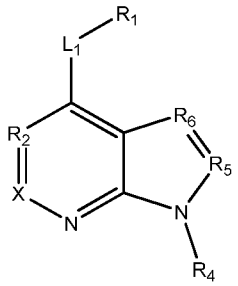


wherein X is C-CH3; L^1 is NH; R^1 is CH_2(2,5-dihydrofuranyl)-R^{99}; R^2 is N; R^4 is hydrogen; R^5 is N; and R^6 is CH;

wherein R^{99} is independently a hydrogen, methyl group, methoxy group, oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_2Cl, -SO_3H, -SO_4H, -SO_2NH_2, -$NHNH_2$, -ONH_2, -$NHC(O)NHNH_2$, -$NHC(O)$ NH_2, -$NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted 2,5-dihydrofuranyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted 2,5-dihydrothienyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted 2,5-dihydro-1H-pyrrolyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclopentenyl, or substituted or unsubstituted 1,3-oxathiolanyl, substituted or unsubstituted phosphate, substituted or unsubstituted monophosphate, substituted or unsubstituted diphosphate, or substituted or unsubstituted triphosphate. In some embodiments, R^{99} is

independently a methoxy group. In some embodiments, R^{99} is independently a hydrogen. In some embodiments, R^{99} is independently a methyl group.

[0166] In some embodiments, the invention relates to a compound having formula:



wherein X is independently selected from a -CH, -$CHCH_3$, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted 2,5-dihydrofuranyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted 2,5-dihydrothienyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted 2,5-dihydro-1H-pyrrolyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclopentenyl, or substituted or unsubstituted 1,3-oxathiolanyl, independently be R^{99}-substituted, where R^{99} is as described herein, including embodiments thereof.

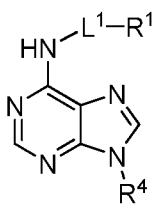
L^1 is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and R^4 is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is an NH;

R^5 is a saturated carbon atom; and

R^6 is an amino group; and wherein the compound is not a compound disclosed with the formula:

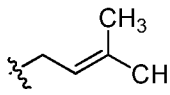
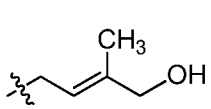
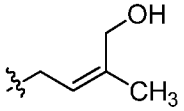
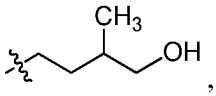
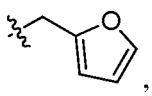
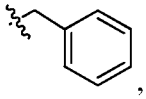
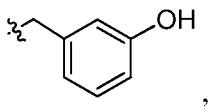
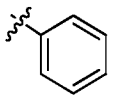
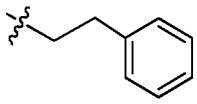


(Formula Ia) wherein

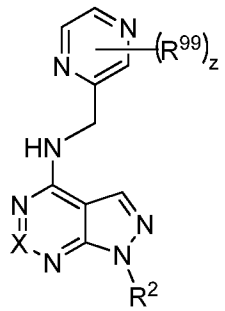
L^1 is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

R^4 is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

wherein if R^4 is hydrogen, then $-L^1-R^1$ is not hydrogen,  ,  ,  ,  ,  ,  ,  ,  , or  .

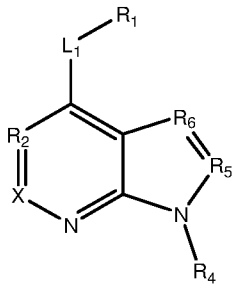
[0167] In some embodiments, the compound of the present invention has the formula:



wherein X is independently selected from a -CH, -CHCH3, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted 2,5-dihydrofuranyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted 2,5-dihydrothienyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted 2,5-dihydro-1H-pyrrolyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclopentenyl, or substituted or unsubstituted 1,3-oxathiolanyl, independently R^{99}-substituted, where R^{99} is as described herein, including embodiments thereof;

wherein R^2 is H; and the symbol z is an integer indpendently selected from 0, 1, 2, 3, 4, or 5;

wherein R^{99} is independently a hydrogen, methyl group, methoxy group, oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)\ NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted 2,5-dihydrofuranyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted 2,5-dihydrothienyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted 2,5-dihydro-1H-pyrrolyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclopentenyl, or substituted or unsubstituted 1,3-oxathiolanyl, substituted or unsubstituted phosphate, substituted or unsubstituted monophosphate, substituted or unsubstituted diphosphate, or substituted or unsubstituted triphosphate. In some embodiments, R^{99} is independently a hydrogen.

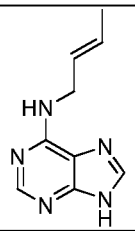
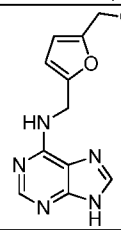
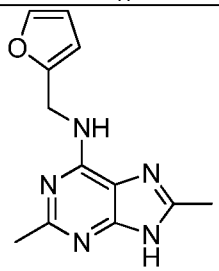
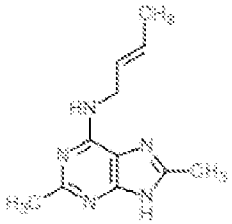
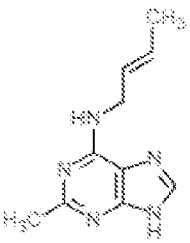


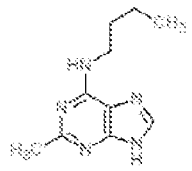
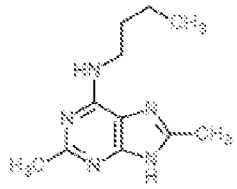
wherein X is CH or C-CH3; L^1 is NH; R^6 is a saturated carbon; R^4 is hydrogen, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 is a N; and R^1 is C (2,5-dihydrofuranyl)-R^{99};

wherein R^{99} is independently a hydrogen, methyl group, methoxy group, oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)\ NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted 2,5-dihydrofuranyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted 2,5-dihydrothienyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted 2,5-dihydro-1H-pyrrolyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted

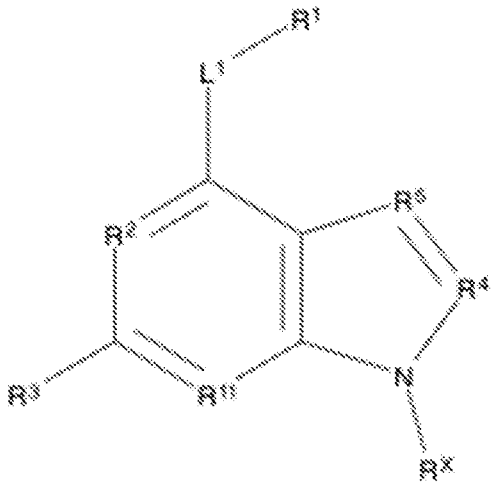
cyclopentenyl, or substituted or unsubstituted 1,3-oxathiolanyl, substituted or unsubstituted phosphate, substituted or unsubstituted monophosphate, substituted or unsubstituted diphosphate, or substituted or unsubstituted triphosphate. In some embodiments, R^{99} is a methoxy group. In some embodiments, R^{99} is a hydrogen. In some embodiments, R^{99} is a methyl group.

[0168] In some embodiments, the present disclosure provides a compound having the Formula of one of the following:

Name	Structure
MTK-B	
MTK-C	
MTK-115 (or MTK-O)	
MTK-115A (Formula VIIIa)	
MTK-63A	

Name	Structure
MTK-63H	
MTK-115D	

[0169] In a first aspect is provided a method of treating a neurodegenerative disease in a patient in need of thereof, the method including administering a therapeutically effective amount of a compound to the patient, wherein the compound has the formula:



(Ib)

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, or substituted or unsubstituted heteroalkylene.

R^1 is hydrogen, oxo, halogen, $-CX_3$, -CN, $-SO_2Cl$, $-SO_nR^{10}$, $-SO_vNR^7R^8$, $-NHNH_2$, $-ONR^7R^8$, $-NHC=(O)NHNH_2$, methylene, ethylene, propylene, butylene, thiophene, furan, $-NHC=(O)NR^7R^8$, $-N(O)_m$, $-NR^7R^8$, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^7R^8$, $-OR^{10}$, $-NR^7SO_2R^{10}$, $-N(R^7)C=(O)R^9$, $-NR^7C(O)-OR^9$, $-NR^7OR^9$, $-OCX_3$, $-OCHX_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

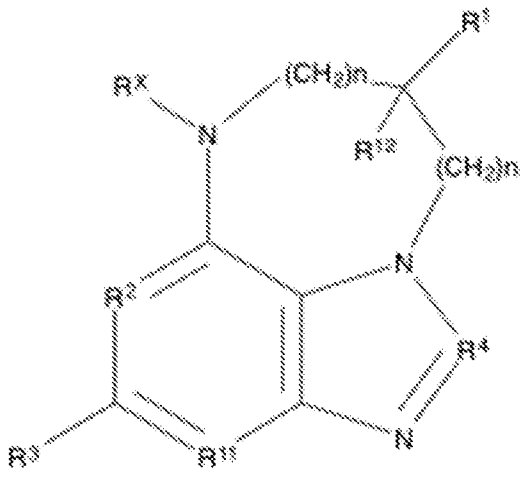
R^2, R^4, R^5, R^{11} are independently -N, -CH, -CD, or -C-L^1-R^6 where in R^6 is independently halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, SO_nR^{10}, $-SO_vNR^7R^8$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)\ NH_2$, $-NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, $-ONR^7R^8$, $-NHC=(O)NHNH_2$, $-NHC=(O)NR^7R^8$, $-N(O)_m$, $-NR^7R^8$, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^7R^8$, $-OR^{10}$, $-NR^7SO_2R^{10}$, $-N(R^7)C=(O)R^9$, $-NR^7C(O)-OR^9$, $-NR^7OR^9$, $-OCX_3$, $-OCHX_2$, $-OCF_3$, $-OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; where R^7 and R^8 are bonded to the same nitrogen atom, they may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. The symbols m and v are independently 1 or 2. The symbol n is independently an integer from 0 to 4. The symbol X is independently –Cl, -Br, -I, or –F;

R^3 is independently H, D, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, SO_nR^{10}, $-SO_vNR^7R^8$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)\ NH_2$, $-NHSO_2H$, $-NHC=(O)H$, -NHC(O)-OH, -NHOH, $-ONR^7R^8$, $-NHC=(O)NHNH_2$, $-NHC=(O)NR^7R^8$, $-N(O)_m$, $-NR^7R^8$, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^7R^8$, $-OR^{10}$, $-NR^7SO_2R^{10}$, $-N(R^7)C=(O)R^9$, $-NR^7C(O)-OR^9$, $-NR^7OR^9$, $-OCX_3$, $-OCHX_2$, $-OCF_3$, $-OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; where R^7 and R^8 are bonded to the same nitrogen atom, they may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. The symbols m and v are independently 1 or 2. The symbol n is independently an integer from 0 to 4. The symbol X is independently –Cl, -Br, -I, or –F;

R^x is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^7, R^8, R^9, and R^{10} are independently hydrogen, deuterium, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -

NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; where R^7 and R^8 are bonded to the same nitrogen atom, they may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. The symbols m and v are independently 1 or 2. The symbol n is independently an integer from 0 to 4. The symbol X is independently –Cl, -Br, -I, or –F;



(IIa)

R^1 is hydrogen, deuterium, oxo, halogen, $-CX_3$, -CN, $-SO_2Cl$, $-SO_nR^{10}$, $-SO_vNR^7R^8$, $–NHNH_2$, $–ONR^7R^8$, $–NHC=(O)NHNH_2$, $–NHC=(O)NR^7R^8$, $-N(O)_m$, $-NR^7R^8$, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^7R^8$, $-OR^{10}$, $-NR^7SO_2R^{10}$, $-N(R^7)C=(O)R^9$, $-NR^7C(O)-OR^9$, $-NR^7OR^9$, $-OCX_3$, $-OCHX_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2, R^4, R^{11} are independently -N, -CH, -CD, or $-C-L^1-R^6$ where in R^6 is independently halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, SO_nR^{10}, $-SO_vNR^7R^8$, $–NHNH_2$, $–ONH_2$, $–NHC=(O)NHNH_2$, $–NHC=(O)\ NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $–ONR^7R^8$, $–NHC=(O)NHNH_2$,$–NHC=(O)NR^7R^8$, $-N(O)_m$, $-NR^7R^8$, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^7R^8$, $-OR^{10}$, $-NR^7SO_2R^{10}$, $-N(R^7)C=(O)R^9$, $-NR^7C(O)-OR^9$, $-NR^7OR^9$, $-OCX_3$, $-OCHX_2$, $-OCF_3$, $-OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; where R^7 and R^8 are bonded to the same nitrogen atom, they may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. The symbols m and v are independently 1 or 2. The symbol n is independently an integer from 0 to 4. The symbol X is independently –Cl, -Br, -I, or –F;

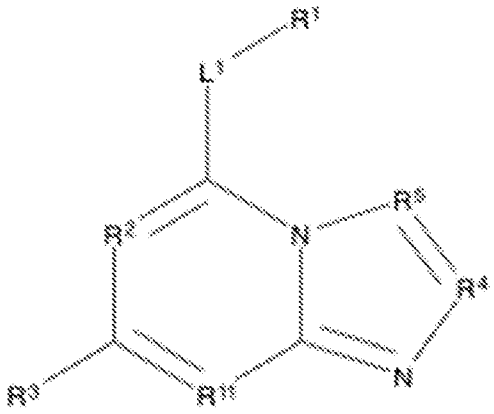
R^3 is independently H, D, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, SO_nR^{10}, $-SO_vNR^7R^8$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-ONR^7R^8$, $-NHC=(O)NHNH_2$, $-NHC=(O)NR^7R^8$, $-N(O)_m$, $-NR^7R^8$, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^7R^8$, $-OR^{10}$, $-NR^7SO_2R^{10}$, $-N(R^7)C=(O)R^9$, $-NR^7C(O)-OR^9$, $-NR^7OR^9$, $-OCX_3$, $-OCHX_2$, $-OCF_3$, $-OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; where R^7 and R^8 are bonded to the same nitrogen atom, they may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. The symbols m and v are independently 1 or 2. The symbol n is independently an integer from 0 to 4. The symbol X is independently –Cl, -Br, -I, or –F;

R^x is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^7, R^8, R^9, and R^{10} are independently hydrogen, deuterium, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; where R^7 and R^8 are bonded to the same nitrogen atom, they may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. The symbols m and v are independently 1 or 2. The symbol n is independently an integer from 0 to 4. The symbol X is independently –Cl, -Br, -I, or –F;

R^{12} is independently H, D,

halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_2Cl, -SO_3H, -SO_4H, -SO_2NH_2, SO_nR^{10}, -$SO_vNR^7R^8$, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O)NH_2, -$NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, –ONR^7R^8, –NHC=(O)$NHNH_2$, –NHC=(O)NR^7R^8, -$N(O)_m$, -NR^7R^8, -$C(O)R^9$, -$C(O)OR^9$, -$C(O)NR^7R^8$, -OR^{10}, -$NR^7SO_2R^{10}$, -$N(R^7)C=(O)R^9$, -$NR^7C(O)$-OR^9, -NR^7OR^9, -OCX_3, -$OCHX_2$, -OCF_3, -$OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; where R^7 and R^8 are bonded to the same nitrogen atom, they may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. The symbols m and v are independently 1 or 2. The symbol n is independently an integer from 0 to 4. The symbol X is independently –Cl, -Br, -I, or –F;



IIIa.

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, or substituted or unsubstituted heteroalkylene.

R^1 is hydrogen, deuterium, oxo,

halogen, -CX_3, -CN, -SO_2Cl, $-SO_nR^{10}$, -$SO_vNR^7R^8$, –$NHNH_2$, –ONR^7R^8, –NHC=(O)$NHNH_2$, methylene, ethylene, propylene, butylene, furan, thiophene, –NHC=(O)NR^7R^8, -$N(O)_m$, -NR^7R^8, -$C(O)R^9$, -$C(O)OR^9$, -$C(O)NR^7R^8$, -OR^{10}, -$NR^7SO_2R^{10}$, -$N(R^7)C=(O)R^9$, -$NR^7C(O)$-OR^9, -NR^7OR^9, -OCX_3, -$OCHX_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

R^2, R^4, R^5, R^{11} are independently -N, -CH, -CD, or -C-L^1-R^6 where in R^6 is independently halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_2Cl, -

SO_3H, -SO_4H, -SO_2NH_2, SO_nR^{10}, -$SO_vNR^7R^8$, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, –ONR^7R^8, –NHC=(O)$NHNH_2$, –NHC=(O)NR^7R^8, -$N(O)_m$, -NR^7R^8, -C(O)R^9, -C(O)OR^9, -C(O)NR^7R^8, -OR^{10}, -$NR^7SO_2R^{10}$, -$N(R^7)$C=(O)R^9, -NR^7C(O)OR^9, -NR^7OR^9, -OCX_3, -$OCHX_2$, -OCF_3, -O CHF_2, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; where R^7 and R^8 are bonded to the same nitrogen atom, they may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. The symbols m and v are independently 1 or 2. The symbol n is independently an integer from 0 to 4. The symbol X is independently –Cl, -Br, -I, or -F.

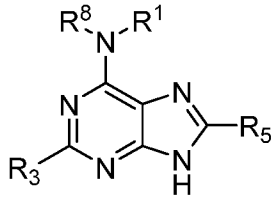
R^3 is independently H, D,
halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_2Cl, -SO_3H, -SO_4H?, -SO_2NH_2, SO_nR^{10}, -$SO_vNR^7R^8$, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, –ONR^7R^8, –NHC=(O)$NHNH_2$, –NHC=(O)NR^7R^8, -$N(O)_m$, -NR^7R^8, -C(O)R^9, -C(O)OR^9, -C(O)NR^7R^8, -OR^{10}, -$NR^7SO_2R^{10}$, -$N(R^7)$C=(O)R^9, -NR^7C(O)-OR^9, -NR^7OR^9, -OCX_3, -$OCHX_2$, -OCF_3, -$OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; where R^7 and R^8 are bonded to the same nitrogen atom, they may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. The symbols m and v are independently 1 or 2. The symbol n is independently an integer from 0 to 4. The symbol X is independently –Cl, -Br, -I, or -F

R^x is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

R^7, R^8, R^9, and R^{10} are independently hydrogen, deuterium,
halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_2Cl, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted

or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; where R^7 and R^8 are bonded to the same nitrogen atom, they may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. The symbols m and v are independently 1 or 2. The symbol n is independently an integer from 0 to 4. The symbol X is independently –Cl, -Br, -I, or -F.

[0170] In other aspects, provided is a method of treating a neurodegenerative disease in a patient in need of thereof, the method including administering a therapeutically effective amount of a compound having the formula XX^1:


(XX^1);

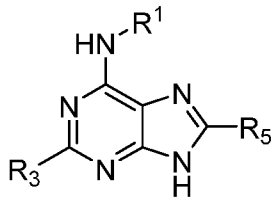
or a pharmaceutically acceptable salt thereof, wherein

R_3 and R_5 are each unsubstituted (C_1-C_4)alkyl;

R^8 is hydrogen or unsubstituted (C_1-C_4)alkyl; and

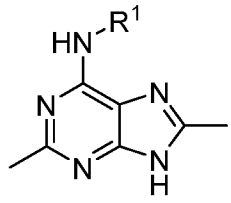
R^1 is a (C_1-C_6)alkyl or (C_2-C_6)alkene, wherein said (C_1-C_6)alkyl is optionally substituted with phenyl, a monocyclic 5-7 membered heterocycloalkyl, or a monocyclic 5-7 membered heteroaryl, each of which are optionally substituted with 1 or 2 (C_1-C_4)alkyl.

[0171] In other aspects, provided is a method of treating a neurodegenerative disease in a patient in need of thereof, the method including administering a therapeutically effective amount of a compound having the formula XX^2


(XX^2);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula XX^1.

[0172] In other aspects, provided is a method of treating a neurodegenerative disease in a patient in need of thereof, the method including administering a therapeutically effective amount of a compound having the formula XX^3



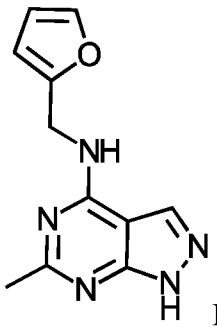
(XX^3);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula XX^2.

[0173] In some embodiments, said (C_1-C_6)alkyl for R_1 in the compound of Formula XX^1, XX^2, or XX^3 for the disclosed methods is optionally substituted with phenyl, furanyl, tetrahydropyranyl, pyridinyl, or pyrizinyl, each of which are optionally substituted with 1 or 2 (C_1-C_4)alkyl.

[0174] In some embodiments, said R_1 in the compound of Formula XXX^1, XX^2, or XX^3 for the disclosed methods is a (C_1-C_5)alkyl or (C_2-C_4)alkene, wherein said (C_1-C_5)alkyl for R_1 is optionally substituted with phenyl, furanyl, tetrahydropyranyl, pyridinyl, or pyrizinyl, and wherein said furanyl is optionally substituted with (C_1-C_4)alkyl.

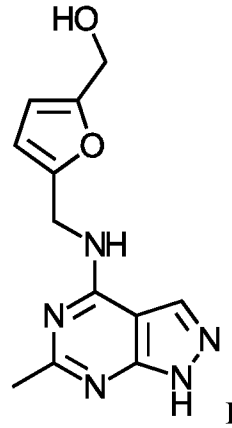
[0175] In some embodiments, the present disclosure provides a compoisiton free of compound having the Formula:



II.

or pharmaceutically acceptable salt thereof.

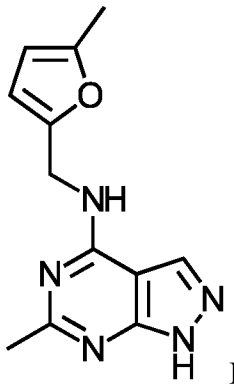
[0176] In some embodiments, the present disclosure provides a compound having the formula



III.

or pharmaceutically acceptable salt thereof.

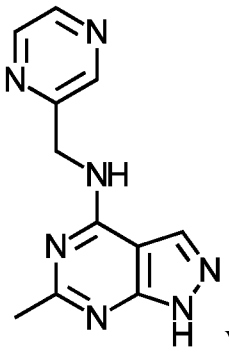
[0177] In some embodiments, the present disclosure provides a compound having the formula



IV.

or pharmaceutically acceptable salt thereof.

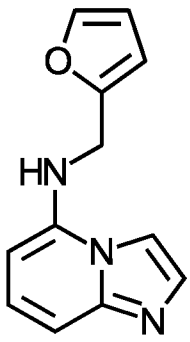
[0178] In some embodiments, the present disclosure provides a compound having the formula:



V.

or pharmaceutically acceptable salt thereof.

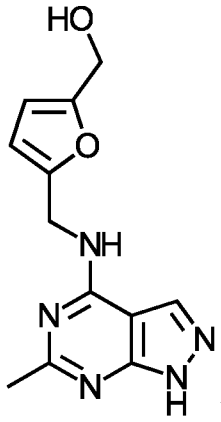
[0179] In some embodiments, the present disclosure provides a compound having the formula:



VI.

or pharmaceutically acceptable salt thereof.

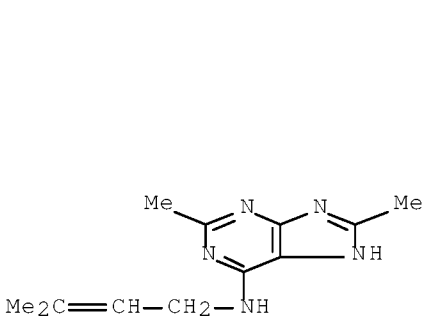
[0180] In some embodiments, the present disclosure provides a compound having the formula:



VII.

or pharmaceutically acceptable salt thereof.

[0181] In one aspect, the following compounds (and pharmaceutically acceptable salts thereof) are excluded from the compounds and formulae described herein:



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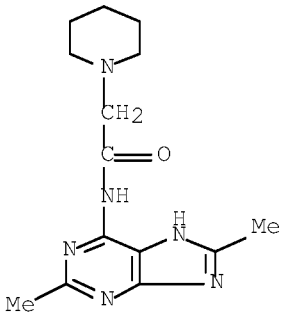

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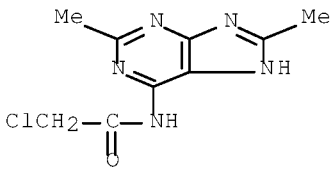
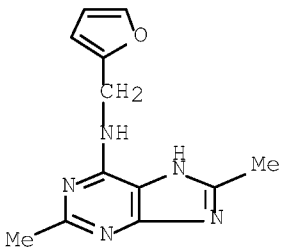
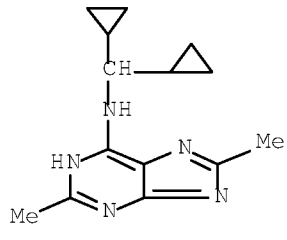


,





and .

[0182] The compounds described herein can also be combined with other compounds or medicaments. The presently described compounds can be used, for example, to inhibit or ameliorate Parkinson's disease and/or Leigh's disease and/or cardiomyopathy and/or fibrosis

in a subject in need thereof. Accordingly, in some embodiments, the present disclosure provides compositions comprising a compound described herein and optionally at least one other compound for treatment or prevention of Leigh's disease in a subject in need thereof. The present disclosure provides compositions comprising a compound described herein and at least one other compound that treats or prevents a neurodegenerative disease in a subject in need thereof. The present disclosure provides compositions comprising a compound described herein and at least one other compound that treats or prevents a mitochondrial disease in a subject in need thereof. The present disclosure provides compositions comprising a compound described herein and at least one other compound that treats or prevents a cardiomyopathy in a subject in need thereof. The present disclosure provides compositions comprising a compound described herein and at least one other compound that treats or prevents fibrosis in a subject in need thereof. In some embodiments, the fibrosis is idiopathic fibrosis. In some embodiments, the fibrosis is liver fibrosis, kidney fibrosis or pulmonary fibrosis. In some embodiments, the fibrosis is idiopathic pulmonary fibrosis.

[0183] The compound(s) can be modified by cellular or synthetic processes to become an active compound(s), which can act as a substrate for the enzyme PINK1. In some embodiments, the compound(s) can be modified to include a biphosphate or a triphosphate group. In some embodiments, the active compound(s) are analogs of adenosine triphosphate (ATP). In some embodiments, the active compound(s) are analogs of kinetin triphosphate (KTP). In some embodiments, the active compound(s) can bind to the N-terminal kinase domain of PINK1. In some embodiments, the active compound(s) can bind to the N-terminal kinase domain of PINK1 with a higher catalytic efficiency than its endogenous substrate ATP. In some embodiments, the active compound(s) can bind to the N-terminal kinase domain of mutated or damaged PINK1, including but not limited to cases where mutated of damaged PINK1 does not bind to ATP or does not bind to ATP with endogenous catalytic efficiency. By acting as a precursor to the active compound(s), the compound(s) have increased membrane permeability, as ATP, KTP and their analogs are membrane impermeable. By acting as a substrate, the compound(s), once converted to the active form, can increase the activity of PINK1. In cases where PINK1 is mutated or damaged and does not exhibit normal levels of activity, the compound(s), once converted to the active form, can restore PINK1 activity.

[0184] Accordingly, in some embodiments, the present disclosure provides methods of treating or preventing Parkinson's disease in a subject comprising administering to the subject one or more compounds, or a pharmaceutically acceptable salt thereof, of any one of

the compounds described herein or a pharmaceutical composition comprising one or more of the compounds described herein, or pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides methods of treating or preventing Leigh's disease in a subject comprising administering to the subject one or more compounds, or a pharmaceutically acceptable salt thereof, of any one of the compounds described herein or a pharmaceutical composition comprising one or more of the compounds described herein, or pharmaceutically acceptable salt thereof. In some embodiments, the treating of Parkinson's or Leigh's disease comprises ameliorating symptoms by stimulating PINK1 or a mutated PINK1.

[0185] In some embodiments, a method of treating one or more of the following mitochondrial diseases in a subject is provided: LHON, MELAS, and Charcot Marie Tooth. In some embodiments, the method comprises administering to a subject one or more compounds described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising one or more compounds described herein, or pharmaceutically acceptable salt thereof. In some embodiments, the method comprises administering to a subject a compound or pharmaceutically acceptable salt thereof that acts as a PINK1 substrate with one or more compounds described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising one or more compounds described herein, or pharmaceutically acceptable salt thereof. In some embodiments, the cholesterol therapeutic is niacin or acifran. In some embodiments, the subject is a subject in need thereof.

[0186] In some embodiments, one or more compounds described herein are administered to a subject. In some embodiments, one or more compounds described herein are administered to a subject in need thereof.

[0187] In some embodiments, one or more compounds described herein are administered to a subject for treatment and/or prevention of cardiomyopathy. In some embodiments, one or more compounds described herein (or their respective pharmaceutical salts thereof) are administered to a subject in need thereof. In some embodiments, one or more pharmaceutical salts optionally in conjunction with a pharmaceutically acceptable carrier are administered to a subject in need thereof.

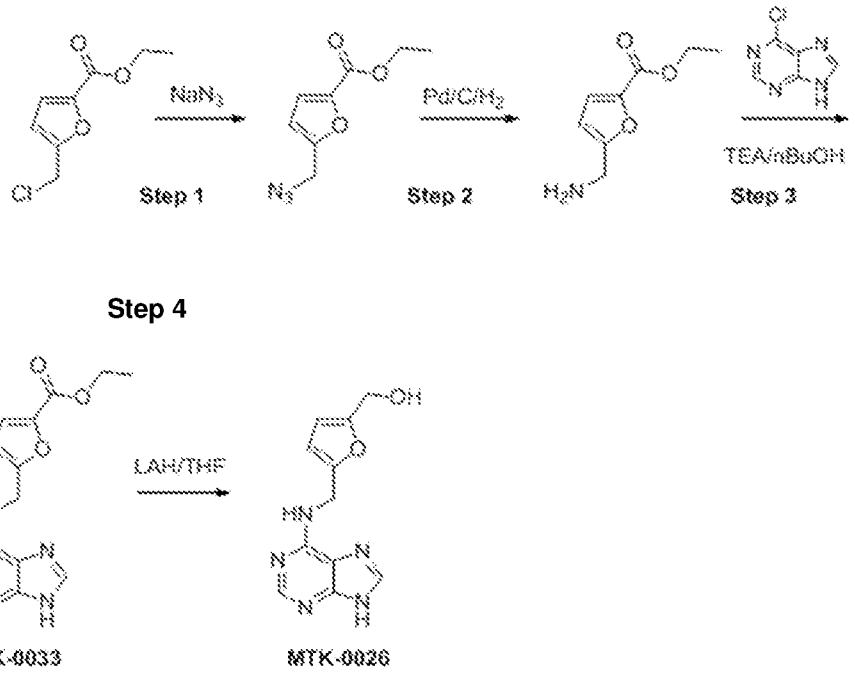
[0188] In some embodiments, the present disclosure provides pharmaceutical compositions comprising a compound or pharmaceutically salt thereof of any compound described herein. In some embodiments, the present disclosure provides pharmaceutical compositions comprising a compound or pharmaceutically salt thereof of any compound described herein.

In some embodiments, the disclosure provides pharmaceutical compositions comprising a pharmaceutically effective amount of one or a plurality of compounds described herein.

[0189] The compounds described herein can be made by can be made according to the methods described herein and in the examples. The methods described herein can be adapted based upon the compounds desired and described herein. In some embodiments, the method of making the compounds is made according to the schemes described herein. In some embodiments, this method can be used to make one or more compounds as described herein and will be apparent to one of skill in the art which compounds can be made according to the methods described herein.

[0190] In some embodiments, a compound is made according to Scheme I.

Scheme I



[0191] The conditions and temperatures can be varied, or the synthesis can be performed according to the examples and compounds described herein.

[0192] This scheme is a non-limiting synthetic schemes and the synthetic route can be modified as would be apparent to one of skill in the art reading the present specification to produce one or more of the compounds described herein.

[0193] The compounds described herein can be administered in any conventional manner by any route where they are active. Administration can be systemic, topical, or oral. For example, administration can be, but is not limited to, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, oral, buccal, sublingual, or ocular routes, or intravaginally, by inhalation, by depot injections, or by implants. The mode of administration

can depend on the conditions or disease to be targeted or treated. The selection of the specific route of administration can be selected or adjusted by the clinician according to methods known to the clinician to obtain the desired clinical response.

[0194] In some embodiments, it may be desirable to administer one or more compounds, or a pharmaceutically acceptable salt thereof, locally to an area in need of treatment. This may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, wherein the implant is of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

[0195] The compounds described herein can be administered either alone or in combination (concurrently or serially) with other pharmaceuticals. For example, the compounds can be administered in combination with other therapeutics that inhibit, reduce or ameliorate symptoms of a neurodegentative disease, a mitochondrial disease, and/or cardiomyopathy. The compounds can also be administered in combination with therapeutics intended to treat neurodegentative disease, a mitochondrial disease, and/or cardiomyopathy, including, but not limited to, Levodopa, Sinemet, Requip, Mirapex, Symmetrel Artane, Cogentin, Eldepryl, Azilect, Tasmar, Comtan and Neupro. The compounds can also be combined with one or more dopamine agonists and/or one or more COMT Inhibitors and/or one or more anticholinergics. Examples of other pharmaceuticals or medicaments are known to one of skill in the art and include, but are not limited to those described herein.

[0196] The means and methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance (see, for example, Modern Pharmaceutics, Banker & Rhodes, Marcel Dekker, Inc. (1979); and Goodman & Gilman's The Pharmaceutical Basis of Therapeutics, 6th Edition, MacMillan Publishing Co., New York (1980)).

[0197] The amount of compound to be administered is that amount which is therapeutically effective. The dosage to be administered will depend on the characteristics of the subject being treated, e.g., the particular animal treated, age, weight, health, types of concurrent treatment, if any, and frequency of treatments, and can be easily determined by one of skill in the art (e.g., by the clinician). The standard dosing for protamine can be used and adjusted (i.e., increased or decreased) depending upon the factors described above. The selection of the specific dose regimen can be selected or adjusted or titrated by the clinician according to methods known to the clinician to obtain the desired clinical response.

[0198] The amount of a compound described herein that will be effective in the treatment and/or prevention of a particular disease, condition, or disorder will depend on the nature and extent of the disease, condition, or disorder, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the compositions will also depend on the route of administration, and the seriousness of the disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. However, a suitable dosage range for oral administration is, generally, from about 0.001 milligram to about 200 milligrams per kilogram body weight, from about 0.01 milligram to about 100 milligrams per kilogram body weight, from about 0.01 milligram to about 70 milligrams per kilogram body weight, from about 0.1 milligram to about 50 milligrams per kilogram body weight, from 0.5 milligram to about 20 milligrams per kilogram body weight, or from about 1 milligram to about 10 milligrams per kilogram body weight. In some embodiments, the oral dose is about 5 milligrams per kilogram body weight.

[0199] In some embodiments, suitable dosage ranges for intravenous (i.v.) administration are from about 0.01 mg to about 500 mg per kg body weight, from about 0.1 mg to about 100 mg per kg body weight, from about 1 mg to about 50 mg per kg body weight, or from about 10 mg to about 35 mg per kg body weight. Suitable dosage ranges for other modes of administration can be calculated based on the forgoing dosages as known by those skilled in the art. For example, recommended dosages for intranasal, transmucosal, intradermal, intramuscular, intraperitoneal, subcutaneous, epidural, sublingual, intracerebral, intravaginal, transdermal administration or administration by inhalation are in the range of from about 0.001 mg to about 200 mg per kg of body weight, from about 0.01 mg to about 100 mg per kg of body weight, from about 0.1 mg to about 50 mg per kg of body weight, or from about 1 mg to about 20 mg per kg of body weight. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. Such animal models and systems are well known in the art.

[0200] The compounds described herein can be formulated for parenteral administration by injection, such as by bolus injection or continuous infusion. The compounds can be administered by continuous infusion subcutaneously over a period of about 15 minutes to about 24 hours. Formulations for injection can be presented in unit dosage form, such as in ampoules or in multi-dose containers, with an optionally added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or

dispersing agents. In some embodiments, the injectable is in the form of short-acting, depot, or implant and pellet forms injected subcutaneously or intramuscularly. In some embodiments, the parenteral dosage form is the form of a solution, suspension, emulsion, or dry powder.

[0201] For oral administration, the compounds described herein can be formulated by combining the compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds to be formulated as tablets, pills, dragees, capsules, emulsions, liquids, gels, syrups, caches, pellets, powders, granules, slurries, lozenges, aqueous or oily suspensions, and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by, for example, adding a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, but are not limited to, fillers such as sugars, including, but not limited to, lactose, sucrose, mannitol, and sorbitol; cellulose preparations such as, but not limited to, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as, but not limited to, the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0202] Orally administered compositions can contain one or more optional agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions may be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compounds. Oral compositions can include standard vehicles such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Such vehicles are suitably of pharmaceutical grade.

[0203] Dragee cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the

tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0204] Pharmaceutical preparations which can be used orally include, but are not limited to, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added.

[0205] For buccal administration, the compositions can take the form of, such as, tablets or lozenges formulated in a conventional manner.

[0206] For administration by inhalation, the compounds described herein can be delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, such as gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0207] The compounds described herein can also be formulated in rectal compositions such as suppositories or retention enemas, such as containing conventional suppository bases such as cocoa butter or other glycerides. The compounds described herein can also be formulated in vaginal compositions such as vaginal creams, suppositories, pessaries, vaginal rings, and intrauterine devices.

[0208] In transdermal administration, the compounds can be applied to a plaster, or can be applied by transdermal, therapeutic systems that are consequently supplied to the organism. In some embodiments, the compounds are present in creams, solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, gels, jellies, and foams, or in patches containing any of the same.

[0209] The compounds described herein can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Depot injections can be administered at about 1 to about 6 months or longer intervals. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an

acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0210] In some embodiments, the compounds can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng., 1987, 14, 201; Buchwald et al., Surgery, 1980, 88, 507 Saudek et al., N. Engl. J. Med., 1989, 321, 574). In some embodiments, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger et al., J. Macromol. Sci. Rev. Macromol. Chem., 1983, 23, 61; see, also Levy et al., Science, 1985, 228, 190; During et al., Ann. Neurol., 1989, 25, 351; Howard et al., J. Neurosurg., 1989, 71, 105). In yet another embodiment, a controlled-release system can be placed in proximity of the target of the compounds described herein, such as the liver, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in the review by Langer, Science, 1990, 249, 1527-1533) may be used.

[0211] It is also known in the art that the compounds can be contained in such formulations with pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The pharmaceutical compositions can also comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. In some embodiments, the compounds described herein can be used with agents including, but not limited to, topical analgesics (e.g., lidocaine), barrier devices (e.g., GelClair), or rinses (e.g., Caphosol).

[0212] In some embodiments, the compounds described herein can be delivered in a vesicle, in particular a liposome (see, Langer, Science, 1990, 249, 1527-1533; Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.).

[0213] Suitable compositions include, but are not limited to, oral non-absorbed compositions. Suitable compositions also include, but are not limited to saline, water, cyclodextrin solutions, and buffered solutions of pH 3-9.

[0214] The compounds described herein, or pharmaceutically acceptable salts thereof, can be formulated with numerous excipients including, but not limited to, purified water, propylene glycol, PEG 400, glycerin, DMA, ethanol, benzyl alcohol, citric acid/sodium citrate (pH3), citric acid/sodium citrate (pH5), tris(hydroxymethyl)amino methane HCl (pH7.0), 0.9% saline, and 1.2% saline, and any combination thereof. In some embodiments, excipient is chosen from propylene glycol, purified water, and glycerin.

[0215] In some embodiments, the formulation can be lyophilized to a solid and reconstituted with, for example, water prior to use.

[0216] When administered to a mammal (e.g., to an animal for veterinary use or to a human for clinical use) the compounds can be administered in isolated form.

[0217] When administered to a human, the compounds can be sterile. Water is a suitable carrier when the compound of Formula I is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical carriers also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[0218] The compositions described herein can take the form of a solution, suspension, emulsion, tablet, pill, pellet, capsule, capsule containing a liquid, powder, sustained-release formulation, suppository, aerosol, spray, or any other form suitable for use. Examples of suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A.R. Gennaro (Editor) Mack Publishing Co.

[0219] In some embodiments, the compounds are formulated in accordance with routine procedures as a pharmaceutical composition adapted for administration to humans. Typically, compounds are solutions in sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration may optionally include a local anesthetic such as lidocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the compound is to be administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the compound is administered by injection, an ampoule of sterile water for

injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0220] The pharmaceutical compositions can be in unit dosage form. In such form, the composition can be divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

[0221] In some embodiments, a composition of the present disclosure is in the form of a liquid wherein the active agent is present in solution, in suspension, as an emulsion, or as a solution/suspension. In some embodiments, the liquid composition is in the form of a gel. In other embodiments, the liquid composition is aqueous. In other embodiments, the composition is in the form of an ointment.

[0222] In some embodiments, the composition is in the form of a solid article. For example, in some embodiments, the ophthalmic composition is a solid article that can be inserted in a suitable location in the eye, such as between the eye and eyelid or in the conjunctival sac, where it releases the active agent as described, for example, U.S. Pat. No. 3,863,633; U.S. Pat. No. 3,867,519; U.S. Pat. No. 3,868,445; U.S. Pat. No. 3,960,150; U.S. Pat. No. 3,963,025; U.S. Pat. No. 4,186,184; U.S. Pat. No. 4,303,637; U.S. Pat. No. 5,443,505; and U.S. Pat. No. 5,869,079. Release from such an article is usually to the cornea, either via the lacrimal fluid that bathes the surface of the cornea, or directly to the cornea itself, with which the solid article is generally in intimate contact. Solid articles suitable for implantation in the eye in such fashion are generally composed primarily of polymers and can be bioerodible or non-bioerodible. Bioerodible polymers that can be used in the preparation of ocular implants carrying one or more of the compounds described herein in accordance with the present disclosure include, but are not limited to, aliphatic polyesters such as polymers and copolymers of poly(glycolide), poly(lactide), poly(epsilon-caprolactone), poly-(hydroxybutyrate) and poly(hydroxyvalerate), polyamino acids, polyorthoesters, polyanhydrides, aliphatic polycarbonates and polyether lactones. Suitable non-bioerodible polymers include silicone elastomers.

[0223] The compositions described herein can contain preservatives. Suitable preservatives include, but are not limited to, mercury-containing substances such as phenylmercuric salts (e.g., phenylmercuric acetate, borate and nitrate) and thimerosal; stabilized chlorine dioxide; quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium

bromide and cetylpyridinium chloride; imidazolidinyl urea; parabens such as methylparaben, ethylparaben, propylparaben and butylparaben, and salts thereof; phenoxyethanol; chlorophenoxyethanol; phenoxypropanol; chlorobutanol; chlorocresol; phenylethyl alcohol; disodium EDTA; and sorbic acid and salts thereof.

[0224] Optionally one or more stabilizers can be included in the compositions to enhance chemical stability where required. Suitable stabilizers include, but are not limited to, chelating agents or complexing agents, such as, for example, the calcium complexing agent ethylene diamine tetraacetic acid (EDTA). For example, an appropriate amount of EDTA or a salt thereof, e.g., the disodium salt, can be included in the composition to complex excess calcium ions and prevent gel formation during storage. EDTA or a salt thereof can suitably be included in an amount of about 0.01% to about 0.5%. In those embodiments containing a preservative other than EDTA, the EDTA or a salt thereof, more particularly disodium EDTA, can be present in an amount of about 0.025% to about 0.1% by weight.

[0225] One or more antioxidants can also be included in the compositions. Suitable antioxidants include, but are not limited to, ascorbic acid, sodium metabisulfite, sodium bisulfite, acetylcysteine, polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, or other agents know to those of skill in the art. Such preservatives are typically employed at a level of from about 0.001% to about 1.0% by weight.

[0226] In some embodiments, the compounds are solubilized at least in part by an acceptable solubilizing agent. Certain acceptable nonionic surfactants, for example polysorbate 80, can be useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, e.g., polyethylene glycol 400 (PEG-400), and glycol ethers.

[0227] Suitable solubilizing agents for solution and solution/suspension compositions are cyclodextrins. Suitable cyclodextrins can be chosen from α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, alkylcyclodextrins (e.g., methyl-β-cyclodextrin, dimethyl-β-cyclodextrin, diethyl-β-cyclodextrin), hydroxyalkylcyclodextrins (e.g., hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin), carboxy-alkylcyclodextrins (e.g., carboxymethyl-β-cyclodextrin), sulfoalkylether cyclodextrins (e.g., sulfobutylether-β-cyclodextrin), and the like. Ophthalmic applications of cyclodextrins have been reviewed in Rajewski et al., Journal of Pharmaceutical Sciences, 1996, 85, 1155-1159.

[0228] In some embodiments, the composition optionally contains a suspending agent. For example, in those embodiments in which the composition is an aqueous suspension or solution/suspension, the composition can contain one or more polymers as suspending

agents. Useful polymers include, but are not limited to, water-soluble polymers such as cellulosic polymers, for example, hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers.

[0229] One or more acceptable pH adjusting agents and/or buffering agents can be included in the compositions, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[0230] One or more acceptable salts can be included in the compositions of the disclosure in an amount required to bring osmolality of the composition into an acceptable range. Such salts include, but are not limited to, those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions. In some embodiments, salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate. In some embodiments, the salt is sodium chloride.

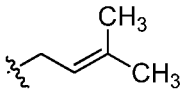
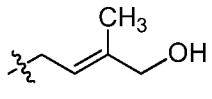
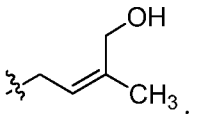
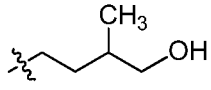
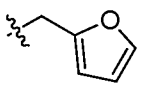
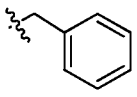
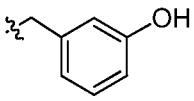
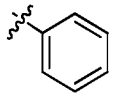
[0231] Optionally one or more acceptable surfactants, preferably nonionic surfactants, or co-solvents can be included in the compositions to enhance solubility of the components of the compositions or to impart physical stability, or for other purposes. Suitable nonionic surfactants include, but are not limited to, polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40; polysorbate 20, 60 and 80; polyoxyethylene/polyoxypropylene surfactants (e.g., Pluronic® F-68, F84 and P-103); cyclodextrin; or other agents known to those of skill in the art. Typically, such co-solvents or surfactants are employed in the compositions at a level of from about 0.01% to about 2% by weight.

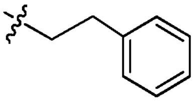
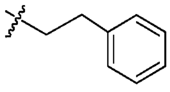
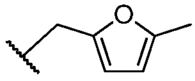
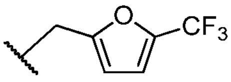
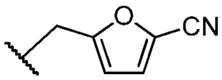
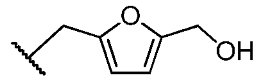
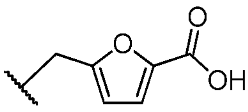
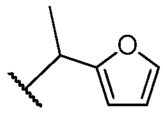
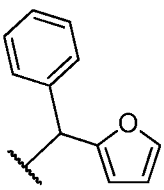
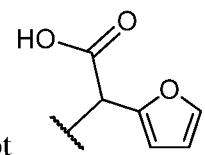
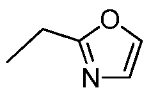
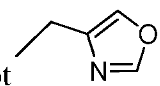
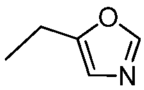
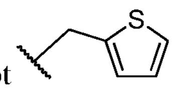
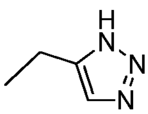
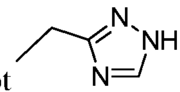
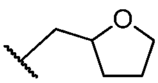
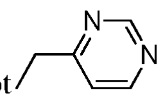
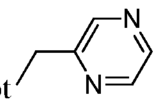
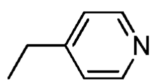
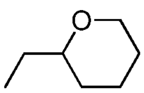
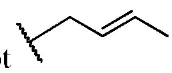
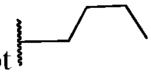
[0232] The present disclosure also provides pharmaceutical packs or kits comprising one or more containers filled with one or more compounds described herein. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration for treating a condition, disease, or disorder described herein. In some embodiments, the kit contains more than one compound described herein. In some embodiments, the kit comprises

a compound described herein in a single injectable dosage form, such as a single dose within an injectable device such as a syringe with a needle.

[0233] The present disclosure also provides one or more compounds described above, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising one or more compounds described above, for use in the manufacture of a medicament for the treatment of flushing and/or in a mammal or subject.

[0234] In some embodiments, the compound or pharmaceutical composition comprising the compounds discosed herein, or the pharmaceutically acceptable salts herein, are neo-substrates of PINK1. In some embodiments, the neo-substrate is not kinetin. In some embodiments, the neo-substrate is not kinetin riboside. In some embodiments, the neo-substrate is not kinetin riboside 5' monophosphate. In some embodiments, the neo-substrate is not kinetin riboside 5' diphosphate. In some embodiments, the neo-substrate is not kinetin riboside 5' triphosphate. In some embodiments, the neo-substrate is not a derivative (e.g. prodrug) of kinetin, kinetin riboside, kinetin riboside 5' monophosphate, kinetin riboside 5' diphosphate, or kinetin riboside 5' triphosphate. In some embodiments, the neo-substrate is not N6-(delta 2-Isopentenyl)-adenine. In some embodiments, the neo-substrate is not N6-(delta 2-Isopentenyl)-adenosine, N6-(delta 2-Isopentenyl)-adenosine 5' monophosphate, N6-(delta 2-Isopentenyl)-adenosine 5' diphosphate, N6-(delta 2-Isopentenyl)-adenosine 5' triphosphate, or a derivative (e.g. prodrug) thereof. In some embodiments, the neo-substrate is not a cytokinin. In some embodiments, the neo-substrate is not a cytokinin riboside, cytokinin riboside 5' monophosphate, cytokinin riboside 5' diphosphate, cytokinin riboside 5' triphosphate, or a derivative (e.g. prodrug) thereof.

[0235] In some embodiments, $-L^1-R^1$ is not hydrogen. In embodiments, $-L^1-R^1$ is not  . In embodiments, $-L^1-R^1$ is not  . In embodiments, $-L^1-R^1$ is not  . In embodiments, $-L^1-R^1$ is not  . In embodiments, $-L^1-R^1$ is R^1 is not  . In embodiments, $-L^1-R^1$ is not  . In embodiments, $-L^1-R^1$ is not  . In embodiments, $-L^1-R^1$ is not  . In embodiments, $-L^1-R^1$ is not

  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  . In embodiments, –L^1-R^1 is not  .

[0236] For each and every method described herein, the mammal or subject can be a mammal or subject in need thereof.

[0237] The present disclosure also provides the use of one or more compounds described above, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising one or more compounds described above, in the modulation of PINK1.

[0238] As used herein, "modulation" can refer to either inhibition or enhancement of a specific activity. For example, the modulation of PINK1 activity can refer to the inhibition and/or activation of PINK1 dependent activities, such as a decrease in Parkin recruitment. In some embodiments, the modulation refers to the inhibition or activation of Parkin recruitment. In some embodiments, the compounds described herein activate PINK1 activity by a factor from about 1% to about 50%. The activity of PINK1 can be measured by any method including but not limited to the methods described herein.

[0239] The compounds described herein are neo-substrates of PINK1. The ability of the compounds to stimulate or inhibit PINK1 activity may be measured using any assay known in the art used to detect Parkin recruitment or PINK1 phosphorylation, or the absence of such signaling/activity. "PINK1 activity" refers to the ability of PINK1 to phosphorylate any substrate. Such activity can be measured, e.g., in a cell(s), by expressing mutant PINK1, administering the compounds disclosed herein and measuring the degree to which cells expressing the mutant PINK1 were able to phosphorylate an enzymatically active substrate as compared to a cell(s) expressing wild-type PINK1.

[0240] PINK1 activity can be measured by changes in the time necessary to recruit 50% of a substrate ("R_{50}"). In some embodiments, the compounds reduce a R50 by a factor of about 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, or 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 1% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 2% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 3% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 4% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 5% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 6% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 7% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 8% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 9% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 10% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 15% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 20% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 25% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor

from about 30% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 35% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 40% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 45% to about 50%. In some embodiments, the compounds reduce a R_{50} by a factor from about 10% to about 40%. In some embodiments, the compounds reduce a R_{50} by a factor from about 10% to about 30%. In some embodiments, the compounds reduce a R_{50} by a factor from about 10% to about 20%.

[0241] Plasmids expressing PINK1 can be transfected into an isolated cell and expressed in an isolated cell, expressed in a membrane derived from a cell, expressed in tissue or in an animal. For example, neuronal cells, cells of the immune system, transformed cells, or membranes can be used to test the PINK1 activity described above. Modulation is tested using one of the in vitro or in vivo assays described herein. Other assays generally known can also be used to test the compounds. Signal transduction can also be examined in vitro with soluble or solid state reactions, using a chimeric molecule such as an extracellular domain of a receptor covalently linked to a heterologous signal transduction domain, or a heterologous extracellular domain covalently linked to the transmembrane and or cytoplasmic domain of a receptor. Furthermore, ligand-binding domains of the protein of interest can be used in vitro in soluble or solid state reactions to assay for ligand binding.

[0242] Ligand binding to an PINK1. Binding can be performed in solution, in a bilayer membrane, attached to a solid phase, in a lipid monolayer, or in vesicles. For example, in an assay, the binding of the natural ligand to its receptor is measured in the presence of a candidate modulator, such as the compound described herein. Alternatively, the binding of the candidate modulator may be measured in the presence of the natural ligand. Often, competitive assays that measure the ability of a compound to compete with binding of the natural ligand to the receptor are used. Binding can be tested by measuring, e.g., changes in spectroscopic characteristics (e.g., fluorescence, absorbance, refractive index), hydrodynamic (e.g., shape) changes, or changes in chromatographic or solubility properties.

[0243] The activity of the compounds can also be measured using assays involving β-arrestin recruitment. β-arrestin serves as a regulatory protein that is distributed throughout the cytoplasm in unactivated cells. Ligand binding to an appropriate GPR109a is associated with redistribution of β-arrestin from the cytoplasm to the cell surface, where it associates with the GPR109a. Thus, receptor activation and the effect of candidate modulators on ligand-induced receptor activation, can be assessed by monitoring β-arrestin recruitment to the cell surface. This is frequently performed by transfecting a labeled β-arrestin fusion protein (*e.g.*,

β-arrestin-green fluorescent protein (GFP)) into cells and monitoring its distribution using confocal microscopy (see, *e.g.*, Groarke *et al.*, J. Biol. Chem. 274(33):23263 69 (1999)).

[0244] Another technology that can be used to evaluate GPR109a-protein interactions in living cells involves bioluminescence resonance energy transfer (BRET). A detailed discussion regarding BRET can be found in Kroeger *et al.*, J. Biol. Chem., 276(16):12736 43 (2001).

[0245] Other assays can involve determining the activity of receptors which, when activated by ligand binding, result in a change in the level of intracellular cyclic nucleotides, *e.g.*, cAMP, by activating or inhibiting downstream effectors such as adenylate cyclase. In one embodiment, changes in intracellular cAMP can be measured using immunoassays. The method described in Offermanns & Simon, J. Biol. Chem. 270:15175 15180 (1995) may be used to determine the level of cAMP. Also, the method described in Felley-Bosco *et al.*, Am. J. Resp. Cell and Mol. Biol. 11:159 164 (1994) may be used to determine the level of cGMP. Further, an assay kit for measuring cAMP a is described in U.S. Pat. No. 4,115,538, herein incorporated by reference.

[0246] In another embodiment, transcription levels can be measured to assess the effects of a test compound on ligand-induced signal transduction. A host cell containing the protein of interest is contacted with a test compound in the presence of the natural ligand for a sufficient time to effect any interactions, and then the level of gene expression is measured. The amount of time to effect such interactions may be empirically determined, such as by running a time course and measuring the level of transcription as a function of time. The amount of transcription may be measured by using any method known to those of skill in the art to be suitable. For example, mRNA expression of the protein of interest may be detected using northern blots or their polypeptide products may be identified using immunoassays. Alternatively, transcription based assays using reporter genes may be used as described in U.S. Pat. No. 5,436,128, herein incorporated by reference. The reporter genes can be, *e.g.*, chloramphenicol acetyltransferase, firefly luciferase, bacterial luciferase, β-galactosidase and alkaline phosphatase. Furthermore, the protein of interest can be used as an indirect reporter via attachment to a second reporter such as green fluorescent protein (see, *e.g.*, Mistili & Spector, Nature Biotechnology 15:961 964 (1997)).

[0247] The amount of transcription is then compared to the amount of transcription in either the same cell in the absence of the test compound, or it may be compared with the amount of transcription in a substantially identical cell that lacks the protein of interest. A substantially identical cell may be derived from the same cells from which the recombinant cell was

prepared but which had not been modified by introduction of heterologous DNA. Any difference in the amount of transcription indicates that the test compound has in some manner altered the activity of the protein of interest.

[0248] Additional assays can also be used. For example, the activity of the compound can be measured in a cell based assay. For example, a nucleic acid molecule encoding GPR109a, such as Accession NP_808219.1, can be incorporated into an expression vector and transfected or transformed into a cell. In some embodiments, the expression vector is a plasmid or virus. In some embodiments, the expression of the nucleic acid molecule is operably linked to a promoter. The promoter can be constitutive or respond to a drug or other response element so that the expression can be controlled. The type of expression vector is not critical and any expression vector can be used that is suitable for the cell type. In some embodiments, the plasmid is pCMV-Prolink. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a Chinese Hamster Ovary (CHO-1) cell. In some embodiments, the cell is an EA-arrestin parental line CHO-1 cell, which is available from DiscoveRx Corporation (Fremont, CA). The expression of the receptor can be stable so that that stable cell lines can be selected. The selection of stably expressing receptor cell lines can be done to routine methods, such as selecting for expression under G418 (Geneticin). The expression of the receptor can also be transient.

[0249] After the receptor is expressed in a cell the cells can be grown in appropriate media in the appropriate cell plate. The cells can be plated, for example at 5000-10000 cells per well in a 384 well plate. In some embodiments, the cells are plated at about 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, or 10000 cells/per well. The plates can have any number of wells and the number of cells can be modified accordingly.

[0250] In some embodiments, to measure cAMP activity that is mediated by the receptor, responses can be determined by measuring changes in intracellular cAMP using. cAMP can be measured by any known method or kit. Examples of a kit that can be used, include but are not limited to, CisBio HTRF cAMP HiRange kit (cat # 62AM6PEJ) based on time-resolved fluorescence resonance energy transfer (TR-FRET). The compounds (*e.g.* test or control) can be contacted with the cells for a period of time and then cAMP can be measured.

[0251] In some embodiments, a compound's effect on the modulation of PINK1 will be measured using cells expressing mutant and wild-type verisons of PINK1. PINK1 is generally known. In some embodiments, the enzymatic rescue is measured. Enzymatic rescue experiments are experiments in which cells expressing mutated forms of the PINK1 with reduced or deficient enzymatic activity are contacted with compounds of the present

invention and are able to re-activate the mutated PINK1 enzymatic activity. PINK1 molecules are known. In some embodiments, the compounds of the present invention are able to enzymatically rescue human PINK1 (accession number AY358957, which is incorporated by reference in its entirety) having the following amino acid sequence: MLWWLVLLLLPTLKSVFCSLVTSLYLPNTEDLSLWLWPKPDLHSGTRTEVSTHTVPSKPGTASPCWPL AGAVPSPTVSRLEALTRAVQVAEPLGSCGFQGGPCPGRRRD. In some embodiment, the compounds of the present invention are able to enzymatically rescue mouse PINK1 (accession number XM_924521, which is incorporated by reference in its entirety) having the following amino acid sequence:

MAVRQALGRGLQLGRALLLRFAPKPGPLFGWGKPGPAAAWGRGE
RPGQVVSPGAQPRPVGLPLPDRYRFFRQSVAGLAARIQRQFMVRARGGAGPCGRAVFL
AFGLGLGLIEEKQAEGRRAASACQEIQAIFTQKTKRVSDPLDTRCWQGFRLEDYLIGQ
AIGKGCNAAVYEATMPTLPQHLEKAKHLGLIGKGPDVVLKGADGEQAPGTPTFPFAIK
MMWNISAGSSSEAILSKMSQELVPASRVALAGEYGAVTYRRSRDGPKQLAPHPNIIRV
FRAFTSSVPLLPGALADYPDMLPPHYYPEGLGHGRTLFLVMKNYPCTLRQYLEEQTPS
SRLATMMTLQLLEGVDHLVQQGIAHRDLKSDNILVEWDSDGCPWLVISDFGCCLADQH
VGLRLPFNSSSVERGGNGSLMAPEVSTAHSGPSAVIDYSKADTWAVGAIAYEIFGLAN
PFYGQGSAHLESRSYQEAQLPEMPESVPPEARRLVRSLLQREASKRPSARLAANVLHL
SLWGEHLLALKNLKLDKMIAWLLQQSAATLLADRLREKSCVETKLQMLFLANLECEAL
CQAALLLSSWRAAP.

[0252] In some embodiments, the compounds of the present invention are able to enzymatically rescue rat PINK1 (accession number XM_216565, which is incorporated by reference in its entirety) having the following amino acid sequence:

MAVRQALGRGLQLGRALLLRFAPKPGPVSGWGKPGPGAAWGRGE
RPGRVSSPGAQPRPLGLPLPDRYRFFRQSVAGLAARIQRQFVVRARGGAGPCGRAVFL
AFGLGLGLIEEKQAESRRAASACQEIQAIFTQKNKQVSDPLDTRRWQGFRLEDYLIGQ
AIGKGCNAAVYEATMPTLPQHLEKAKHLGLLGKGPDVVSKGADGEQAPGAPAFPFAIK
MMWNISAGSSSEAILSKMSQELEALGSANRKGTLQQFRR

[0253] The present disclosure also provides the use of one or more compounds described above, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising one or more compounds described above, in the treatment of Leigh's disease, Parkinson's disease, and/or any other mitochondrial disease or neurodegenerative disease. In some embodiments, the mammal is a mammal in need thereof.

[0254] Any medicament having utility in an application described herein can be used in co-therapy, co-administration or co-formulation with a composition as described above. Such additional medicaments include, medicines for cholesterol, such as but not limited to niacin, acifran, a statin, such as, but not limited to, lovastatin, atorvastatin, fluvastatin, pitavastatin, rosuvastatin, simvastatin, and the like. Other additional medicaments include, but are not limited to, ezetimibe, Trilipix (fenofibric acid), and the like. Other medicaments and

compositions include, but are not limited to, fish oil, red yeast rice, omega fatty acids, and the like.

[0255] The additional medicament can be administered in co-therapy (including co-formulation) with the one or more of the compounds described herein.

[0256] In some embodiments, the response of the disease or disorder to the treatment is monitored and the treatment regimen is adjusted if necessary in light of such monitoring.

[0257] Frequency of administration is typically such that the dosing interval, for example, the period of time between one dose and the next, during waking hours is from about 2 to about 12 hours, from about 3 to about 8 hours, or from about 4 to about 6 hours. It will be understood by those of skill in the art that an appropriate dosing interval is dependent to some degree on the length of time for which the selected composition is capable of maintaining a concentration of the compound(s) in the subject and/or in the target tissue (e.g., above the EC_{50} (the minimum concentration of the compound which modulates the receptor's activity by 90%). Ideally the concentration remains above the EC_{50} for at least 100% of the dosing interval. Where this is not achievable it is desired that the concentration should remain above the EC_{50} for at least about 60% of the dosing interval, or should remain above the EC_{50} for at least about 40% of the dosing interval.

[0258] In order that the disclosure disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the disclosure in any manner. Throughout these examples, there may be molecular cloning reactions, and other standard recombinant DNA techniques described and these were carried out according to methods described in Maniatis et al., Molecular Cloning - A Laboratory Manual, 2nd ed., Cold Spring Harbor Press (1989), using commercially available reagents, except where otherwise noted.

[0259] The following examples are provided to describe the invention in greater detail. They are intended to illustrate, not to limit, the invention. Various publications, including patents, published applications, technical articles and scholarly articles are cited throughout the specification. Each of these cited publications is incorporated by reference herein in its entirety.

EXAMPLES

Example 1: Synthesis of Compounds

Abbreviations list:

-General

anhy.	Anhydrous
aq.	Aqueous
min	minute(s)
mL	Milliliter
mmol	millimole(s)
mol	mole(s)
MS	mass spectrometry
NMR	nuclear magnetic resonance
TLC	thin layer chromatography
HPLC	high-performance liquid chromatography

-Spectrum

Hz	Hertz
δ	chemical shift
J	coupling constant
s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	Multiplet
br	Broad
qd	quartet of *doublets*
dquin	doublet of quintets
dd	*doublet* of *doublets*
dt	*doublet* of triplets

- Solvents and Reagents

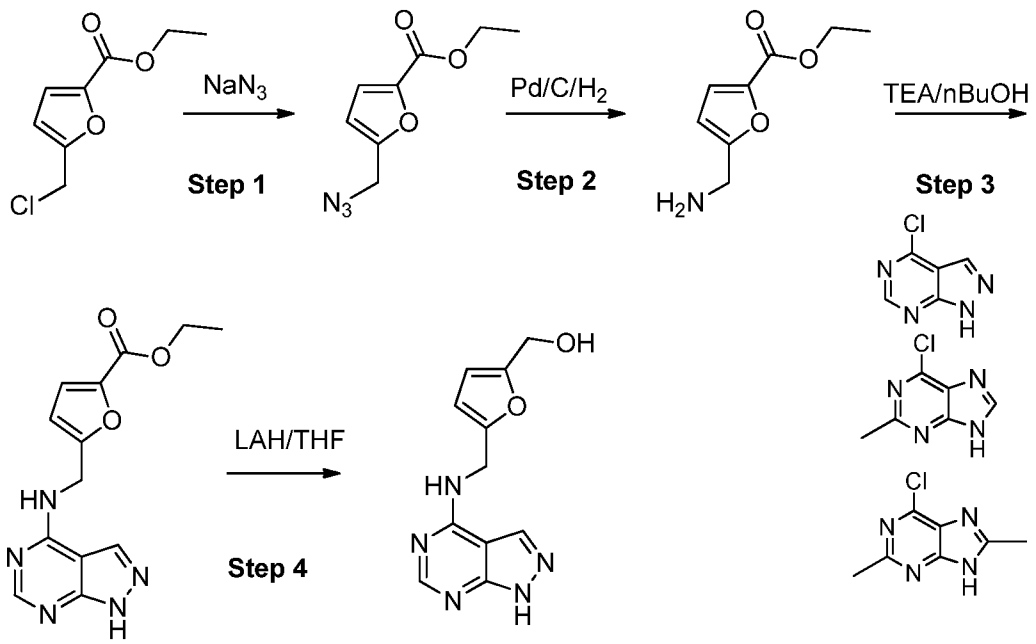
$CHCl_3$	Chloroform
DCM	Dichloromethane
DMF	Dimethylformamide
Et_2O	diethyl ether
EtOH	ethyl alcohol
EtOAc	ethyl acetate
MeOH	methyl alcohol
MeCN	Acetonitrile
PE	petroleum ether
THF	Tetrahydrofuran
AcOH	acetic acid
HCl	hydrochloric acid
H_2SO_4	sulfuric acid
NH_4Cl	ammonium chloride
KOH	potassium hydroxide
NaOH	sodium hydroxide
K_2CO_3	potassium carbonate
Na_2CO_3	sodium carbonate
TFA	trifluoroacetic acid
Na_2SO_4	sodium sulfate

$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium bicarbonate
LiHMDS	lithium hexamethyldisilylamide
NaHMDS	sodium hexamethyldisilylamide
LAH	lithium aluminum hydride
$NaBH_4$	sodium borohydride
LDA	lithium diisopropylamide
Et_3N	Triethylamine
DMAP	4-(dimethylamino)pyridine
DIPEA	*N,N*-diisopropylethylamine
NH_4OH	ammonium hydroxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBt	1-hydroxybenzotriazole
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetra-methyluronium
Xphos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
BINAP	2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl

General synthesis notes

[0260] In the following example, the reagents (chemicals) were purchased from commercial sources (such as Alfa, Acros, Sigma Aldrich, TCI and Shanghai Chemical Reagent Company), and used without further purification. Flash chromatography was performed on an Ez Purifier III using column with silica gel particles of 200-300 mesh. Analytical and preparative thin layer chromatography (TLC) plates were HSGF 254 (0.15-0.2 mm thickness, Shanghai Anbang Company, China). Nuclear magnetic resonance (NMR) spectra were obtained on a Brucker AMX-400 NMR (Brucker, Switzerland). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Mass spectra were given with electrospray ionization (ESI) from a Waters LCT TOF Mass Spectrometer (Waters, USA). HPLC chromatographs were record on an Agilent 1200 Liquid Chromatography (Agilent, USA, column: Ultimate 4.6mmx50mm, 5μm, mobile phase A: 0.1% formic acid in water; mobile phase B: acetonitrile). Microwave reactions were run on an Initiator 2.5 Microwave Synthesizer (Biotage, Sweden).

General procedure:



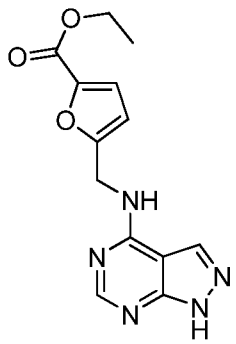
[0261] Step 1: to a mixture of ethyl 5-(chloromethyl)furan-2-carboxylate (1g, 5.32 mmol) in DMF (5 mL) was added NaN_3 (346 mg, 5.32mmol). The mixture was heated to 50°C overnight. TLC show consumption of the start material, one new spot appeared. The mixture was then diluted with brine (20 mL), extracted with DCM (10 mL, twice). The organic layer was combined, dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to afford the crude product, which was used for the next step without purification.

[0262] Step 2: to a mixture of the crude ethyl 5-(azidomethyl)furan-2-carboxylate in ethanol was added 10% palladium on carbon (50 mg), the mixture was held stirring under H_2 atmosphere overnight. TLC show consumption of the start material, one new spot appeared. The mixture was filtered through a pad of celite; the filtrate was concentrated to afford the crude product, which was used directly for the next step without purification. LC-MS: m/z 170.2 $(M+H)^+$

[0263] Step 3: To a solution of 6-chloropurine (1 eq.) in n-butanol were added TEA (2.0 eq) and the corresponding amine (1.2 eq). The mixture was sealed and stirred at 100°C for 12 h. The mixture was filtered, and the precipitation was washed with EA and water twice, and dried under vacuum to provide the desired product. Further purification was done by a reversed phase chromatography, using 0-100% methanol and water as the eluting solvent.

MTK-0101/NB658-034

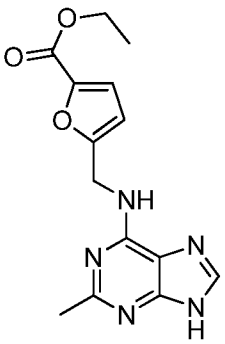
[ethyl 5-((1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)methyl)furan-2-carboxylate]



^{1}H NMR (400 MHz, METHANOL-d_4) δ: 8.30 (s, 1H), 8.12 (s, 1H), 7.19 (d, J = 3.5 Hz, 1H), 6.52 (d, J = 3.5 Hz, 1H), 4.87 (s, 2H), 4.33 (q, J = 7.3 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H). LC-MS: m/z 288.2 $(M+H)^+$

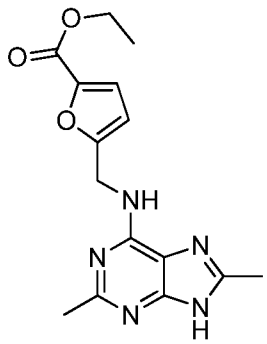
MTK-0118/NB664-033

[ethyl 5-(((2-methyl-9H-purin-6-yl)amino)methyl)furan-2-carboxylate]



^{1}H NMR (400 MHz, CHLOROFORM-d) δ: 8.13 (br. s., 1H), 7.14 (d, J = 3.5 Hz, 1H), 6.56 (br. s., 1H), 5.00 (br. s., 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H). LC-MS: m/z 302.2 $(M+H)^+$

MTK-0119/NB664-034 [ethyl 5-(((2,8-dimethyl-9H-purin-6-yl)amino)methyl)furan-2-carboxylate]

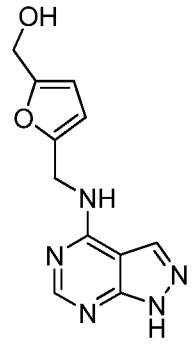


^{1}H NMR (400 MHz, Methanol -d_4) δ: 12.47 (br. s., 1H), 7.91 (br. s., 1H), 7.20 (d, J = 3.5 Hz, 1H), 6.42 (d, J = 3.2 Hz, 1H), 4.74 (br. s., 2H), 4.26 (q, J = 7.2 Hz, 2H), 2.42 (s, 3H), 2.38 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H). LC-MS: m/z 316.2 $(M+H)^+$

[0264] Step 4: To the solution of ethyl 5-(((1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)methyl)furan-2-carboxylate (1 eq) in THF was added $LiAlH_4$(2.0 eq) at 0°C. The mixture was stirred at r.t. overnight. The reaction was quenched with $Na_2SO_4.10H_2O$.The mixture was filtered, and the filtrate was concentrated. The residue was purified by prep-HPLC to provide the desired product.

MTK-0102/NB658-036

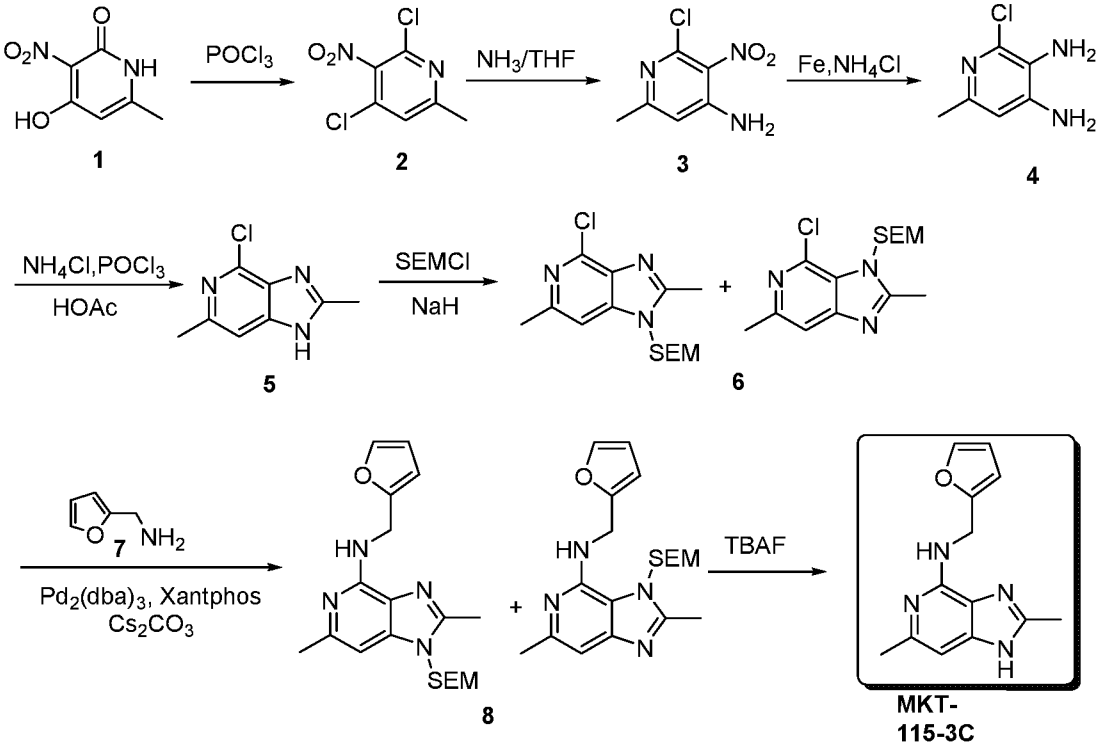
[(5-((1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)methyl)furan-2-yl)methanol]



^{1}H NMR (400 MHz, METHANOL-d_4) δ: 8.29 (s, 1H), 8.11 (s, 1H), 6.25 - 6.33 (m, 2H), 4.79 (s, 2H), 4.50 (s, 2H). LC-MS: m/z 246.2 $(M+H)^+$

Synthesis of N-(furan-2-ylmethyl)-2,6-dimethyl-1H-imidazo[4,5-c]pyridin-4-amine

Synthetic Scheme:



[0265] Step 1: 2,4-dichloro-6-methyl-3-nitropyridine. The solution of compound **1** (5 g, 29 mmol) in $POCl_3$ (20 mL) was stirred at 100°C for 2 hours. After cooling, the mixture was concentrated, poured into cold water and then extracted with EtOAc (50 mL X3). The combined organic layer was washed with $NaHCO_3$ (50 mL), brine (50 mL), filtered and concentrated, purified by column chromatography on silica gel eluting with PE: EtOAc= 5:1 to give compound **2** (4 g, 66%) as a gray solid.

[0266] Step 2: 2-chloro-6-methyl-3-nitropyridin-4-amine. The mixture of compound **2** (4 g, 19 mmol) and NH_3/MeOH (20 mL) in THF (40 mL) was stirred 50 °C overnight. After cooling, the mixture was concentrated, poured into water and then extracted with EtOAc (50 mL X3). The combined organic layer was washed with $NaHCO_3$ (50 mL), brine (50 mL), filtered and concentrated, purified by column chromatography on silica gel eluting with PE: EtOAc= 3:1 to give compound **3** (1.9 g, 52%) as a yellow solid.

[0267] Step 3: 2-chloro-6-methylpyridine-3,4-diamine. The mixture of compound **3** (1.9 g, 10 mmol), Fe (2.8 g, 51 mmol) and NH_4Cl (2.8 g, 51 mmol) in EtOH: H_2O=5: 1 (44 mL) was stirred at 80°C (reflux) overnight. After cooling, the mixture was filtered and the filtrate was concentrated to get compound **4** (1.5 g, 94%) as a yellow solid, which was used to next step directly.

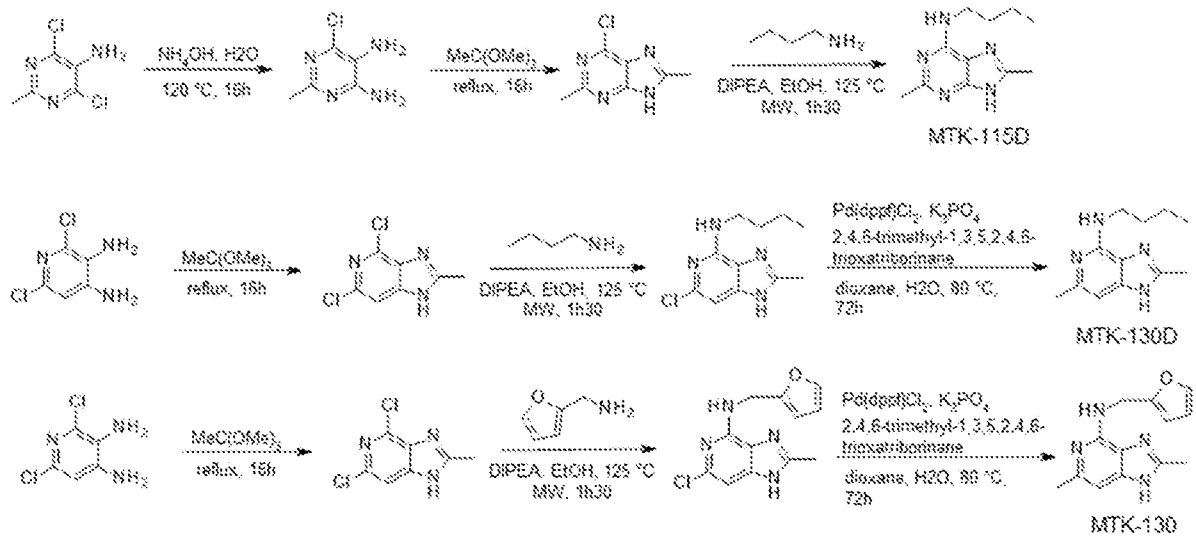
[0268] Step 4: 4-chloro-2,6-dimethyl-1H-imidazo[4,5-c]pyridine. The mixture of compound **4** (500 mg, 3.2 mmol), NH_4Cl (673 mg, 12.7 mmol) and AcOH (230 mg, 3.8 mmol) in $POCl_3$ (2.5 mL) was stirred at 120 °C overnight. The mixture was diluted with EtOAc and basified to pH= 8-9 using saturated $NaHCO_3$ solution. The EtOAc layer was separated, washed with brine (50 mL), filtered and concentrated, purified by column chromatography on silica gel eluting with PE: EtOAc= 1:1 to give compound **5** (450 mg, 78%) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ: 7.32 (s, 1H), 2.52 (s, 3H), 2.49 (s, 3H).

[0269] Step 5: 4-chloro-2,6-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-c]pyridine. To a solution of compound **5** (450 mg, 2.5 mmol) in DMF (10 mL) was added NaH (149 mg, 3.7 mmol) at 0 °C. After stirring for 30 min, SEMCl (619 mg, 3.7 mmol) was added. The mixture was stirred at 0 °C for 1 hour then poured into water and extracted with EtOAc (50 mL), washed with brine (10 mL), filtered and concentrated to get compound **6** (925 mg, quantitative), which was used for next step directly.

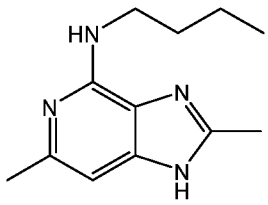
[0270] Step 6: N-(furan-2-ylmethyl)-2,6-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-c]pyridin-4-amine. The mixture of compound 6 (250 mg, 0.8 mmol), compound **7** (97 mg, 1.0 mmol), $Pd_2(dba)_3$ (73 mg, 0.08 mmol), xantphos (70 mg, 0.12 mmol) and Cs_2CO_3 (520 mg, 1.6 mmol) in DMF (10 mL)was stirred at 120 °C overnight. After cooling, the mixture was poured into water and then extracted with EtOAc (10 mL X 3). The combined organic layer was washed with brine (20 mL), filtered and concentrated, purified by column chromatography on silica gel eluting with PE: EtOAc= 1:1 to give compound **8** (200 mg, 67%) as yellow oil, which was confirmed by LCMS.

[0271] Step 7: N-(furan-2-ylmethyl)-2,6-dimethyl-1H-imidazo[4,5-c]pyridin-4-amine. To a solution of compound **8** (200 mg, 0.5 mmol) in THF (2 mL) was added TBAF (2 mL, 1M in THF). The mixture was stirred at 60°C overnight. After cooling, the mixture was concentrated and purified by prep-HPLC to get compound **MTK-115-3C** (**aka MTK-130**)(30 mg, 23%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ: 12.77 (br, 1H), 8.82 (br, 1H), 7.62 (s, 1H), 6.92 (s, 1H), 6.41(t, 2H), 5.08 (s, 2H), 2.52 (s, 3H), 2.49 (s, 3H); LCMS: $[M+H]^+$ 243.8

General Procedure for Formation of MTK-115D and MTK-130D and alternative procedure for MTK-115-3C (MTK-130)



Compound	^{1}H NMR		MS: m/z
MTK-115	($CDCl_3$)		244 $[M+1]^+$
	2.64	3H, s	
	2.67	3H, s	
	4.89	2H, br	
	6.10	1H, br	
	6.30	2H, m	
	7.34	1H, s	
MTK-115D	($CDCl_3$)		
	0.97	3H, t	
	1.46	2H, m	
	1.66	2H, m	
	2.65	3H, s	
	2.66	3H, s	
	3.7	2H, br	
	5.75	1H, br	

Compound	^{1}H NMR		MS: m/z
 MTK-130D	(CD_3OD)		219 $[M+1]^+$
	1.02	8 H, m	
	1.51	2H, m	
	1.74	2H, m	
	2.54	6H, d	
	3.67	2H, m	
	6.81	1H, d	

Example 2: Viral Model of Idiopathic Pulmonary Fibrosis

Animals and animal treatment

[0272] Wild-type C57BL/6 and *Pink1*$^{+/-}$ mice were inoculated intranasally with saline solution or 5×10^4 PFU MHV68 as described in the time course below by way of preparation previously described (11, 35, 37, 38). For some experiments, mice received an intraperitoneal dose of experimental compound MTK-115 identified below or vehicle control. Each compound was dissolved in DMSO then diluted in saline for a final inraperitoneal injection dose of .89mg/kg. The time course for treatment was as follows:

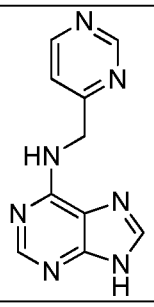
Time zero, Day 1: drug starts and continues daily (1 dose per day)

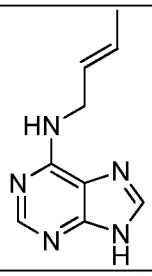
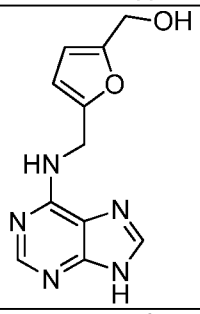
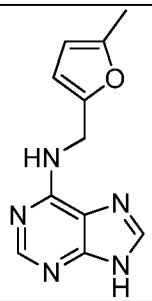
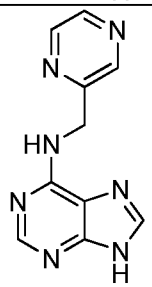
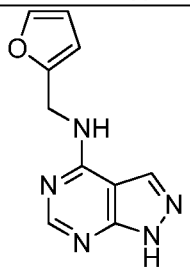
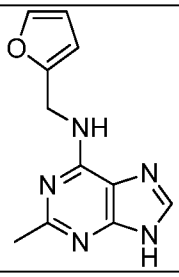
Day 3: viral insult 1

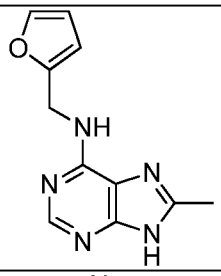
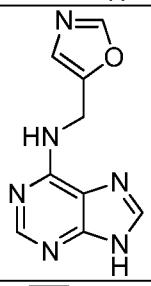
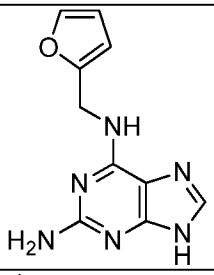
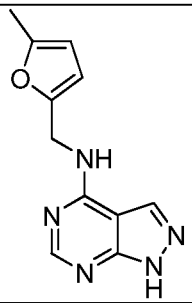
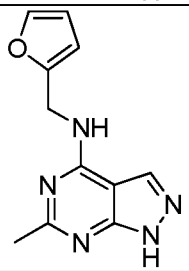
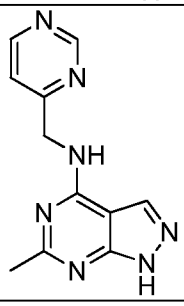
Day 11: viral insult 2

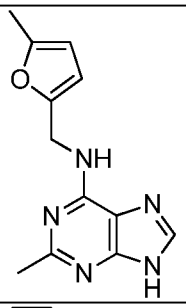
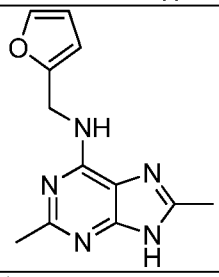
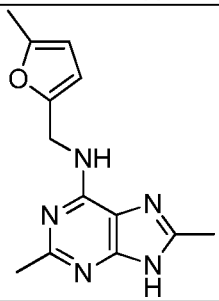
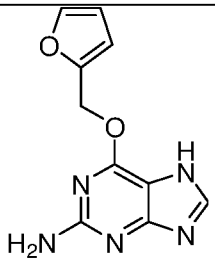
Day 25: Sacrifice Mice

Table 1. Compounds

Designation	MTK #	Structure
MTK-A	MTK-0011	

Designation	MTK #	Structure
MTK-B	MTK-0012	
MTK-C	MTK-0026	
MTK-D	MTK-0043	
MTK-E	MTK-0044	
MTK-F	MTK-0051	
MTK-G	MTK-0063	

Designation	MTK #	Structure
MTK-H	MTK-0064	
MTK-I	MTK-0065	
MTK-J	MTK-0068	
MTK-K	MTK-0095	
MTK-L	MTK-0103	
MTK-M	MTK-0106	

Designation	MTK #	Structure
MTK-N	MTK-0112	
MTK-O	MTK-0115	
MTK-P	MTK-0120	
MTK-Q	New Compound	

Histopathology and Quantitative PCR

[0273] After sacrifice, lungs were perfused with 2% paraformaldehyde, followed by paraffin embedding or saturation in 30% sucrose for 24 hours for frozen sections. Paraffin sections were stained with H&E or Masson trichrome and analyzed under x40 magnification to determine changes in histopathology and fibrosis respectively. Lung samples were assayed for Fibronectin, TNF-Alpha, TGF-Beta, and Collagen 1 transcript levels using quantitative PCR (Fig. 1). To ensure that viral insult was consistent across animals, lung and spleen samples were assayed for copies of ORF50 / GADPH (Fig. 2), and following Bronchoalveolar lavage neutrophil, macrophage, and lymphocytes cell counts were also assayed (Fig. 3).

Example 3: PINK1-specific Mitophagy Assay

[0274] mt-mKeima was cloned into a pCHAC-MCS-1-IRES-MCS2 vector. PINK1D110–YFP–23FKBP wild-type was cloned into pRetroQ-AcGFP-C1 at NheI/ XhoI sites by Gibson assembly kit. The HA-tag was removed, and stop codon introduced. Wild-type HeLa cells stably expressing FRB-Fis1, mt-mKeima, Parkin, and wild-type PINK1D110–YFP–23FKBP were generated using retroviral transduction as described previously. Flag/HA-receptors were stably expressed in these cells by lentivirus transduction as described previously then treated with varying concentrations (see Table 2) of the experimental compounds for 5 days, followed by 1 uM rapalog for 24 h. Cells were then resuspended in sorting buffer (145 mM NaCl, 5 mM KCl, 1.8 mM CaCl2, 0.8 mM MgCl2, 10 mM HEPES, 10 mM glucose, 0.1% BSA) containing 10 mg ml21 DAPI. Analysis was performed using Summit software (v6.2.6.16198) on a Beckman Coulter MoFlo Astrios cell sorter. Measurements of lysosomal mt-mKeima were made using dual-excitation ratiometric pH measurements at 488 (pH7) and 561 (pH4) nm lasers with 620/29 nm and 614/20 nm emission filters, respectively. For each sample, 50,000 events were collected and subsequently gated for YFP/mt-mKeima double-positive cells that were DAPI-negative. Data were analysed using FlowJo (v10, Tree Star).

Table 2. Mitophagy results: Cells were either untreated or treated with rapalog (rapamycin analog) or rapalog + experimental compound (at noted concentration) and analysed by FACS for lysosomal-positive mt-mKeima. The table below shows the percentage of cells undergoing mitophagy at the time at which the FACS analysis was conducted.

Compound	UNTREATED	Rapalog	12.5 uM	25 uM	50 uM
115-A	1.66	7.62	7.26	7.76	8.41
115-D	1.06	10.1	16.7	18.1	18.6
115	1.31	10.4	13.4	16	18.4

Example 4: Western blot of Mutant Huntington Phosphorylation at Serine 16

[0275] Cells were treated with experimental compound for 12 hrs then lysed in either NP-40 lysis buffer (50mM Tris-HCl pH 8.0, 150mM NaCl,1% NP-40) or RIPA lysis buffer (50mM Tris-HCl pH 8.0, 150mM NaCl, 1% NP-40, 0.25% sodium deoxycholate, 1mM EDTA) containing protease and phosphatase inhibitors (Roche). Lysates were centrifuged at 17000 x g for 12 minutes and the supernatant was collected for immunoblot analysis. Equal amounts

of protein were separated by SDS-PAGE on pre-cast 2-20% polyacrylamide gradient gels (Biorad) and electroblotted onto Immobilin poly-vinyl difluoride (PVDF) membrane (EMD Millipore). Membranes were blocked in TBS-T (50mM Tris-HCl, pH 7.5, 150mM NaCl, 0.1% Tween-20) containing 5% non-fat dry milk for 1.5 hours at room temperature, followed by overnight incubation with primary antibodies diluted in blocking buffer at 4°C (anti-N17-S13pS16p 1:2500; anti-p53-S392p 1:1500; anti-GAPDH 1:7500). After three 15-minute TBS-T washes, membranes were incubated with HRP-conjugated secondary antibodies diluted in blocking buffer (1:50000) for 45 minutes at room temperature, and visualized using Immobilin enhanced chemiluminesence HRP substrate (EMD Millipore) on a MicroChemi system (DNR Bio-imaging Systems). Bands were quantified using NIH Image J software and normalized to GAPDH controls (Fig. 4).

Example 5: Pharmacokinetics of Five Compounds in Male SD Rat After Single IV & PO Dosed

[0276] Compounds tested were as follows: kinetin (MW=215.21); MTK-115 (MW=243.26); MTK-115D (MW=219.29); MTK-115A (MW=217.27); and MTK-63A (MW=203.24). Formulation concentrations were 0.2 mg/mL for IV delivery; 0.5 mg/mL for PO delivery. Dosing was as follows: IV: 1 mg/kg, 5 mL/kg; PO: 5 mg/kg, 10 mL/kg. Results are as follows:

Plasma Concentrations (ng/mL) and PK Parameters of kinetin in Male SD Rat After 1 mg/kg IV Dosed

Time point (Hours)	Animal Study No.			Mean	SD
	101M	102M	103M		
0.08	176.2	225.9	184.5	195.5	26.6
0.25	78.8	116.8	100.8	98.8	19.1
0.5	18.9	28.8	27.9	25.2	5.5
1	1.2	1.9	1.6	1.6	0.4
2	BLQ	0.2	BLQ	0.2	NA
4	BLQ	BLQ	BLQ	NA	NA
8	BLQ	BLQ	BLQ	NA	NA
24	BLQ	BLQ	BLQ	NA	NA
HL_Lambda_z ($T_{1/2}$,hr)	0.12	0.19	0.12	0.14	0.04
T_{max} (hr)	0.08	0.08	0.08	0.08	0.00
C_{max} (ng/mL)	176.2	225.9	184.5	195.5	26.6

AUC_{last} (hr*ng/mL)	56.8	78.0	65.3	66.7	10.7
AUC_{INF_pred} (hr*ng/mL)	57.0	78.0	65.6	66.9	10.6
MRT_{INF_pred} (hr)	0.18	0.20	0.20	0.19	0.01
$Vz_{\_pred}$ (L/kg)	3.15	3.43	2.74	3.11	0.34
$Cl_{\_pred}$ (L/hr/kg)	17.54	12.82	15.24	15.20	2.36
λz Calculation Time Range (hr)	0.25-1	0.08-2	0.25-1	NA	NA

Plasma Concentrations (ng/mL) and PK Parameters of kinetin in Male SD Rat After 5 mg/kg PO Dosed

Time point (Hours)	Animal Study No.			Mean	SD
	201M	202M	203M		
0.25	169.1	59.1	41.0	89.7	69.3
0.5	67.5	30.6	28.7	42.3	21.9
1	20.2	21.4	25.7	22.4	2.9
2	22.8	11.0	11.9	15.2	6.6
4	5.0	4.5	4.9	4.8	0.3
8	BLQ	0.2	BLQ	0.2	NA
24	BLQ	BLQ	BLQ	NA	NA
HL_Lambda_z ($T_{1/2}$,hr)	1.08	1.05	1.32	1.15	0.15
T_{max} (hr)	0.25	0.25	0.25	0.25	0.00
C_{max} (ng/mL)	169.1	59.1	41.0	89.7	69.3
AUC_{last} (hr*ng/mL)	121.9	72.7	63.0	85.9	31.6
AUC_{INF_pred} (hr*ng/mL)	129.9	73.0	72.0	91.7	33.1
MRT_{INF_pred} (hr)	1.32	1.63	1.88	1.61	0.28
$Vz_{\_F\_pred}$ (L/kg)	60.02	103.9	132.3	98.8	36.4
$Cl_{\_F\_pred}$ (L/hr/kg)	38.50	68.45	69.40	58.78	17.57
λz Calculation Time Range (hr)	0.5-4	0.5-8	0.5-4	NA	NA
F(%)	36.56	21.80	18.90	25.75	9.47

Plasma Concentrations (ng/mL) and Brain Concentrations (ng/g) of kinetin in Male SD Rat After 1 mg/kg IV Dosed

Time Hours	Rat No.	Plasma conc (ng/mL)	Brain conc (ng/g)	B/P Ratio
1.00	104	1.9	1.2	0.63
	105	4.0	6.6	1.65
	106	5.7	4.8	0.84
	Average	3.9	4.2	1.04
	SD	1.9	2.7	0.54

Plasma Concentrations (ng/mL) and PK Parameters of MTK-115 in Male SD Rat After 1 mg/kg IV Dosed

Time point (Hours)	Animal Study No.			Mean	SD
	301M	302M	303M		
0.08	1849.9	950.0	1481.7	1427.2	452.4
0.25	1150.9	608.4	799.8	853.0	275.1
0.5	496.0	220.6	300.6	339.1	141.7
1	174.6	75.8	95.2	115.2	52.3
2	32.7	5.4	6.6	14.9	15.4
4	BLQ	BLQ	BLQ	NA	NA
8	BLQ	BLQ	BLQ	NA	NA
24	BLQ	BLQ	BLQ	NA	NA
HL_Lambda_z ($T_{1/2}$,hr)	0.39	0.28	0.27	0.31	0.07
T_{max} (hr)	0.08	0.08	0.08	0.08	0.00
C_{max} (ng/mL)	1849.9	950.0	1481.7	1427.2	452.4
AUC_{last} (hr*ng/mL)	902.0	437.2	623.3	654.2	233.9
AUC_{INF_pred} (hr*ng/mL)	919.7	439.5	625.9	661.7	242.1
MRT_{INF_pred} (hr)	0.41	0.34	0.32	0.36	0.05
$Vz_{\_pred}$ (L/kg)	0.61	0.91	0.62	0.71	0.17
$Cl_{\_pred}$ (L/hr/kg)	1.09	2.28	1.60	1.65	0.60
λz Calculation Time Range (hr)	0.5-2	0.5-2	0.5-2	NA	NA

Plasma Concentrations (ng/mL) and PK Parameters of MTK-115 in Male SD Rat After 5 mg/kg PO Dosed

Time point (Hours)	Animal Study No.			Mean	SD
	401M	402M	403M		
0.25	364.9	704.8	757.1	608.9	213.0
0.5	558.7	963.4	666.2	729.4	209.6
1	769.2	1200.2	494.7	821.4	355.6
2	733.7	1224.7	762.7	907.0	275.5
4	1043.6	1801.0	1375.1	1406.6	379.7
8	93.6	231.1	144.9	156.5	69.5
24	BLQ	BLQ	BLQ	NA	NA
HL_Lambda_z ($T_{1/2}$,hr)	1.15	1.35	1.23	1.24	0.10
T_{max} (hr)	4.00	4.00	4.00	4.00	0.00
C_{max} (ng/mL)	1043.6	1801.0	1375.1	1406.6	379.7
AUC_{last} (hr*ng/mL)	5296.2	9139.9	6369.3	6935.1	1983.3
AUC_{INF_pred} (hr*ng/mL)	5451.4	9590.1	6626.8	7222.8	2132.7
MRT_{INF_pred} (hr)	3.38	3.61	3.65	3.54	0.14
$Vz_{\_F\_pred}$ (L/kg)	1.52	1.02	1.34	1.29	0.26
$Cl_{\_F\_pred}$ (L/hr/kg)	0.92	0.52	0.75	0.73	0.20
λz Calculation Time Range (hr)	4-8	4-8	4-8	NA	NA
F(%)	161.92	279.43	194.72	212.02	60.64

Plasma Concentrations (ng/mL) and Brain Concentrations (ng/g) of MTK-115 in Male SD Rat After 1 mg/kg IV Dosed

Time Hours	Rat No.	Plasma conc (ng/mL)	Brain conc (ng/g)	B/P Ratio
1.00	304	365.3	58.8	0.16
	305	98.4	16.2	0.16
	306	251.2	45.0	0.18
	Average	238.3	40.0	0.17
	SD	133.9	21.7	0.01

Plasma Concentrations (ng/mL) and PK Parameters of MTK-115D in Male SD Rat After 1 mg/kg IV Dosed

Time point (Hours)	Animal Study No.			Mean	SD
	501M	502M	503M		
0.08	1435.1	1831.5	1721.9	1662.8	204.7
0.25	754.2	725.0	782.1	753.8	28.6
0.5	126.6	129.7	157.8	138.0	17.2
1	8.5	6.8	8.7	8.0	1.0
2	BLQ	BLQ	BLQ	NA	NA
4	BLQ	BLQ	BLQ	NA	NA
8	BLQ	BLQ	BLQ	NA	NA
24	BLQ	BLQ	BLQ	NA	NA
HL_Lambda_z ($T_{1/2}$,hr)	0.12	0.11	0.12	0.12	0.00
T_{max} (hr)	0.08	0.08	0.08	0.08	0.00
C_{max} (ng/mL)	1435.1	1831.5	1721.9	1662.8	204.7
AUC_{last} (hr*ng/mL)	468.6	551.6	546.0	522.1	46.4
AUC_{INF_pred} (hr*ng/mL)	470.0	552.7	547.4	523.4	46.3
MRT_{INF_pred} (hr)	0.17	0.15	0.17	0.16	0.01
$Vz_{\_pred}$ (L/kg)	0.37	0.29	0.31	0.32	0.04
$Cl_{\_pred}$ (L/hr/kg)	2.13	1.81	1.83	1.92	0.18
λz Calculation Time Range (hr)	0.08-1	0.08-1	0.25-1	NA	NA

Plasma Concentrations (ng/mL) and PK Parameters of MTK-115D in Male SD Rat After 5 mg/kg PO Dosed

Time point (Hours)	Animal Study No.			Mean	SD
	601M	602M	603M		
0.25	998.0	72.6	428.1	499.6	466.8
0.5	720.6	115.9	491.7	442.7	305.3
1	567.0	91.1	250.7	302.9	242.2
2	1707.0	241.5	373.0	773.8	810.8
4	1671.0	708.3	424.0	934.4	653.5
8	4.7	2.8	BLQ	3.8	1.3
24	BLQ	BLQ	BLQ	NA	NA
HL_Lambda_z ($T_{1/2}$,hr)	0.66	0.50	0.51	0.56	0.09
T_{max} (hr)	2.00	4.00	0.50	2.17	1.76
C_{max} (ng/mL)	1707.0	708.3	491.7	969.0	648.2

AUC_{last} (hr*ng/mL)	8527.9	2622.7	1462.9	4204.5	3788.8
AUC_{INF_pred} (hr*ng/mL)	8534.7	2624.7	1466.2	4208.5	3791.1
MRT_{INF_pred} (hr)	3.04	3.57	2.1	2.92	0.72
$Vz_{\_F\_pred}$ (L/kg)	0.56	1.38	2.5	1.49	0.99
$Cl_{\_F\_pred}$ (L/hr/kg)	0.59	1.90	3.4	1.97	1.41
λz Calculation Time Range (hr)	2-8	4-8	0.5-1	NA	NA
F(%)	326.7	100.5	56.04	161.1	145.1

Plasma Concentrations (ng/mL) and Brain Concentrations (ng/g) of MTK-115D in Male SD Rat After 1 mg/kg IV Dosed

Time Hours	Rat No.	Plasma conc (ng/mL)	Brain conc (ng/g)	B/P Ratio
1.00	504	18.5	2.4	0.13
	505	3.3	NA	NA
	506	23.4	3.6	0.15
	Average	15.1	3.0	0.14
	SD	10.5	0.8	0.02

Plasma Concentrations (ng/mL) and PK Parameters of MTK-115A in Male SD Rat After 5 mg/kg PO Dosed

Time point (Hours)	Animal Study No.			Mean	SD
	801M	802M	803M		
0.25	768.8	804.0	807.7	793.5	21.5
0.5	700.6	846.3	795.4	780.8	73.9
1	88.9	157.9	503.2	250.0	222.0
2	169.4	384.5	549.8	367.9	190.7
4	462.6	417.8	1477.5	786.0	599.3
8	0.5	0.5	1.7	0.9	0.7
24	BLQ	BLQ	BLQ	NA	NA
HL_Lambda_z ($T_{1/2}$,hr)	0.86	0.30	0.65	0.6	0.3
T_{max} (hr)	0.25	0.50	4.00	1.6	2.10
C_{max} (ng/mL)	768.8	846.3	1477.5	1030.9	388.7
AUC_{last} (hr*ng/mL)	2164.5	2467.9	6138.2	3590.2	2211.8
AUC_{INF_pred} (hr*ng/mL)	2166.3	2467.9	6141.2	3591.8	2213.0
MRT_{INF_pred} (hr)	2.92	2.63	3.26	2.94	0.31
$Vz_{\_F\_pred}$ (L/kg)	2.86	0.87	0.76	1.50	1.18

$Cl_{\_F\_pred}$ (L/hr/kg)	2.31	2.03	0.81	1.72	0.79
λz Calculation Time Range (hr)	0.5-8	0.25-1	2-8	NA	NA
F(%)	124.02	141.41	351.71	205.72	126.74

Plasma Concentrations (ng/mL) and Brain Concentrations (ng/g) of MTK-115A in Male SD Rat After 1 mg/kg IV Dosed

Time Hours	Rat No.	Plasma conc (ng/mL)	Brain conc (ng/g)	B/P Ratio
1.00	704	5.1	NA	NA
	705	5.2	NA	NA
	706	5.9	NA	NA
	Average	5.4	NA	NA
	SD	0.4	NA	NA

Plasma Concentrations (ng/mL) and PK Parameters of MTK-63A in Male SD Rat After 1 mg/kg IV Dosed

Time point (Hours)	Animal Study No.			Mean	SD
	901M	902M	903M		
0.08	1137.2	993.1	1167.7	1099.3	93.3
0.25	504.6	340.7	379.6	408.3	85.6
0.5	100.9	57.7	108.8	89.1	27.5
1	9.5	6.3	11.0	8.9	2.4
2	BLQ	BLQ	1.5	1.5	NA
4	BLQ	BLQ	BLQ	NA	NA
8	BLQ	BLQ	BLQ	NA	NA
24	BLQ	BLQ	BLQ	NA	NA
HL_Lambda_z ($T_{1/2}$,hr)	0.13	0.13	0.20	0.15	0.04
T_{max} (hr)	0.08	0.08	0.08	0.08	0.00
C_{max} (ng/mL)	1137.2	993.1	1167.7	1099.3	93.3
AUC_{last} (hr*ng/mL)	358.6	289.0	360.2	335.9	40.7
AUC_{INF_pred} (hr*ng/mL)	360.3	289.9	360.4	336.9	40.7
MRT_{INF_pred} (hr)	0.17	0.14	0.17	0.16	0.02
$Vz_{\_pred}$ (L/kg)	0.53	0.63	0.82	0.66	0.15
$Cl_{\_pred}$ (L/hr/kg)	2.78	3.45	2.77	3.00	0.39
λz Calculation Time Range (hr)	0.08-1	0.08-1	0.08-2	NA	NA

Plasma Concentrations (ng/mL) and PK Parameters of MTK-63A in Male SD Rat After 5 mg/kg PO Dosed

Time point (Hours)	Animal Study No.			Mean	SD
	1001M	1002M	1003M		
0.25	304.8	334.5	376.7	338.7	36.1
0.5	59.7	196.5	107.3	121.2	69.4
1	10.8	30.5	22.7	21.3	9.9
2	71.8	77.9	63.6	71.1	7.2
4	22.9	29.8	23.7	25.5	3.8
8	5.3	BLQ	5.8	5.6	0.4
24	BLQ	BLQ	BLQ	NA	NA
HL_Lambda_z ($T_{1/2}$,hr)	1.63	1.44	1.77	1.6	0.2
T_{max} (hr)	0.25	0.3	0.25	0.25	0.00
C_{max} (ng/mL)	304.8	334.5	376.7	338.7	36.1
AUC_{last} (hr*ng/mL)	293.7	326.8	329.5	316.7	20.0
AUC_{INF_pred} (hr*ng/mL)	305.5	388.9	343.7	346.0	41.7
MRT_{INF_pred} (hr)	2.41	2.08	2.26	2.25	0.16
$Vz_{\_F\_pred}$ (L/kg)	38.55	26.76	37.07	34.13	6.42
$Cl_{\_F\_pred}$ (L/hr/kg)	16.37	12.86	14.55	14.59	1.76
λz Calculation Time Range (hr)	2-8	2-4	2-8	NA	NA
F(%)	17.49	19.46	19.62	18.85	1.19

Plasma Concentrations (ng/mL) and Brain Concentrations (ng/g) of MTK-63A in Male SD Rat After 1 mg/kg IV Dosed

Time Hours	Rat No.	Plasma conc (ng/mL)	Brain conc (ng/g)	B/P Ratio
1.00	904	4.5	1.8	0.40
	905	4.4	0.6	0.14
	906	4.8	1.8	0.38
	Average	4.6	1.4	0.30
	SD	0.2	0.7	0.15

Example 6 - Cytoxocity Experiments

[0277] Compounds were incubated for 24hrs at 50uM in Parkin-expressing HeLa cells with intact wt PINK1. After 24hrs, cells were DAPI stained according to standard protocols and assayed via FACS. Results are shown in **Fig. 6**.

Example 7 - PK Experiments

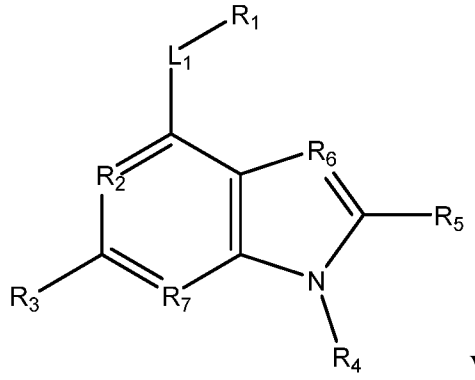
[0278] Compounds were prepared in a formulation of 4%DMSO, 15%Solutol HS 15, 81%PBS and then administered to male SD rats via oral gavage at 5mg/kg (n=3 per compound). Plasma draws were taken at 15m, 30m, 1hr, 2hr, 4hr, 8hr, and 24hrs, then analyzed by mass spectrometry for presence of the compound. Data were then plotted, and AUC values calculated. Results are shown in **Fig. 7**.

Example 8 - Blood Brain Barrier (BBB) Experiments

[0279] Kinetin data published by Shetty et al. For 130, 130D, compounds were prepared in a formulation of 4%DMSO, 15%Solutol HS 15, 81%PBS and then administered to male ICR mice via oral gavage at 5mg/kg (n=3 per compound). Mice were sacrificed at 1hr, plasma samples taken, perfused, and their brains removed. Plasma and brain tissue were analyzed by mass spec for presence of the compound, and brain to plasma ratios calculated. Results are shown in **Fig. 8**.

What Is Claimed Is:

1. A compound comprising the following formula:



VIII

or pharmaceutically acceptable salt thereof, wherein

L_1 is selected from the group consisting of: a bond, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon; an amine and $–NH-CH_2-$;

R_7 is selected from the group consisting of: a saturated or unsaturated C or N, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon, and a substituted or unsubstituted aminohydrocarbon;

R_1 is selected from the group consisting of: a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted alkene, a substituted or unsubstituted heteroalkene, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl;

R_2 and R_6 are independently selected from the group consisting of: a substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, -CH-, O, S and N;

R_4 is selected from the group consisting of a hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkyne, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkyne, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl; and

R_3 and R_5 are independently selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted

cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl.

2. The compound of claim 1, wherein R_7 is a saturated or unsaturated C or N, methyl, ethyl, propyl, butyl, alkene, or alkyne.

3. The compound of claim 1 or 2, wherein L_1 is an aminoalkyl, or -NH-CH2-.

4. The compound of any of claims 1 to 3, wherein R_1 is C_{1-4}alkyl, C_{1-4}alkyne, C_{1-4}alkene, or a 5 or 6 membered cycloalkyl, heterocycloalkyl, heterocycloalkyne, aryl, or a substituted or unsubstituted furan or thiophene group.

5. The compound of any of claims 1 to 4, wherein R_1 is C_3alkyl, C_3alkyne, a 5 membered heteroaryl, -C=C-C, -C-C-C, or a substituted or unsubstituted furan group.

6. The compound of any of claims 1 to 5, wherein R_2 and R_6 are independently selected from -CH-, S and N.

7. The compound of any of claims 1 to 6, wherein R_2 and R_6 are each N.

8. The compound of any of claims 1 to 7, wherein R_4 is hydrogen.

9. The compound of any of claims 1 to 8, wherein R_3 and R_5 are independently selected from unsubstituted C_{1-8}alkyl, C_{1-8}alkene, C_{1-8}alkyne, C_{1-8}heteroalkyl, and C_{1-8}heteroalkyne.

10. The compound of any of claims 1 to 9, wherein R_3 and R_5 are independently selected from unsubstituted C_{1-4}alkyl, C_{1-4}alkene, and C_{1-4}alkyne.

11. The compound of any of claims 1 to 10, wherein R_3 and R_5 are each methyl.

12. The compound of claim 1, wherein:
L_1 is an aminoalky;

R_7 is a C-H or N;

R_1 is selected from the group consisting of: a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted alkene, and a substituted or unsubstituted furan group;

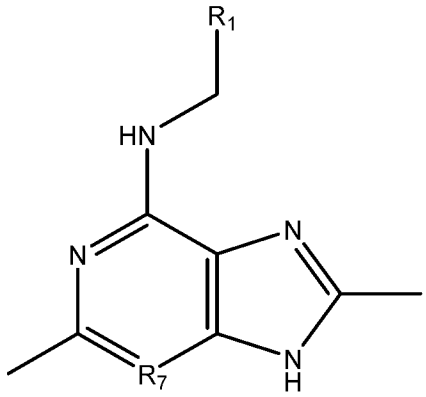
R_2 and R_6 are independently selected from the group consisting of: a substituted or unsubstituted alkyl, a substituted or unsubstituted heteroalkyl, -CH- and N;

R_4 is selected from the group consisting of: a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted alkene, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl; and

R_3 and R_5 are independently selected from the group consisting of: a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl.

13. The compound of claim 12, wherein R_1 is a substituted or unsubstituted furan or thiophene group.

14. The compound of claim 1, wherein the compound has the following formula:



X,

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from the group consisting of: C_{2-6}alkyl, C_{2-6}alkyne, C_{2-6}alkene, a substituted or unsubstituted furan group, and a 5 or 6 membered cycloalkyl, cycloalkene, methylene, ethylene, propylene, butylene, heterocycloalkyl, aryl, thiophene or heteroaryl; and

R_7 is a C-H or N

15. The compound of claim 14, wherein R_1 is C_{2-6}alkyl, cycolopentyl, furan or thiophene group, each group optionally substituted with methyl, ethyl, propyl, methylene, ethylene, propylene, butylene, methoxy, ethoxy, carboxy, carboxymethly, carboxyethyl, hydroxyl, or halogen.

16. The compound of any of claims 1 to 15, wherein each of the substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyne, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkyne, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl is independently selected from the group consisting of:

substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted 2,5-dihydrofuranyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted 2,5-dihydrothienyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted 2,5-dihydro-IH -pyrrolyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclopentenyl, and substituted or unsubstituted 1,3-oxathiolanyl.

17. The compound of any of claims 1 to 4 or 6 to 13, wherein

L_1 is -NH-CH_2-;

R_7 is a saturated C or N;

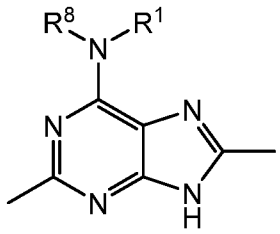
R_1 is a C_{1-4}alkyl, a C_{1-4}alkene, or a substituted or unsubstituted furan group;

R_2 and R_6 are each N;

R_4 is H; and

R_3 and R_5 are each methyl.

18. A compound of the Formula:



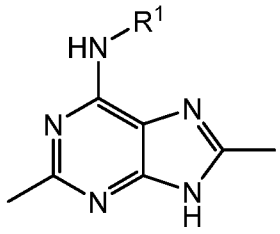
;

or a pharmaceutically acceptable salt thereof, wherein

R^8 is hydrogen or unsubstituted C_1-C_4alkyl; and

R^1 is a (C_1-C_6)alkyl optionally substituted with a substituted or unsubstituted heteroaryl.

19. The compound of claim 18, wherein the compound is of the formula:



;

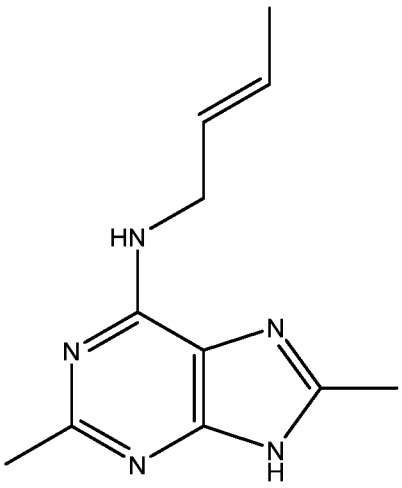
or a pharmaceutically acceptable salt thereof.

20. The compound of claim 18 or 19, wherein R^1 is a (C_1-C_6)alkyl optionally substituted with a substituted or unsubstituted pyranyl.

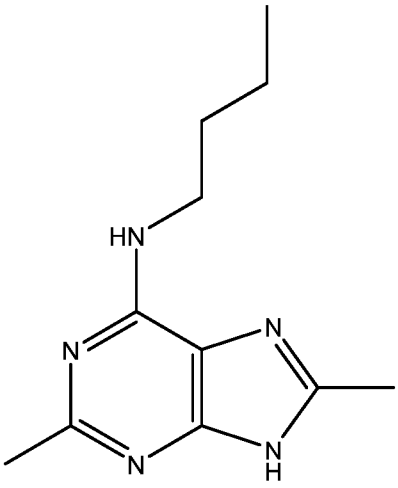
21. The compound of any one of claims 18 to 20, wherein R^1 is a (C_1-C_6)alkyl optionally substituted with an unsubstituted pyranyl.

22. The compound of any one of claims 18 to 21, wherein R^1 is a (C_1-C_4)alkyl optionally substituted with an unsubstituted pyranyl.

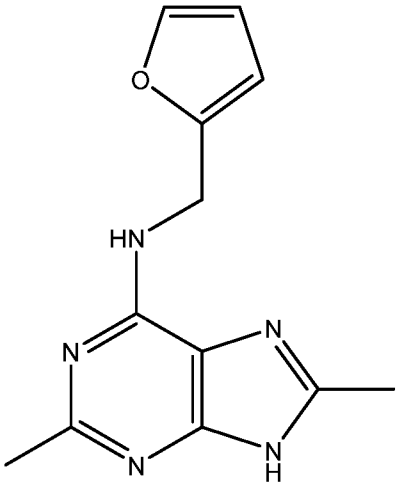
23. The compound of any of claims 1 through 4, 6 through 13, or 17, wherein the compound is selected from the following compounds or a pharmaceutically acceptable salt thereof:



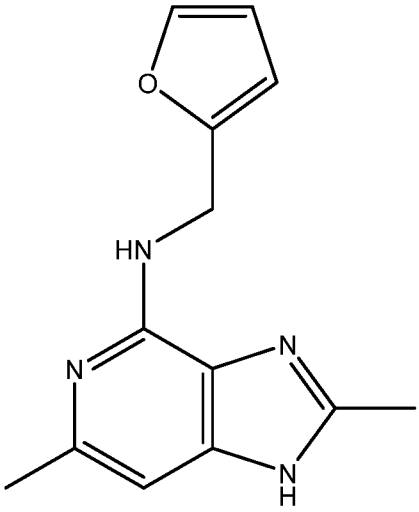
VIIIa,



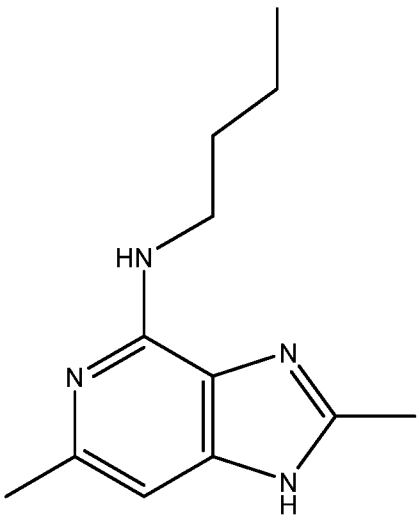
VIIIb,



VIIIc,

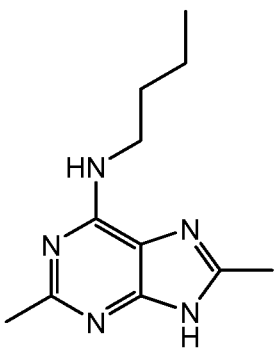
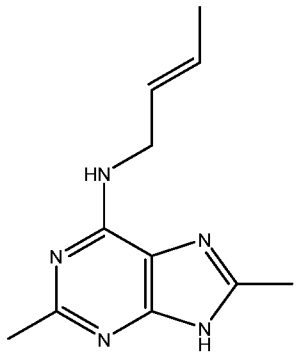


VIIId, and



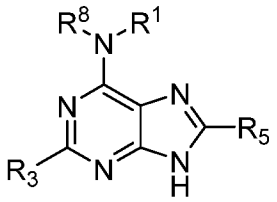
VIIIe.

24. A compound having the formula:


or

;

or a pharmaceutically acceptable salt thereof.

25. A compound having the formula:

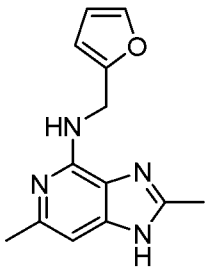

;

or a pharmaceutically acceptable salt thereof, wherein

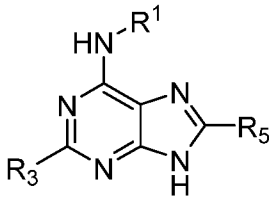
R_3 and R_5 are each unsubstituted $(C_1\text{-}C_4)$alkyl;

R^8 is hydrogen or unsubstituted $(C_1\text{-}C_4)$alkyl; and

R^1 is a $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$alkene, wherein said $(C_1\text{-}C_6)$alkyl is optionally substituted with phenyl, a monocyclic 5-7 membered heterocycloalkyl, or a monocyclic 5-7 membered heteroaryl, each of which are optionally substituted with 1 or 2 $(C_1\text{-}C_4)$alkyl;

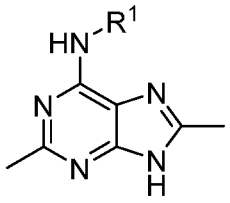
provided the compound is not  or a pharmaceutically acceptable salt thereof.

26. The compound of claim 25, wherein the compound is of the Formula:


;

or a pharmaceutically acceptable salt thereof.

27. The compound of claim 25 or 26, wherein the compound is of the Formula:



;

or a pharmaceutically acceptable salt thereof.

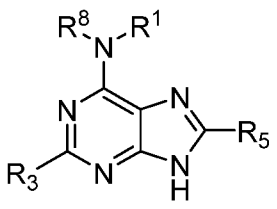
28. The compound of any one of claims 25 to 27, wherein said $(C_1\text{-}C_6)$alkyl for R_1 is optionally substituted with phenyl, furanyl, tetrahydropyranyl, pyridinyl, or pyrizinyl, each of which are optionally substituted with 1 or 2 $(C_1\text{-}C_4)$alkyl.

29. The compound of any one of claims 25 to 28, wherein R_1 is a $(C_1\text{-}C_5)$alkyl or $(C_2\text{-}C_4)$alkene, wherein said $(C_1\text{-}C_5)$alkyl for R_1 is optionally substituted with phenyl, furanyl, tetrahydropyranyl, pyridinyl, or pyrizinyl, and wherein said furanyl is optionally substituted with $(C_1\text{-}C_4)$alkyl.

30. A pharmaceutical composition comprising:
(i) a compound of any of claims 1 to 29; and
(ii) a pharmaceutically acceptable carrier.

31. A method of treating and/or preventing a neurodegenerative disease, a mitochondrial disease, fibrosis, or cardiomyopathy in a subject comprising: administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, or a composition according to claim 30.

32. A method of treating and/or preventing a neurodegenerative disease, a mitochondrial disease, fibrosis, or cardiomyopathy in a subject comprising: administering to the subject a therapeutically effective amount of a compound having the formula:



;

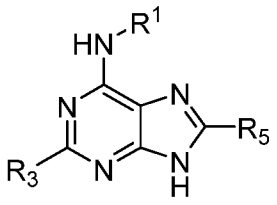
or a pharmaceutically acceptable salt thereof, wherein

R_3 and R_5 are each unsubstituted $(C_1\text{-}C_4)$alkyl;

R^8 is hydrogen or unsubstituted $(C_1\text{-}C_4)$alkyl; and

R^1 is a $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$alkene, wherein said $(C_1\text{-}C_6)$alkyl is optionally substituted with phenyl, a monocyclic 5-7 membered heterocycloalkyl, or a monocyclic 5-7 membered heteroaryl, each of which are optionally substituted with 1 or 2 $(C_1\text{-}C_4)$alkyl.

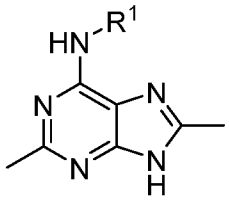
33. The method of claim 32, wherein the compound is of the Formula:



;

or a pharmaceutically acceptable salt thereof.

34. The method of claim 32 or 33, wherein the compound is of the Formula:



;

or a pharmaceutically acceptable salt thereof.

35. The method of any one of claims 32 to 34, wherein said $(C_1\text{-}C_6)$alkyl for R_1 is optionally substituted with phenyl, furanyl, tetrahydropyranyl, pyridinyl, or pyrizinyl, each of which are optionally substituted with 1 or 2 $(C_1\text{-}C_4)$alkyl.

36. The method of any one of claims 32 to 35, wherein R_1 is a $(C_1\text{-}C_5)$alkyl or $(C_2\text{-}C_4)$alkene, wherein said $(C_1\text{-}C_5)$alkyl for R_1 is optionally substituted with phenyl, furanyl, tetrahydropyranyl, pyridinyl, or pyrizinyl, and wherein said furanyl is optionally substituted with $(C_1\text{-}C_4)$alkyl.

37. The method of any one of claims 31 to 36, wherein the neurodegenerative disease is Parkinson's disease, Huntington's disease, or amyotrophic lateral sclerosis.

38. The method of any one of claims 31 to 37, wherein the neurodegenerative disease is Huntington's disease.

39. The method of any one of claims 31 to 36, wherein the method is a method of treating a neurodegenerative disease, a mitochondrial disease, fibrosis, or cardiomyopathy in a subject.

40. The method of any one of claims 31 to 36, wherein the method is a method of preventing a neurodegenerative disease, a mitochondrial disease, fibrosis, or cardiomyopathy in a subject.

41. Use of any of the compounds of claims 1 to 29, or the compound described in any one of Claims 32-36, in the manufacture of a medicament for the treatment of a neurodegenerative disease, a mitochondrial disease, fibrosis, or cardiomyopathy.

42. The use of claim 41, wherein the neurodegenerative disease is Parkinson's disease, Huntington's disease, or amyotrophic lateral sclerosis.

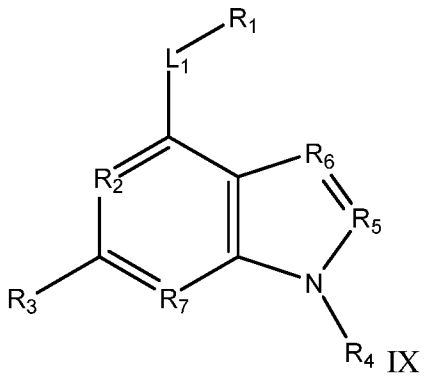
43. The use of claim 41, wherein the neurodegenerative disease is Huntington's disease.

44. A pharmaceutical composition comprising a therapeutically effective amount of any one or a plurality of compounds of claims 1 to 24 and a pharmaceutically acceptable carrier, or or the compound described in any one of claims 32 to 36 and a pharmaceutically acceptable carrier for use in treatment of a neurodegenerative disease, a mitochondrial disease, or cardiomyopathy.

45. The pharmaceutical composition of claim 44, wherein the neurodegenerative disease is Parkinson's disease, Huntington's disease, or amyotrophic lateral sclerosis.

46. The pharmaceutical composition of claim 44, wherein the neurodegenerative disease is Huntington's disease.

47. A method of treating and/or preventing fibrosis in a subject comprising administering to the subject a therapeutically effective amount of one or more compositions comprising a compound comprising the following formula or pharmaceutically acceptable salt thereof:



IX

wherein L_1 is selected from the group consisting of: a bond, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon; an amine, an aminohydrocarbon, an aminoalkyl, an aminoalkene, and –NH-CH_2-;

R_7 is selected from the group consisting of: a saturated or unsaturated C or N, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon, and a substituted or unsubstituted aminohydrocarbon;

R_1 is selected from the group consisting of: a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted alkene, a substituted or unsubstituted heteroalkene, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl;

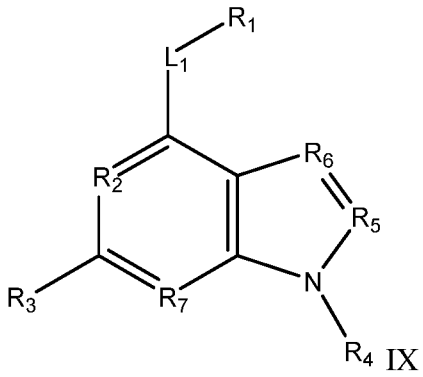
R_2 and R_6 are independently selected from the group consisting of: a substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, -CH-, O, S and N;

R_4 is selected from the group consisting of a hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkyne, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkyne, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl; and

R_3 and R_5 are independently selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted

alkene, a substituted or unsubstituted heteroalkene, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl.

48. A method of activating PINK1 in a cell of a subject comprising administering to the subject a therapeutically effective amount of one or more compositions comprising a compound comprising the following formula or pharmaceutically acceptable salt thereof:



IX

wherein L_1 is selected from the group consisting of: a bond, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon; an amine, an aminohydrocarbon, an aminoalkyl, an aminoalkene, and –NH-CH_2-;

R_7 is selected from the group consisting of: a saturated or unsaturated C or N, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon, and a substituted or unsubstituted aminohydrocarbon;

R_1 is selected from the group consisting of: a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted alkene, a substituted or unsubstituted heteroalkene, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl;

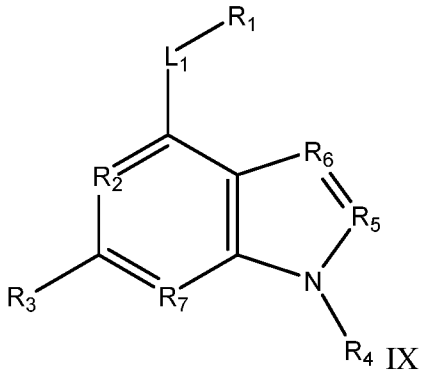
R_2 and R_6 are independently selected from the group consisting of: a substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, -CH-, O, S and N;

R_4 is selected from the group consisting of a hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkyne, substituted or unsubstituted heteroalkyl, substituted

or unsubstituted heteroalkyne, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl; and

R_3 and R_5 are independently selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted alkene, a substituted or unsubstituted heteroalkene, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl.

49. A method of activating PINK1 in a cell comprising contacting the cell with an effective amount of one or more compositions comprising a compound comprising the following formula or pharmaceutically acceptable salt thereof:



IX

wherein L_1 is selected from the group consisting of: a bond, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon; an amine, an aminohydrocarbon, an aminoalkyl, an aminoalkene, and –NH-CH_2-;

R_7 is selected from the group consisting of: a saturated or unsaturated C or N, a substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon, and a substituted or unsubstituted aminohydrocarbon;

R_1 is selected from the group consisting of: a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted alkene, a

substituted or unsubstituted heteroalkene, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl;

R_2 and R_6 are independently selected from the group consisting of: a substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, -CH-, O, S and N;

R_4 is selected from the group consisting of a hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkyne, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkyne, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl; and

R_3 and R_5 are independently selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkyne, a substituted or unsubstituted alkene, a substituted or unsubstituted heteroalkene, a substituted or unsubstituted heteroalkyl, a substituted or unsubstituted heteroalkyne, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted cycloalkyne, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heterocycloalkyne, a substituted or unsubstituted aryl, and a substituted or unsubstituted heteroaryl.

Fig. 1

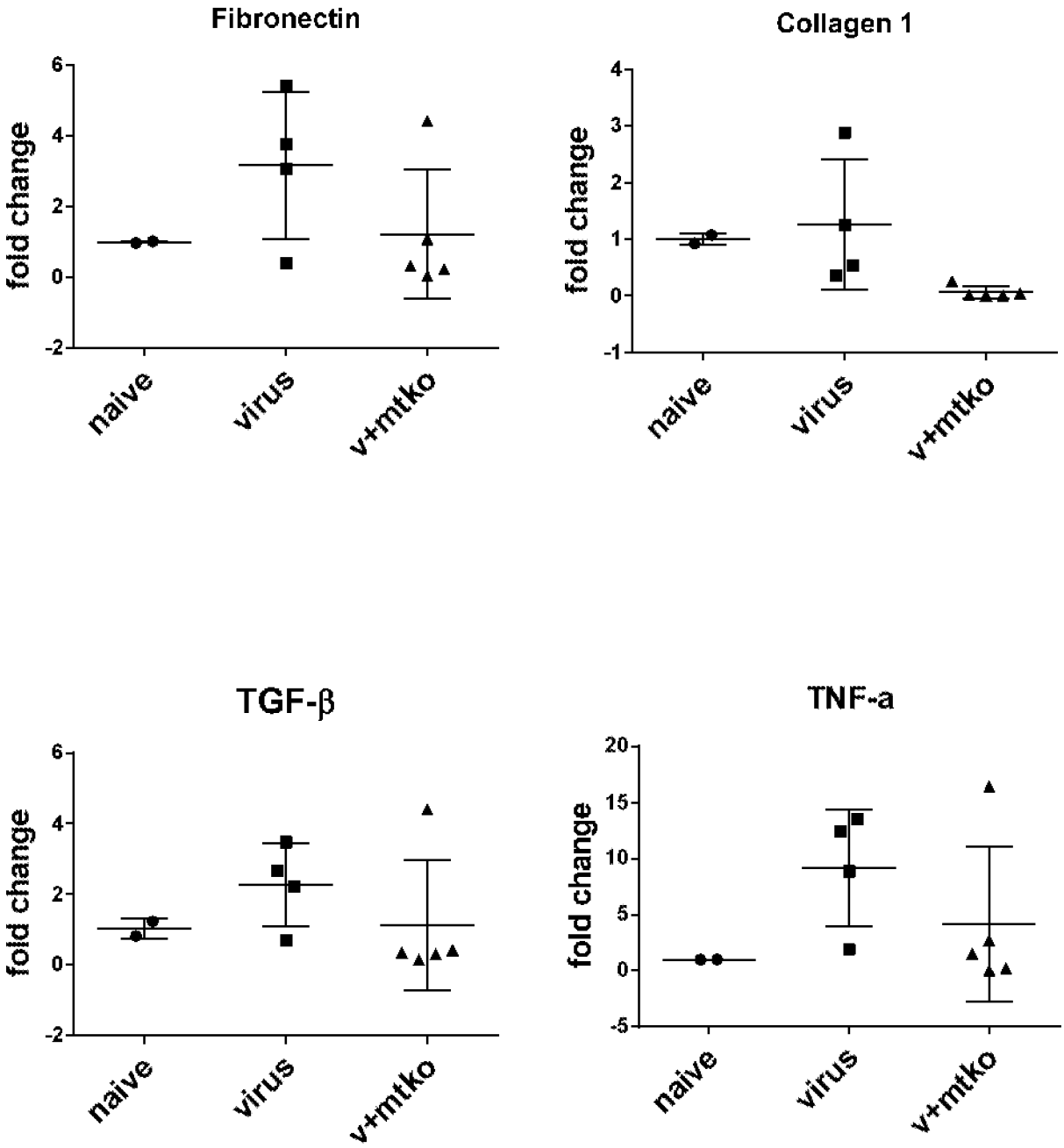

Fibronectin
fold change
6
4
2
0
-2
naive
virus
v+mtko
Collagen 1
fold change
4
3
2
1
0
-1
naive
virus
v+mtko
TGF-β
fold change
6
4
2
0
-2
naive
virus
v+mtko
TNF-a
fold change
20
15
10
5
0
-5
naive
virus
v+mtko

Fig. 2

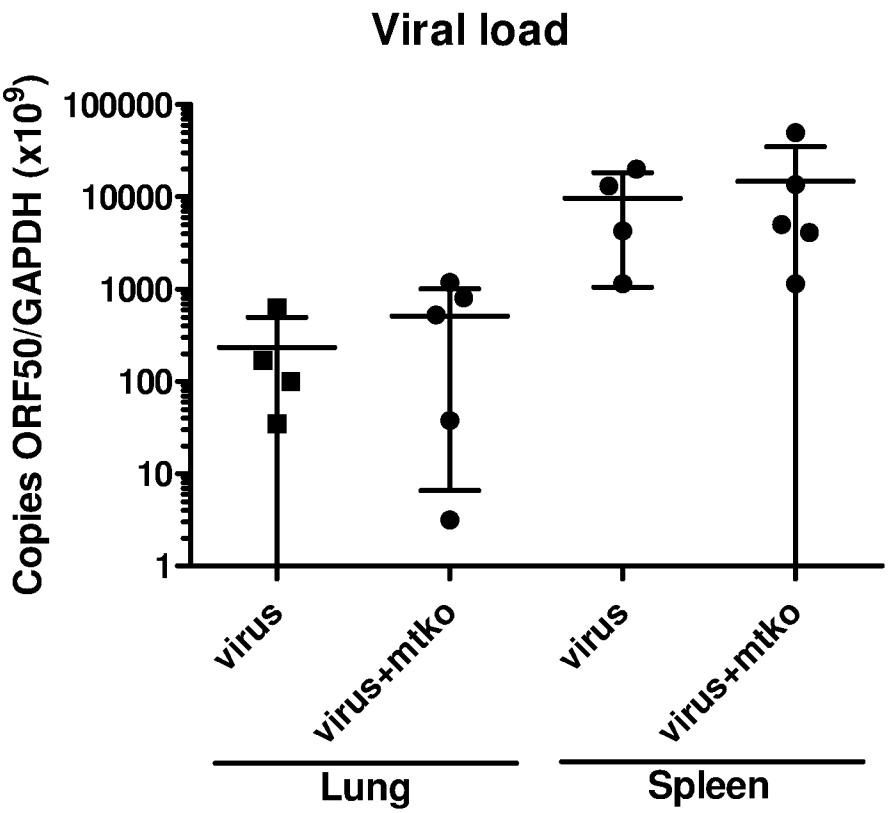

Viral load
Copies ORF50/GAPDH (x10^9)
100000
10000
1000
100
10
1
virus
virus+mtko
virus
virus+mtko
Lung
Spleen

Fig. 3

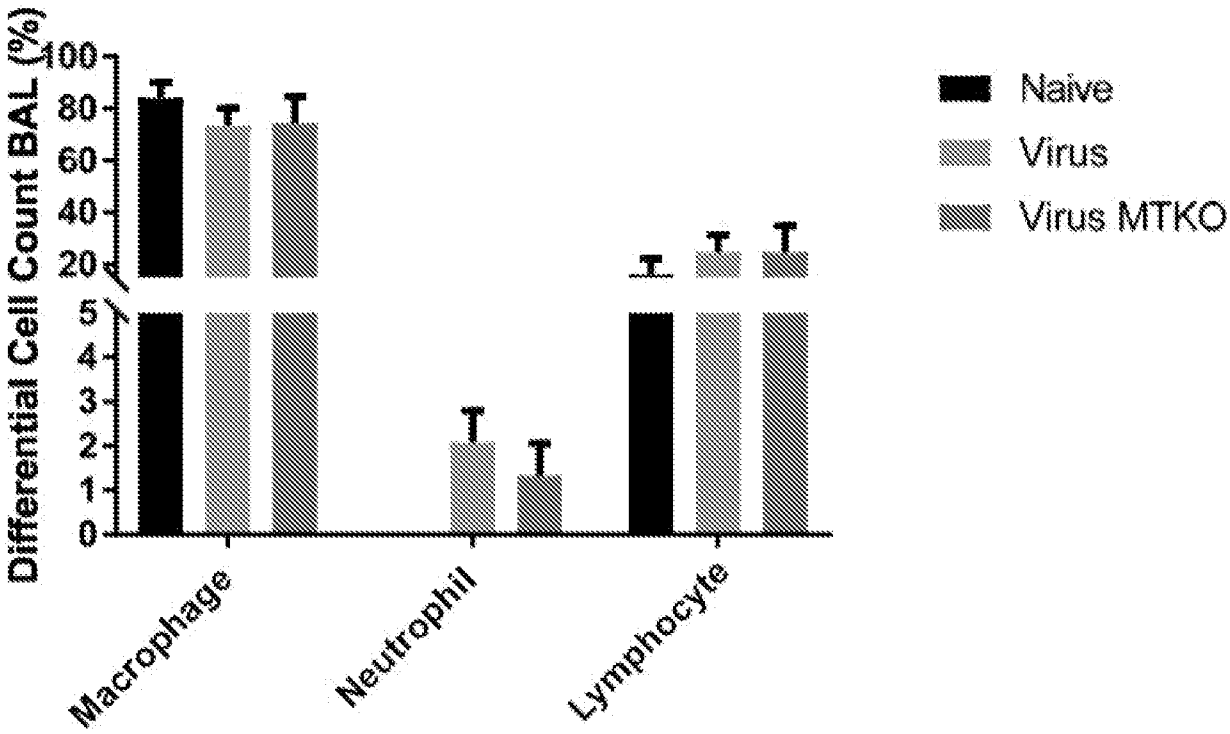
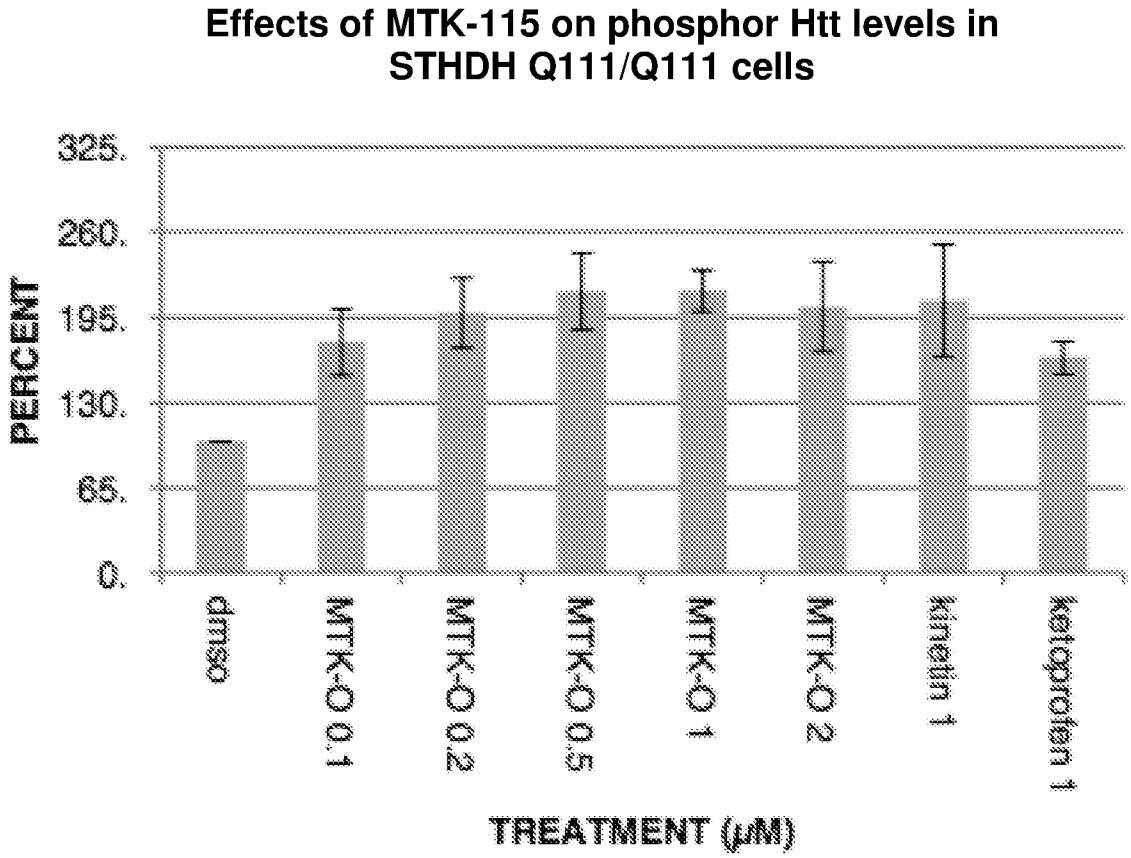
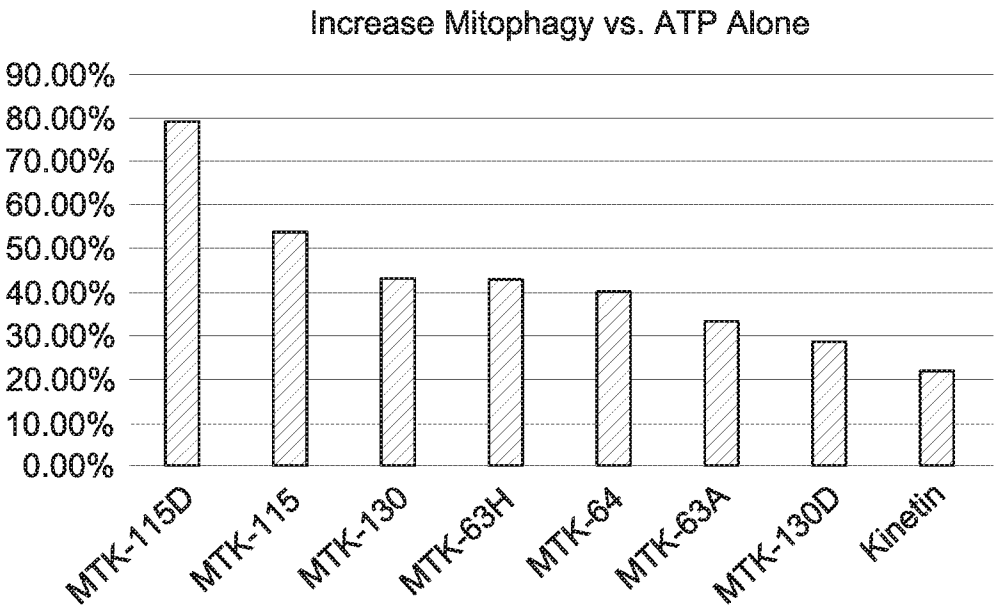

Differential Cell Count BAL (%)
100
80
60
40
20
5
4
3
2
1
0
Macrophage
Neutrophil
Lymphocyte
Naive
Virus
Virus MTKO

Fig. 4


Effects of MTK-115 on phosphor Htt levels in STHDH Q111/Q111 cells
PERCENT
325.
260.
195.
130.
65.
0.
dmso
MTK-O 0.1
MTK-O 0.2
MTK-O 0.5
MTK-O 1
MTK-O 2
kinetin 1
ketoprofen 1
TREATMENT (μM)


Increase Mitophagy vs. ATP Alone
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
MTK-115D
MTK-115
MTK-130
MTK-63H
MTK-64
MTK-63A
MTK-130D
Kinetin

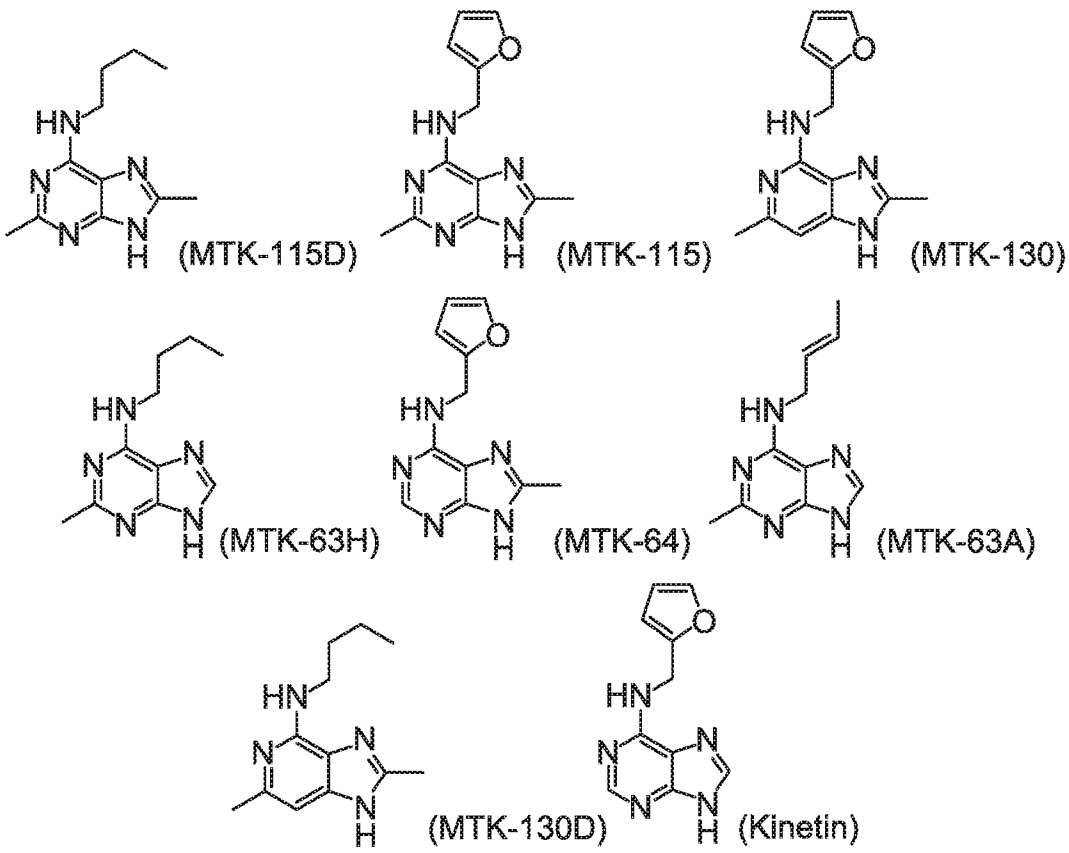
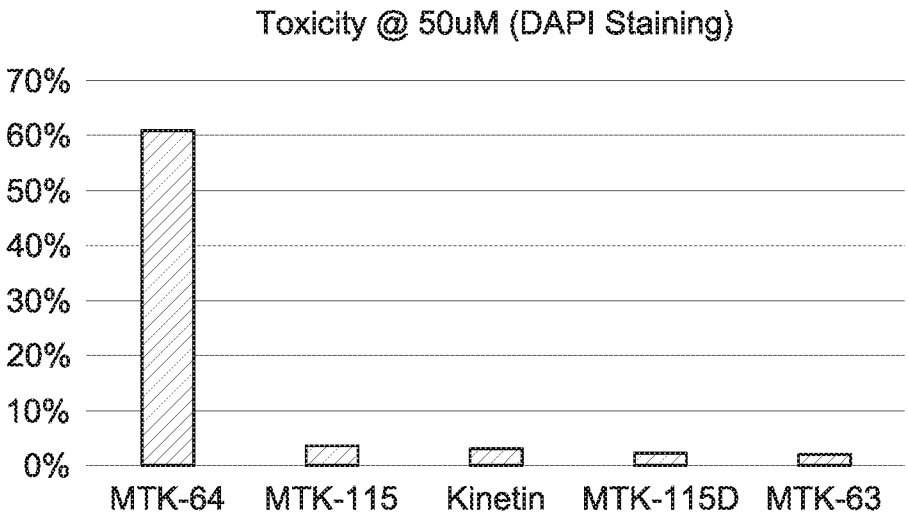

(MTK-115D)
(MTK-115)
(MTK-130)
(MTK-63H)
(MTK-64)
(MTK-63A)
(MTK-130D)
(Kinetin)

Fig. 5


Toxicity @ 50uM (DAPI Staining)
70%
60%
50%
40%
30%
20%
10%
0%
MTK-64
MTK-115
Kinetin
MTK-115D
MTK-63

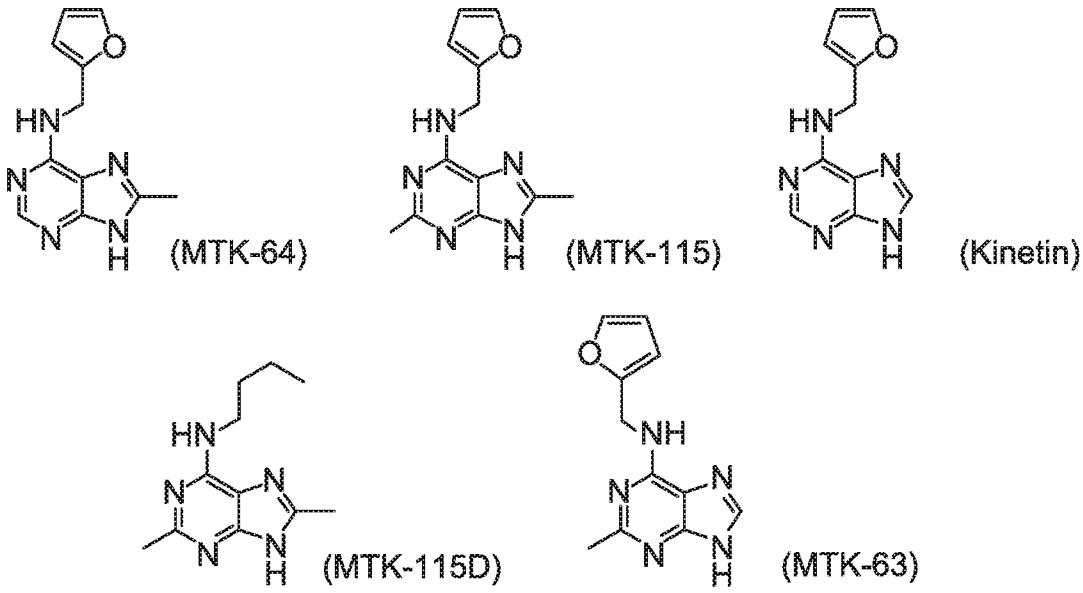
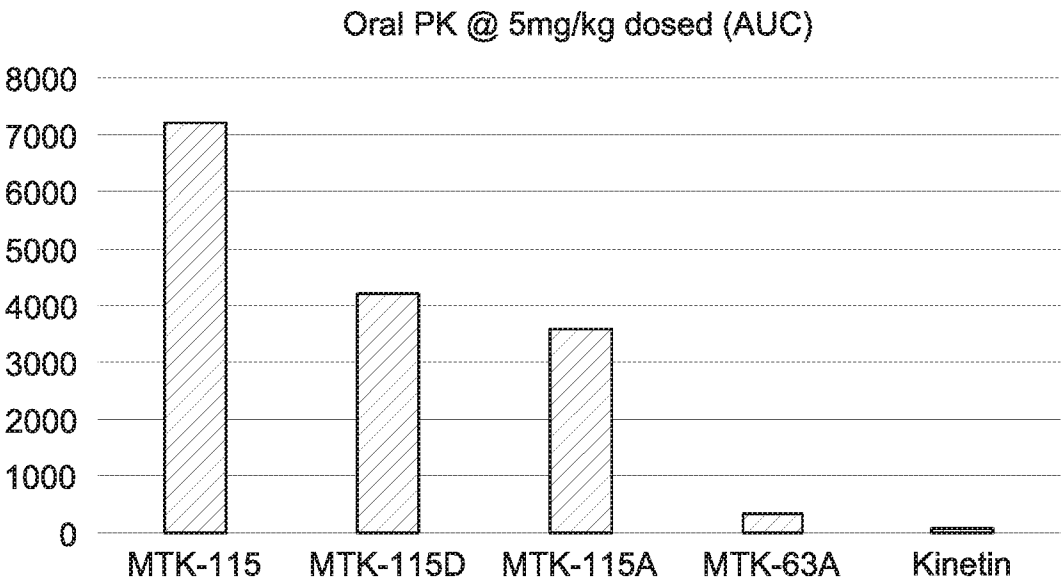

(MTK-64)
(MTK-115)
(Kinetin)
(MTK-115D)
(MTK-63)

Fig. 6


Oral PK @ 5mg/kg dosed (AUC)
8000
7000
6000
5000
4000
3000
2000
1000
0
MTK-115
MTK-115D
MTK-115A
MTK-63A
Kinetin

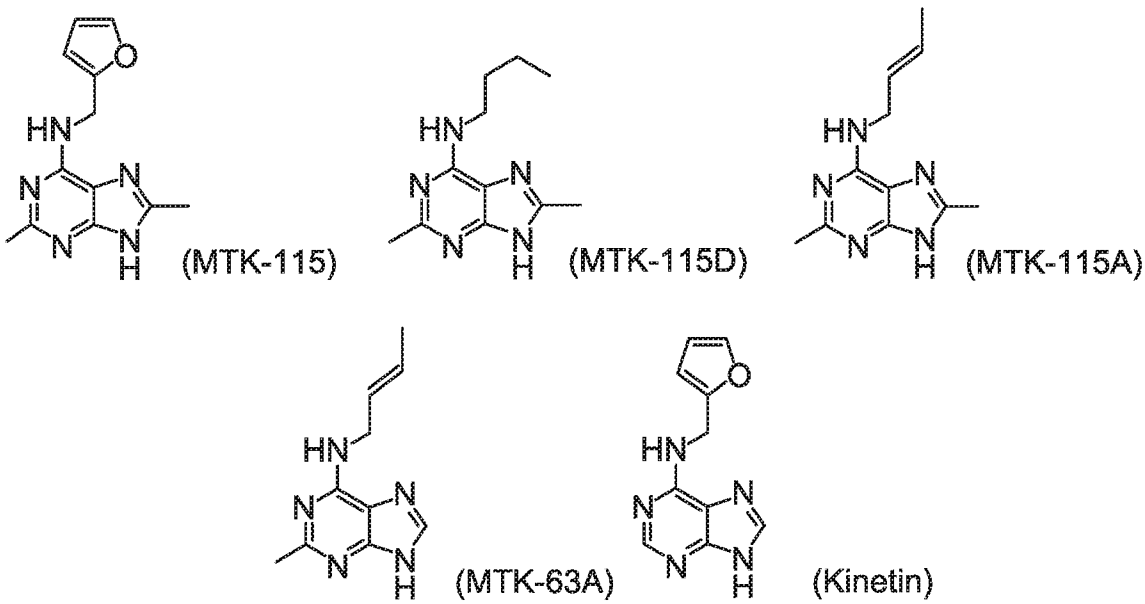
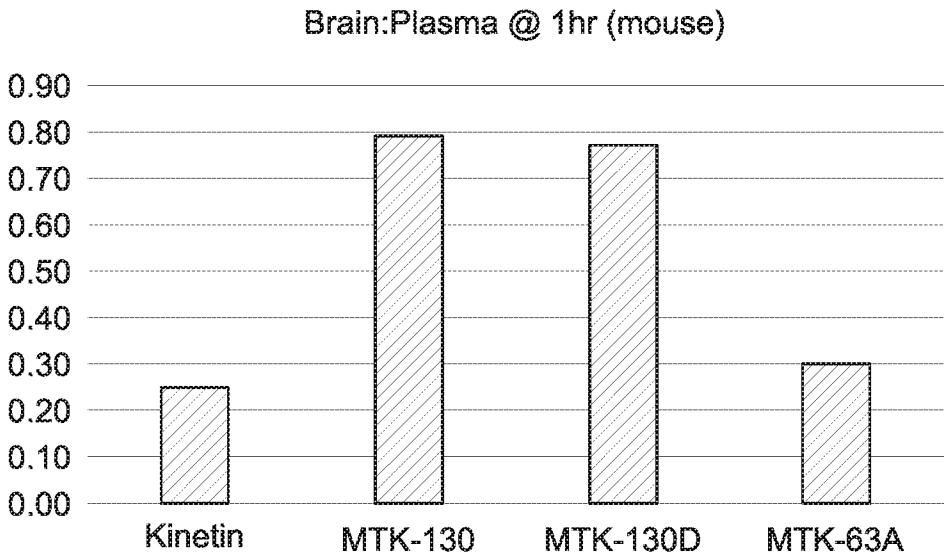

HN
N
N
N
N
H
O
(MTK-115)
(MTK-115D)
(MTK-115A)
(MTK-63A)
(Kinetin)

Fig. 7


Brain:Plasma @ 1hr (mouse)
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Kinetin
MTK-130
MTK-130D
MTK-63A

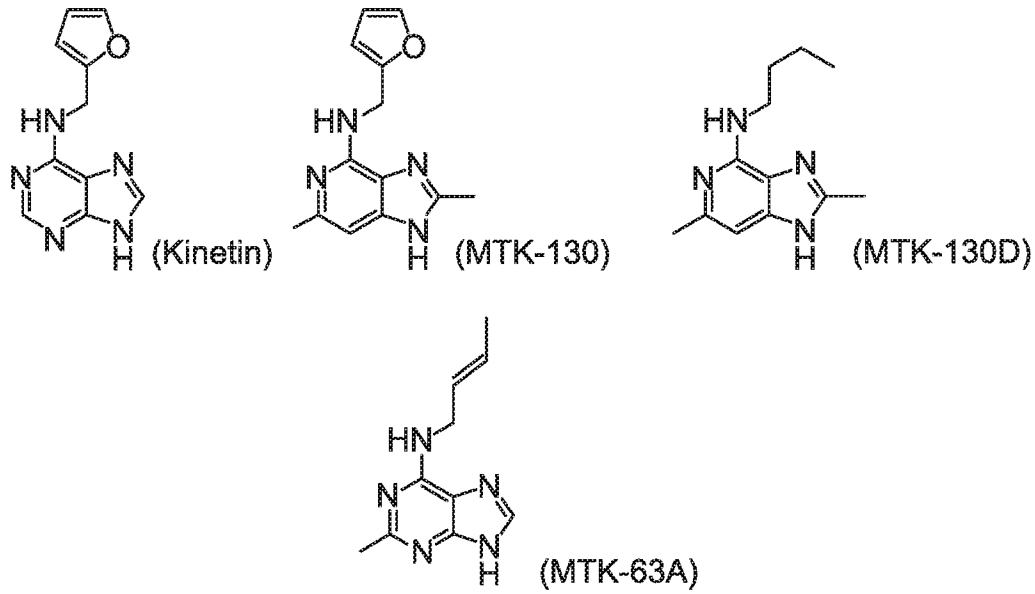

HN
N
N
N
N
H
O
(Kinetin)
(MTK-130)
(MTK-130D)
(MTK-63A)

Fig. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/38756

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/90, C07D 291/00, C07D 473/00 (2018.01)
CPC - C07D 405/12, C07D 471/04, C07D 473/34

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)
See Search History Document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/04552 A1 (F. HOFFMAN-LA ROCHE AG) 05 February 1998 (05.02.1998); pg. 16, ln 14	1-2
A	WO 2015/123365 A1 (MITOKININ LLC) 20 August 2015 (20.08.2015); entire document	1-2
A	WO 2014/124458 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 14 August 2014 (14.08.2014); entire document	1-2
A	"Pubchem CID 20729823" Date Created: 05 December 2007 (05.12.2007) Date Accessed: 15 October 2018 (15.10.2018); pg. 4, compound listed	1-2

☐ 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	Date of mailing of the international search report
15 October 2018	30 OCT 2018

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/38756

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
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:

3. ☒ Claims Nos.: 4-11, 16-17, 21-23, 28-31 and 35-46
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:
(see supplemental page)

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 additional fees, this Authority did not invite payment of 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.:
1-2

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.

--continued from Box No. III--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: Claims 1-3, 12-15, 18-20 and 24-27, directed to a compound of claim 1, a compound of formula VIII. The compound of claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by a compound of Formula VIII wherein L1 is a bond; R7 is CH; R1 is hydrogen; R2 and R6 are CH; R4 is hydrogen; R3 and R5 are substituted or unsubstituted alkyl. It is believed that claims 1-2 reads on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of Formula VIII wherein L1 is a NH-CH2; R7 is CH; R1 is hydrogen; R2 and R6 are CH; R4 is hydrogen; R3 and R5 are substituted or unsubstituted alkyl (i.e., claims 1-3 and 12).

Group II: Claims 32-34 and 47-49, directed to a method of treating and/or preventing a neurodegenerative disease, a mitochondrial disease, fibrosis, or cardiomyopathy in a subject/a method of activating PINK1 in a cell of a subject.

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of claim 1, formula I, which is not required by any other invention of Group I+ or II.

Group II includes the technical feature of a method of treating and/or preventing a neurodegenerative disease, a mitochondrial disease, fibrosis, or cardiomyopathy in a subject/a method of activating PINK1 in a cell of a subject, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a compound of claim 1.

The inventions of Groups I+ and II share the technical feature of a compound of claim 1.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by a document entitled "Pubchem CID 20729823 " (hereinafter Pubchem-823). Pubchem-823 discloses a compound of claim 1, formula VIII wherein L1 is NH-CH2; R7 is N; R1 is unsubstituted alkyl; R2 and R6 are N; R4 is hydrogen; R3 and R5 are unsubstituted alkyl (pg. 4, compound listed) (drawn as tautomeric structure).

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ or II. The inventions of Group I+ and II thus lack unity under PCT Rule 13.

Note: Claims 4-11, 16-17, 21-23, 28-31 and 35-46 have been found to be unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Note: Claim 1 lacks clarity regarding formula VIII wherein R7 is saturated or unsaturated C or N as the structure of formula VIII explicitly shows a double bond to R7; or wherein R2 and R6 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl; as they are atoms in a closed ring structure; for the purpose of this ISR; R7 is assumed to be CH, N, or C-R', wherein R' is substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon, and a substituted or unsubstituted aminohydrocarbon; and R2 and R6 are assumed to be -CH-, O, S, N, or C-R", wherein R" is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl.

Note: Claims 47-49 lacks clarity regarding formula IX wherein R7 is saturated or unsaturated C or N as the structure of formula XI explicitly shows a double bond to R7; or wherein R2 and R6 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl; as they are atoms in a closed ring structure; or wherein R5 is any of the selections listed as it is an atom in a closed ring; for the purpose of this ISR; R7 is assumed to be CH, N, or C-R', wherein R' is substituted or unsubstituted hydrocarbon, a substituted or unsubstituted heterohydrocarbon, and a substituted or unsubstituted aminohydrocarbon; R2 and R6 are assumed to be -CH-, O, S, N, or C-R", wherein R" is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl; and R5 is assumed to be C-R5 (see structure of claim 1, formula VIII, as example).