

BIHETEROARYL COMPOUNDS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Appl. No. 61/817,966, filed on May 1, 2013, which is incorporated herein by reference in its entirety.

5 FIELD OF THE INVENTION

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, and in particular to inhibitors of DLK useful for treating neurodegeneration diseases and disorders.

BACKGROUND OF THE INVENTION

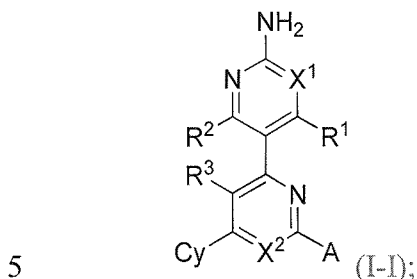
10 Neuron or axon degeneration plays a central role in the proper development of the nervous system and is a hall mark of many neurodegenerative diseases including for example, amyotrophic lateral sclerosis (ALS), glaucoma, Alzheimer's disease, and Parkinson's disease, as well a traumatic injury to the brain and spinal cord. Recent patent publication WO2011/050192, incorporated herein by reference, describes the role of the Dual Leucine
15 Zipper Kinase (DLK), also referred to as MAP3K12, to cause neuronal cell death. Neurodegenerative diseases and injuries are devastating to patients and caregivers, and also result in great financial burdens, with annual costs currently exceeding several hundred billion dollars in the United States alone. Most current treatments for these diseases and conditions are inadequate. Adding to the urgency of the problems created by these diseases is
20 the fact that many such diseases are age related, and thus their incidence is increasing rapidly as population demographics change. There is a great need for the development of effective approaches to treating neurodegenerative diseases and nervous system injuries, including for example, through the inhibition of DLK in neurons.

SUMMARY OF THE INVENTION

25 The ~~In one aspect the~~ present disclosure provides for compounds of Formula I-I:

C₁₋₄ (halo)alkyl-C(=O)N(H)-, C₁₋₄ (halo)alkyl-N(H)-C(=O)-, ((halo)alkyl)₂N-C(=O)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)₂N-C(=O)O-, C₁₋₄ alkylthio, C₁₋₄ alkylamino and C₁₋₄ dialkylamino.

In one aspect the present disclosure provides for a compound of Formula I-I)



or salts thereof wherein

R¹, R² and R³ are each independently H, F, Cl, Br, I, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

10 X¹ is C-R⁴, wherein R⁴ is selected from the group consisting of -F, -Cl, -Br, I, -(L¹)₀₋₁-C₁₋₆ alkyl, -(L¹)₀₋₁-C₁₋₆ haloalkyl, -(L¹)₀₋₁-C₁₋₆ heteroalkyl, -(L²)₀₋₁-C₃₋₈ cycloalkyl, -(L²)₀₋₁-3 to 7 membered heterocycloalkyl, -(L²)₀₋₁-6-10 membered aryl, -(L²)₀₋₁-5-10 membered heteroaryl, wherein L¹ is selected from the group consisting of -O-, -N(H)-, -S-, -N(C₁₋₆ alkyl)-, =O, and L² is selected from the group consisting of -O-, -N(H)-, -N(C₁₋₆ alkyl)-, -S-, =O, C₁₋₄ alkylene, C₁₋₄ alkenylene, C₁₋₄ alkynylene, C₁₋₄ alkoxy, C₁₋₄ aminoalkylene, C₁₋₄ thioalkylene and C₁₋₄ heteroalkylene, and wherein R⁴ is optionally
 15 substituted on carbon atoms and heteroatoms with R⁴ substituents selected from the group consisting of F, Cl, Br, I, C₁₋₆ alkyl, C₁₋₆ haloalkyl, 3-5 membered cycloalkyl, 3-5 membered heterocycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylthio, =O, -NH₂, -CN, -NO₂ and -SF₅;

or R¹ and R⁴ taken together form a 5 to 6 membered heterocycloalkyl;

20 X² is N or CH;

A is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ dialkylamino, 3 to 12 membered cycloalkyl, 3 to 12 membered heterocycloalkyl, and 5 to 6 membered heteroaryl, wherein A is optionally substituted with 1-5 R^A substituents selected from the group

consisting of F, Cl, Br, I, -OH, -CN, -NO₂, -SF₅, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ heteroalkyl, -(L^A)₀₋₁₋₃₋₈ membered cycloalkyl, -(L^A)₀₋₁₋₃₋₈ membered heterocycloalkyl, -(L^A)₀₋₁₋₅ to 6 membered heteroaryl, -(L^A)₀₋₁-C₆ aryl, -(L^A)₀₋₁-NR^{R1a}R^{R1b}, -(L^A)₀₋₁-OR^{R1a}, -(L^A)₀₋₁-SR^{R1a}, -(L^A)₀₋₁-N(R^{R1a})C(=Y¹)OR^{R1c}, -(L^A)₀₋₁-OC(=O)N(R^{R1a})(R^{R1b}),

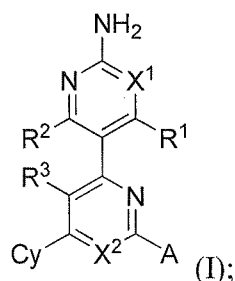
5 -(L^A)₀₋₁-N(R^{R1a})C(=O)N(R^{R1a})(R^{R1b}), -(L^A)₀₋₁-C(=O)N(R^{R1a})(R^{R1b}), -(L^A)₀₋₁-N(R^{R1a})C(=O)R^{R1b}, -(L^A)₀₋₁-C(=O)OR^{R1a}, -(L^A)₀₋₁-OC(=O)R^{R1a}, -(L^A)₀₋₁-P(=O)(OR^{R1a})(OR^{R1b}), -(L^A)₀₋₁-S(O)₁₋₂R^{R1c}, -(L^A)₀₋₁-S(O)₁₋₂N(R^{R1a})(R^{R1b}), -(L^A)₀₋₁-N(R^{R1a})S(O)₁₋₂N(R^{R1a})(R^{R1b}) and -(L^A)₀₋₁-N(R^{R1a})S(O)₁₋₂(R^{R1c}), wherein L^A is selected from the group consisting of C₁₋₄ alkylene, C₁₋₄ heteroalkylene, C₁₋₄ alkoxy, C₁₋₄ aminoalkylene, C₁₋₄ thioalkylene, C₂₋₄ alkenylene, and C₂₋₄ alkynylene; wherein R^{R1a} and R^{R1b} are independently selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, 3-8 membered cycloalkyl, phenyl, benzyl, 5 to 6 membered heteroaryl and 3 to 8 membered heterocycloalkyl; R^{R1c} is selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, 3 to 8 membered cycloalkyl, phenyl, benzyl, 5 to 6 membered heteroaryl and 3 to 7 membered heterocycloalkyl; Y¹ is O or S, and wherein R^A is optionally substituted on carbon atoms and heteroatoms with R^{RA} substituents selected from, F, Cl, Br, I, -NH₂, -OH, -CN, -NO₂, =O, -SF₅, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ (halo)alkyl-C(=O)-, C₁₋₄ (halo)alkyl-S(O)₀₋₂-, C₁₋₄ (halo)alkyl-N(H)S(O)₀₋₂-, C₁₋₄ (halo)alkyl-S(O)₀₋₂N(H)-, (halo)alkyl-N(H)-S(O)₀₋₂N(H)-, C₁₋₄ (halo)alkyl-C(=O)N(H)-, C₁₋₄ (halo)alkyl-N(H)-C(=O)-, ((halo)alkyl)₂N-C(=O)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)₂N-C(=O)O-, C₁₋₄ alkylthio, C₁₋₄ alkylamino and C₁₋₄ dialkylamino; and

Cy is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, 3 to 12 membered cycloalkyl, 3 to 12 membered heterocycloalkyl, and 5 to 6 membered heteroaryl, wherein Cy is optionally substituted on carbon or heteroatoms with R^{Cy} substituents selected from the group consisting of F, Cl, Br, I, -OH, -CN, -NO₂, -SF₅, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ heteroalkyl, -(L^{Cy})₀₋₁₋₃₋₈ membered cycloalkyl, -(L^{Cy})₀₋₁₋₃₋₈ membered heterocycloalkyl, -(L^{Cy})₀₋₁₋₅ to 6 membered heteroaryl, -(L^{Cy})₀₋₁-phenyl, -(L^{Cy})₀₋₁-NR^{RCa}R^{RCb}, -(L^{Cy})₀₋₁-OR^{RCa}, -(L^{Cy})₀₋₁-SR^{RCa}, -(L^{Cy})₀₋₁-N(R^{RCa})C(=Y¹)OR^{RCc},

30 -(L^{Cy})₀₋₁-OC(=O)N(R^{RCa})(R^{RCb}), -(L^{Cy})₀₋₁-N(R^{RCa})C(=O)N(R^{RCa})(R^{RCb}), -(L^{Cy})₀₋₁-C(=O)N(R^{RCa})(R^{RCb}), -(L^{Cy})₀₋₁-N(R^{RCa})C(=O)R^{RCb}, -(L^{Cy})₀₋₁-C(=O)OR^{RCa}, -(L^{Cy})₀₋₁-OC(=O)R^{RCa}, -(L^{Cy})₀₋₁-P(=O)(OR^{RCa})(OR^{RCb}), -(L^{Cy})₀₋₁-S(O)₁₋₂R^{RCc}, -(L^{Cy})₀₋₁-S(O)₁₋₂N(R^{RCa})(R^{RCb}), -(L^{Cy})₀₋₁-N(R^{RCa})S(O)₁₋₂N(R^{RCa})(R^{RCb}) and -(L^{Cy})₀₋₁-N(R^{RCa})S(O)₁₋₂(R^{RCc}), wherein L^{Cy} is selected from the group consisting of C₁₋₄ alkylene, C₁₋₄ heteroalkylene, C₁₋₄ alkoxy, C₁₋₄ aminoalkylene, C₁₋₄ thioalkylene, C₂₋₄ alkenylene, and C₂₋₄ alkynylene; wherein R^{RCa} and R^{RCb} are independently selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, 3-8 membered cycloalkyl, phenyl, benzyl, 5 to 6 membered heteroaryl and 3 to 8 membered heterocycloalkyl; R^{RCc} is selected

from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, 3 to 8 membered cycloalkyl, phenyl, benzyl, 5 to 6 membered heteroaryl and 3 to 7 membered heterocycloalkyl; Y¹ is O or S, and wherein R^{Cy} is optionally substituted on carbon atoms and heteroatoms with from 1 to 5 R^{RCy} substituents selected from, F, Cl, Br, I, -NH₂, -OH, -CN, -NO₂, -O⁻, =O, -SF₅, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ alkyl-C(=O)-, C₁₋₄ (halo)alkyl-C(=O)-, C₁₋₄ (halo)alkyl-S(O)₀₋₂-, C₁₋₄ (halo)alkyl-N(H)S(O)₀₋₂-, C₁₋₄ (halo)alkyl-S(O)₀₋₂N(H)-, (halo)alkyl-N(H)-S(O)₀₋₂N(H)-, C₁₋₄ (halo)alkyl-C(=O)N(H)-, C₁₋₄ (halo)alkyl-N(H)-C(=O)-, ((halo)alkyl)₂N-C(=O)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)₂N-C(=O)O-, C₁₋₄ alkylthio, C₁₋₄ alkylamino and C₁₋₄ dialkylamino.

10 ~~The In one aspect the~~ present disclosure provides for compounds of Formula I:



or salts thereof wherein

R¹, R² and R³ are each independently H, F, Cl, Br, I, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

15 **X¹** is N or C-R⁴, wherein R⁴ is selected from the group consisting of -F, -Cl, -Br, I, -(L¹)₀₋₁-C₁₋₆ alkyl, -(L¹)₀₋₁-C₁₋₆ haloalkyl, -(L¹)₀₋₁-C₁₋₆ heteroalkyl, -(L²)₀₋₁-C₃₋₈ cycloalkyl, -(L²)₀₋₁-3 to 7 membered heterocycloalkyl, -(L²)₀₋₁-6-10 membered aryl, -(L²)₀₋₁-5-10 membered heteroaryl, wherein L¹ is selected from the group consisting of -O-, -N(H)-, -S-, -N(C₁₋₆ alkyl)-, =O, and L² is selected from the group consisting of -O-, -N(H)-, -N(C₁₋₆ alkyl)-, -S-, =O, C₁₋₄ alkylene, C₁₋₄ alkenylene, C₁₋₄ alkynylene, C₁₋₄ alkoxy, C₁₋₄ aminoalkylene, C₁₋₄ thioalkylene and C₁₋₄ heteroalkylene, and wherein R⁴ is optionally substituted on carbon atoms and heteroatoms with R^{R4} substituents selected from the group consisting of F, Cl, Br, I, C₁₋₆ alkyl, C₁₋₆ haloalkyl, 3-5 membered cycloalkyl, 3-5 membered heterocycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylthio, =O, -NH₂, -CN, -NO₂ and -SF₅;

25 **X²** is N or CH;

A is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ dialkylamino, 3 to 12 membered cycloalkyl, 3 to 12 membered heterocycloalkyl, wherein A is optionally substituted with 1-5 R^A substituents selected from the group consisting of F, Cl, Br, I, -OH, -CN, -NO₂, -SF₅, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ heteroalkyl, -(L^A)₀₋₁₋₃₋₈ membered
5 cycloalkyl, -(L^A)₀₋₁₋₃₋₈ membered heterocycloalkyl, -(L^A)₀₋₁₋₅ to 6 membered heteroaryl,

(halo)alkyl-OC(=O)N(H)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)₂N-C(=O)O-, C₁₋₄ alkylthio, C₁₋₄ alkylamino and C₁₋₄ dialkylamino.

In one embodiment of Formula I-I or Formula I, the compound is selected from the group as set forth in Table 1.

5 In another aspect, the present disclosure provides for compositions comprising a compound of Formula I-I or Formula I as defined above, or any embodiment thereof and a pharmaceutically acceptable carrier, diluent or excipient.

~~In another aspect, the present disclosure provides for a compound as defined above for use in therapy.~~

10 The present disclosure provides for a method for inhibiting or preventing degeneration of a central nervous system (CNS) neuron or a portion thereof, the method comprising administering to the CNS neuron a compound of Formula I-I or Formula I. ~~In another aspect, the present disclosure provides for use of a compound of Formula I-I or Formula I in the manufacture of a medicament for the inhibition or prevention of~~
15 ~~degeneration of a central nervous system (CNS) neuron or a portion thereof.~~ In certain embodiments, said administering to the CNS neuron is performed in vitro. In other embodiments, the method further comprises grafting or implanting the CNS neuron into a human patient after administration of the agent. In other embodiment, said CNS neuron is present in a human patient. In other embodiments, said administering to the CNS neuron
20 comprises administration of said compound of Formula I-I or Formula I in a pharmaceutically acceptable carrier, diluent or excipient. In another embodiment said administering to the CNS neuron is carried out by an administration route selected from the group consisting of parenteral, subcutaneous, intravenous, intraperitoneal, intracerebral, intralesional, intramuscular, intraocular, intraarterial interstitial infusion and implanted
25 delivery device. In another embodiment, said method further comprises administering one or more additional pharmaceutical agents. In another embodiment, said administering of a compound of Formula I-I or Formula I results in a decrease in JNK phosphorylation, JNK activity and/or JNK expression. In another embodiment, the administering of a compound of Formula I-I or Formula I results in a decrease of cJun phosphorylation, cJun activity, and/or
30 cJun expression. In another embodiment, the administering of a compound of Formula I-I or Formula I results in a decrease in p38 phosphorylation, p38 activity, and/or p38 expression. In another embodiments, the administering of a compound of Formula I-I or Formula I inhibits DLK activity. In some embodiments, DLK is inhibited by or at least by or at most by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99% or more, or 100%.

patient a therapeutically effective amount of a compound of Formula I-I or Formula I, or a pharmaceutically acceptable salt thereof. In another aspect, the present disclosure provides for use of a compound of Formula I-I or Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the inhibition or prevention of degeneration of a central nervous system (CNS) neuron in a patient having or at risk of developing a neurodegenerative disease or condition, wherein said neurodegenerative disease or condition is selected from the group consisting of: Alzheimer's disease, Huntington's disease, Parkinson's disease, Parkinson's-plus diseases, amyotrophic lateral sclerosis (ALS), ischemia, stroke, intracranial hemorrhage, cerebral hemorrhage, trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, progressive muscular atrophy, primary lateral sclerosis (PLS), pseudobulbar palsy, progressive bulbar palsy, spinal muscular atrophy, inherited muscular atrophy, invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, porphyria, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies, frontotemporal dementia, demyelinating diseases, Guillain-Barré syndrome, multiple sclerosis, Charcot-Marie-Tooth disease, prion disease, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), bovine spongiform encephalopathy, Pick's disease, epilepsy, AIDS demential complex, nerve damage caused by exposure to toxic compounds selected from the group consisting of heavy metals, industrial solvents, drugs and chemotherapeutic agents; injury to the nervous system caused by physical, mechanical or chemical trauma, glaucoma, lattice dystrophy, retinitis pigmentosa, age-related macular degeneration (AMD), photoreceptor degeneration associated with wet or dry AMD, other retinal degeneration, optic nerve drusen, optic neuropathy and optic neuritis.

The present disclosure provides for a method for decreasing or preventing one or more symptoms of a neurodegenerative disease or condition in a patient suffering therefrom comprising administering to said patient a therapeutically effective amount of a compound of Formula I-I or Formula I or a pharmaceutically acceptable salt thereof. In another aspect, there is provided use of a compound of Formula I-I or Formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for decreasing or preventing one or more symptoms of a neurodegenerative disease or condition in a patient suffering therefrom, wherein said neurodegenerative disease or condition is selected from the group consisting of: Alzheimer's disease, Huntington's disease, Parkinson's disease, Parkinson's-plus diseases, amyotrophic lateral sclerosis (ALS), ischemia, stroke, intracranial hemorrhage, cerebral hemorrhage, trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, progressive muscular atrophy, primary lateral sclerosis (PLS), pseudobulbar palsy, progressive bulbar palsy, spinal muscular atrophy,

inherited muscular atrophy, invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, porphyria, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies, frontotemporal dementia, demyelinating diseases,

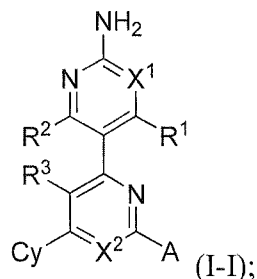
- 5 Guillain-Barré syndrome, multiple sclerosis, Charcot-Marie-Tooth disease, prion disease, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), bovine spongiform encephalopathy, Pick's disease, epilepsy, AIDS
demential complex, nerve damage caused by exposure to toxic compounds selected from the
group consisting of heavy metals, industrial solvents, drugs and chemotherapeutic agents;
10 injury to the nervous system caused by physical, mechanical or chemical trauma, glaucoma,
lattice dystrophy, retinitis pigmentosa, age-related macular degeneration (AMD),
photoreceptor degeneration associated with wet or dry AMD, other retinal degeneration,
optic nerve drusen, optic neuropathy and optic neuritis .

- The present disclosure provides for a method for decreasing the progression of a
15 neurodegenerative disease or condition in a patient suffering therefrom comprising
administering to said patient a therapeutically effective amount of a compound of Formula
I-I or Formula I or a pharmaceutically acceptable salt thereof. In another aspect, the present
disclosure provides for use of a compound of Formula I-I or Formula I or a pharmaceutically
acceptable salt thereof in the manufacture of a medicament for decreasing the progression of
20 a neurodegenerative disease or condition in a patient suffering therefrom, wherein said
neurodegenerative disease or condition is selected from the group consisting of:
Alzheimer's disease, Huntington's disease, Parkinson's disease, Parkinson's-plus diseases,
amyotrophic lateral sclerosis (ALS), ischemia, stroke, intracranial hemorrhage, cerebral
hemorrhage, trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia
25 gravis, muscular dystrophy, progressive muscular atrophy, primary lateral sclerosis (PLS),
pseudobulbar palsy, progressive bulbar palsy, spinal muscular atrophy, inherited muscular
atrophy, invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet
destruction syndromes, peripheral neuropathies, porphyria, multiple system atrophy,
progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies,
30 frontotemporal dementia, demyelinating diseases, Guillain-Barré syndrome, multiple
sclerosis, Charcot-Marie-Tooth disease, prion disease, Creutzfeldt-Jakob disease,
Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), bovine
spongiform encephalopathy, Pick's disease, epilepsy, AIDS demential complex, nerve
damage caused by exposure to toxic compounds selected from the group consisting of heavy
35 metals, industrial solvents, drugs and chemotherapeutic agents; injury to the nervous system
caused by physical, mechanical or chemical trauma, glaucoma, lattice dystrophy, retinitis
pigmentosa, age-related macular degeneration (AMD), photoreceptor degeneration
associated with wet or dry AMD, other retinal degeneration, optic nerve drusen, optic

neuropathy and optic neuritis. In certain embodiments, said neurodegenerative disease of condition is selected from the group consisting of: Alzheimer's disease, Huntington's disease, Parkinson's disease, Parkinson's-plus diseases, amyotrophic lateral sclerosis (ALS), ischemia, stroke, intracranial hemorrhage, cerebral hemorrhage, trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, progressive muscular atrophy, primary lateral sclerosis (PLS), pseudobulbar palsy, progressive bulbar palsy, spinal muscular atrophy, inherited muscular atrophy, invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, porphyria, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies, frontotemporal dementia, demyelinating diseases, Guillain-Barré syndrome, multiple sclerosis, Charcot-Marie-Tooth disease, prion disease, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), bovine spongiform encephalopathy, Pick's disease, epilepsy, AIDS demential complex, nerve damage caused by exposure to toxic compounds selected from the group consisting of heavy metals, industrial solvents, drugs and chemotherapeutic agents; injury to the nervous system caused by physical, mechanical or chemical trauma, glaucoma, lattice dystrophy, retinitis pigmentosa, age-related macular degeneration (AMD), photoreceptor degeneration associated with wet or dry AMD, other retinal degeneration, optic nerve drusen, optic neuropathy and optic neuritis. In certain embodiment, said neurodegenerative disease of condition in a patient is selected from the group consisting of: Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS), In certain embodiment, said the compound of Formula I-I or Formula I is administered in combination with one or more additional pharmaceutical agents.

CLAIMS

1. A compound of Formula (I-I)



or salts thereof wherein

5 **R¹, R² and R³** are each independently H, F, Cl, Br, I, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

X¹ is N or C-R⁴, wherein R⁴ is selected from the group consisting of -F, -Cl, -Br, I, -(L¹)₀₋₁-C₁₋₆ alkyl, -(L¹)₀₋₁-C₁₋₆ haloalkyl, -(L¹)₀₋₁-C₁₋₆ heteroalkyl, -(L²)₀₋₁-C₃₋₈ cycloalkyl, -(L²)₀₋₁-3 to 7 membered heterocycloalkyl, -(L²)₀₋₁-6-10 membered aryl, -(L²)₀₋₁-5-10 membered heteroaryl, wherein L¹ is selected from the group consisting of -O-, -N(H)-, -S-,
 10 -N(C₁₋₆ alkyl)-, =O, and L² is selected from the group consisting of -O-, -N(H)-, -N(C₁₋₆ alkyl)-, -S-, =O, C₁₋₄ alkylene, C₁₋₄ alkenylene, C₁₋₄ alkynylene, C₁₋₄ alkoxy, C₁₋₄ aminoalkylene, C₁₋₄ thioalkylene and C₁₋₄ heteroalkylene, and wherein R⁴ is optionally substituted on carbon atoms and heteroatoms with R^{R4} substituents selected from the group consisting of F, Cl, Br, I, C₁₋₆ alkyl, C₁₋₆ haloalkyl, 3-5 membered cycloalkyl, 3-5
 15 membered heterocycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylthio, =O, -NH₂, -CN, -NO₂ and -SF₅;

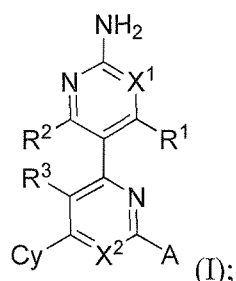
or R¹ and R⁴ taken together form a 5 to 6 membered heterocycloalkyl;

X² is N or CH;

A is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ dialkylamino, 3 to 12 membered cycloalkyl, 3 to 12 membered heterocycloalkyl, and 5 to 6 membered heteroaryl, wherein A is optionally substituted with 1-5 R^A substituents selected from the group consisting of F, Cl, Br, I, -OH, -CN, -NO₂, -SF₅, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈

from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, 3 to 8 membered cycloalkyl, phenyl, benzyl, 5 to 6 membered heteroaryl and 3 to 7 membered heterocycloalkyl; Y¹ is O or S, and wherein R^{Cy} is optionally substituted on carbon atoms and heteroatoms with from 1 to 5 R^{R_{Cy}} substituents selected from, F, Cl, Br, I, -NH₂, -OH, -CN, -NO₂, -O⁻, =O, -SF₅, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ alkyl-C(=O)-, C₁₋₄ (halo)alkyl-C(=O)-, C₁₋₄ (halo)alkyl-S(O)₀₋₂-, C₁₋₄ (halo)alkyl-N(H)S(O)₀₋₂-, C₁₋₄ (halo)alkyl-S(O)₀₋₂N(H)-, (halo)alkyl-N(H)-S(O)₀₋₂N(H)-, C₁₋₄ (halo)alkyl-C(=O)N(H)-, C₁₋₄ (halo)alkyl-N(H)-C(=O)-, ((halo)alkyl)₂N-C(=O)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)₂N-C(=O)O-, C₁₋₄ alkylthio, C₁₋₄ alkylamino and C₁₋₄ dialkylamino.

2. The compound of claim 1, further defined as a compound of Formula (I)



or salts thereof wherein

R¹, R² and R³ are each independently H, F, Cl, Br, I, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

X¹ is ~~N or~~ C-R⁴, wherein R⁴ is selected from the group consisting of -F, -Cl, -Br, I, -(L¹)₀₋₁-C₁₋₆ alkyl, -(L¹)₀₋₁-C₁₋₆ haloalkyl, -(L¹)₀₋₁-C₁₋₆ heteroalkyl, -(L²)₀₋₁-C₃₋₈ cycloalkyl, -(L²)₀₋₁-3 to 7 membered heterocycloalkyl, -(L²)₀₋₁-6-10 membered aryl, -(L²)₀₋₁-5-10 membered heteroaryl, wherein L¹ is selected from the group consisting of -O-, -N(H)-, -S-, -N(C₁₋₆ alkyl)-, =O, and L² is selected from the group consisting of -O-, -N(H)-, -N(C₁₋₆ alkyl)-, -S-, =O, C₁₋₄ alkylene, C₁₋₄ alkenylene, C₁₋₄ alkynylene, C₁₋₄ alkoxy, C₁₋₄ aminoalkylene, C₁₋₄ thioalkylene and C₁₋₄ heteroalkylene, and wherein R⁴ is optionally substituted on carbon atoms and heteroatoms with R^{R₄} substituents selected from the group consisting of F, Cl, Br, I, C₁₋₆ alkyl, C₁₋₆ haloalkyl, 3-5 membered cycloalkyl, 3-5 membered heterocycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylthio, =O, -NH₂, -CN, -NO₂ and -SF₅;

X² is N or CH;

aminoalkylene, C₁₋₄ thioalkylene, C₂₋₄ alkenylene, and C₂₋₄ alkynylene; wherein R^{RCa} and R^{RCb} are independently selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl, 3-8 membered cycloalkyl, phenyl, benzyl, 5 to 6 membered heteroaryl and 3 to 8 membered heterocycloalkyl; R^{RCc} is selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ haloalkyl, 3 to 8 membered cycloalkyl, phenyl, benzyl, 5 to 6 membered heteroaryl and 3 to 7 membered heterocycloalkyl; Y¹ is O or S, and wherein R^{RCy} is optionally substituted on carbon atoms and heteroatoms with from 1 to 5 R^{RCy} substituents selected from, F, Cl, Br, I, -NH₂, -OH, -CN, -NO₂, =O, -SF₅, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ (halo)alkyl-C(=O)-, C₁₋₄ (halo)alkyl-S(O)₀₋₂-, C₁₋₄ (halo)alkyl-N(H)S(O)₀₋₂-, C₁₋₄ (halo)alkyl-S(O)₀₋₂N(H)-, (halo)alkyl-N(H)-S(O)₀₋₂N(H)-, C₁₋₄ (halo)alkyl-C(=O)N(H)-, C₁₋₄ (halo)alkyl-N(H)-C(=O)-, ((halo)alkyl)₂N-C(=O)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)₂N-C(=O)O-, C₁₋₄ alkylthio, C₁₋₄ alkylamino and C₁₋₄ dialkylamino.

3. A compound according to claim 1 or 2, wherein either A or Cy is a polycyclic carbocycle or polycyclic heterocycle.

~~4. A compound according to claim 1, 2 or 3, wherein X¹ is N.~~

~~5. A compound according to claim 1, 2 or 3, wherein X¹ is C-R⁴.~~

~~64. A compound of claim 1, 2, or 3, 4 or 5, wherein X² is N.~~

~~75. A compound of claim, 1, 2, or 3, 4 or 5, wherein X² is C(H).~~

86. A compound according to claim 1, 2, 3, or 5, 6 or 7, wherein R⁴ is selected from the group consisting of -F, -Cl, -CN, -(L²)₀₋₁-C₃₋₈ cycloalkyl, -(L²)₀₋₁-3 to 7 membered heterocycloalkyl, -(L¹)₀₋₁-C₁₋₆ alkyl, -(L¹)₀₋₁-C₁₋₆ haloalkyl, -(L¹)₀₋₁-C₁₋₆ heteroalkyl, -(L²)₀₋₁-6-10 membered aryl and -(L²)₀₋₁-5-10 membered heteroaryl, and is optionally substituted.

97. A compound according to claim 1, 2, 3, 5, or 6, 7 or 8, wherein R⁴ is selected from the group consisting of -F, -Cl, C₃₋₈ cycloalkyl, 3 to 7 membered heterocycloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -(O)-C₃₋₈ cycloalkyl, -(O)-3 to 7 membered heterocycloalkyl, -(O)-C₁₋₆ alkyl and -(O)-C₁₋₆ haloalkyl, and is optionally substituted.

~~108.~~ A compound of claim 1, 2, 3, 5, 6, or 7, 8 or 9, wherein R⁴ is selected from the group consisting of methoxy, monofluoromethoxy, difluoromethoxy, trifluoromethoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, cyclopropoxy, cyclobutoxy, cyclopentoxo, methyl, monofluoromethyl difluoromethyl, trifluoromethyl, cyclopropyl, cyclobutyl and cyclopentyl.

~~119.~~ A compound of claim 1, 2, 3, 4, 5, 6, 7, or 8, 9 or 10, wherein R¹, R² and R³ are each independently selected from the group consisting of F, Cl, CN, hydrogen, C₁₋₄ alkyl and C₁₋₄ haloalkyl.

~~1210.~~ A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, 10 or 11, wherein R¹, R² and R³ are each hydrogen.

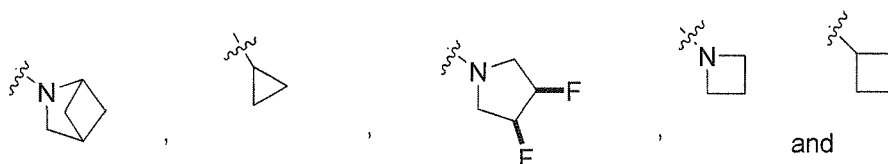
~~1311.~~ A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, 11 or 12, wherein A and Cy are independently selected from the group consisting of pyrrolidine, piperidine, azetidine, azepane, piperazine, 7-azaspiro[3.5]nonane, 3,6-diazabicyclo[3.2.1]octane, 2-oxa-5-azabicyclo[2.2.1]heptane, 2,7-diazaspiro[3.5]nonane, octahydrocyclopenta[c]pyrrole, 2-azaspiro[3.3]heptane, 2,5-diazaspiro[3.4]octane, 6-azaspiro[2.5]octane, 3-azabicyclo[3.1.0]hexane, 3-oxabicyclo[3.1.0]hexane, morpholine, hexahydro-2H-furo[3,2-c]pyrrole, 2-azabicyclo[2.1.1]hexane, 2,5-diazabicyclo[2.2.1]heptane, 2-aza-tricyclo[3.3.1.1-3,7]decane, 2-azabicyclo[2.1.1]hexane, 9-azabicyclo[4.2.1]nonane, 9-azabicyclo[3.3.1]nonane, cyclobutane, cyclopropane, cyclopentane, 2-Thia-5-aza-bicyclo[2.2.1]heptane 2,2-dioxide, 2-azabicyclo[2.2.1]heptane, tetrahydro-2H-pyran, 8-azabicyclo[3.2.1]octane and 3-oxa-8-azabicyclo[3.2.1]octane, and is optionally substituted.

~~1412.~~ A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11, 12 or 13, wherein A is selected from the group consisting of pyrrolidine, piperidine, azetidine, azepane, piperazine, cyclopropane, cyclobutane, cyclopentane, 7-azaspiro[3.5]nonane, 3-oxabicyclo[3.1.0]hexane, 3,6-diazabicyclo[3.2.1]octane, 2-oxa-5-azabicyclo[2.2.1]heptane, 2,7-diazaspiro[3.5]nonane, octahydrocyclopenta[c]pyrrole, 2-azaspiro[3.3]heptane, 2,5-diazaspiro[3.4]octane, 6-azaspiro[2.5]octane, 3-azabicyclo[3.1.0]hexane, morpholine, hexahydro-2H-furo[3,2-c]pyrrole and 2-azabicyclo[2.1.1]hexane, and is optionally substituted.

~~15~~13. A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, ~~13 or 14~~, wherein A is selected from the group consisting of 2-azabicyclo[2.1.1]hexane, 3-azabicyclo[3.1.0]hexane, 3-oxabicyclo[3.1.0]hexane, azetidine, pyrrolidine, cyclopropane, cyclobutane, cyclopentane, and is optionally substituted.

5 ~~16~~14. A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, ~~14 or 15~~, wherein A is selected from the group consisting of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane, (1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane, (1R,5S)-3-azabicyclo[3.1.0]hexane, (1S,5R)-3-azabicyclo[3.1.0]hexane, 3-oxabicyclo[3.1.0]hexane, (1R,5S)-3-oxabicyclo[3.1.0]hexane, (1S,5R)-3-oxabicyclo[3.1.0]hexane, (1S,4S)-2,5-diazabicyclo[2.2.1]heptane and (1R,4R)-2,5-diazabicyclo[2.2.1]heptane, and is optionally substituted.

~~17~~15. A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, ~~11 or 12~~, wherein is A is selected from the group consisting of methyl, ethyl, isopropyl,

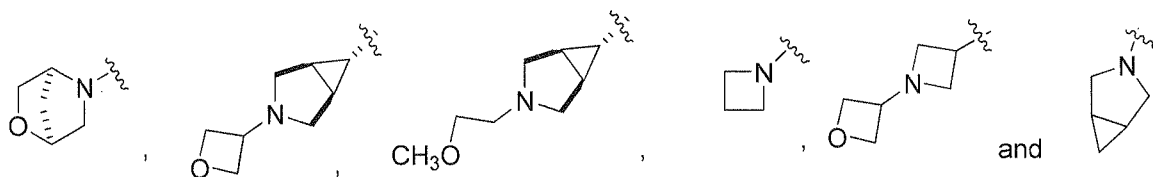


15 ~~18~~16. A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15, ~~16 or 17~~, wherein Cy is selected from the group consisting of 2,5-diazabicyclo[2.2.1]heptane, piperidine, pyrrolidine, azetidine, 2-aza-tricyclo[3.3.1.1-3,7]decane, 2-oxa-5-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.1.0]hexane, 3-oxabicyclo[3.1.0]hexane, 2-azabicyclo[2.1.1]hexane, 9-azabicyclo[4.2.1]nonane, 9-azabicyclo[3.3.1]nonane, 20 cyclobutane, 2-Thia-5-aza-bicyclo[2.2.1]heptane 2,2-dioxide, 2-azabicyclo[2.2.1]heptane, tetrahydro-2H-pyran, 8-azabicyclo[3.2.1]octane, 3-oxa-8-azabicyclo[3.2.1]octane, and is optionally substituted.

~~19~~17. A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16, ~~17 or 18~~, wherein Cy is selected from the group consisting of azetidine, (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane, (1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane, (1R,5S)-3-azabicyclo[3.1.0]hexane, (1S,5R)-3-azabicyclo[3.1.0]hexane, 3-oxabicyclo[3.1.0]hexane, (1R,5S)-3-oxabicyclo[3.1.0]hexane, (1S,5R)-3-oxabicyclo[3.1.0]hexane, (1S,4S)-2,5-diazabicyclo[2.2.1]heptane and (1R,4R)-2,5-diazabicyclo[2.2.1]heptane, and is optionally substituted.

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2018. A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, 11 or 12, wherein Cy is selected from the group consisting of



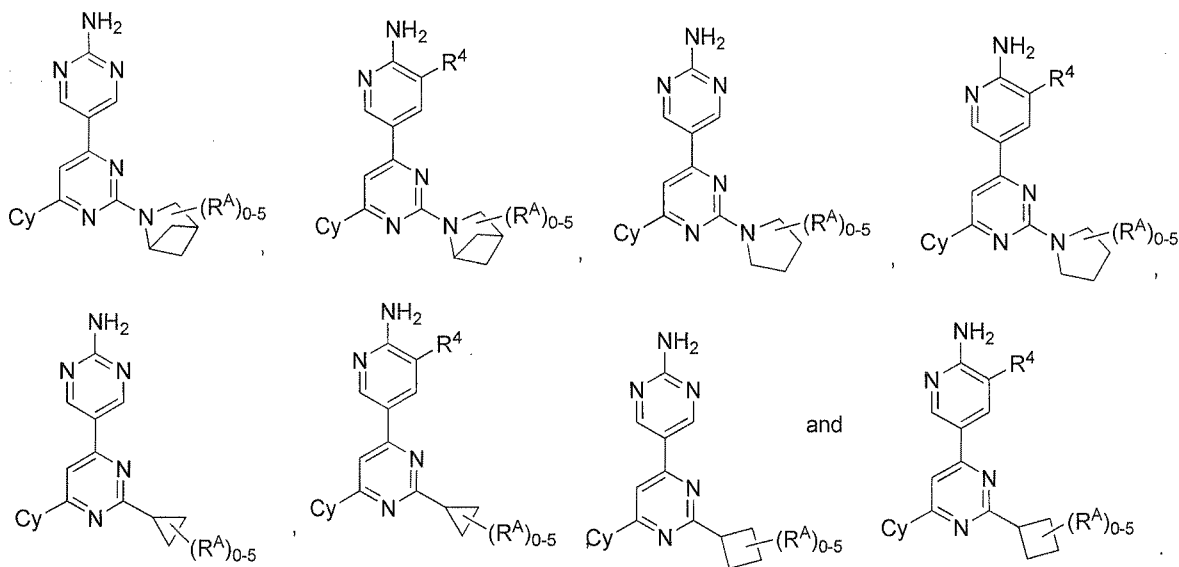
2119. A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17;
 5 or 18, 19 or 20, wherein A is optionally substituted with from 1 to 5 R^A substituents
 selected from the group consisting of F, Cl, Br, I, -OH, -CN, -NO₂, -SF₅, C₁₋₈ alkyl, C₁₋₈
 haloalkyl, C₁₋₈ heteroalkyl, -(L^A)₀₋₁₋₃₋₈ membered cycloalkyl, -(L^A)₀₋₁₋₃₋₈ membered
 heterocycloalkyl, -(L^A)₀₋₁₋₅ to 6 membered heteroaryl, -(L^A)₀₋₁-C₆ aryl, wherein L^A is
 selected from the group consisting of -C(O)-, -C(O)CH₂-, -OCH₂-, -CH₂O-, -CH₂-, -
 10 CH₂CH₂-, -CH₂OCH₂-, -N(H)CH₂-, -N(C₁₋₃ alkyl)CH₂-, CH₂N(H)-, -CH₂N(C₁₋₃ alkyl)-;
 wherein said 3-8 membered cycloalkyl is selected from the group consisting of propane,
 butane, pentane and hexane; wherein said 3 to 8 membered heterocycloalkyl is selected
 from the group consisting of oxetane, tetrahydrofuran, tetrahydropyran, oxepane, azetidine,
 pyrrolidine, piperidine and azepane; wherein said 5 to 6 membered heteroaryl is selected
 15 from the group consisting of pyrrole, pyrazole, imidazole, thiophene, thiazole, oxazole,
 triazole, pyridine, pyrimidine, pyrazine, pyridazine; wherein said C₆ aryl is phenyl; and
 wherein R^A is optionally substituted with from 1 to 5 R^{RA} substituents selected from, F,
 Cl, Br, I, -NH₂, -OH, -CN, -NO₂, =O, -SF₅, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄
 (halo)alkyl-C(=O)-, C₁₋₄ (halo)alkyl-S(O)₀₋₂-, C₁₋₄ (halo)alkyl-N(H)S(O)₀₋₂-, C₁₋₄
 20 (halo)alkyl-S(O)₀₋₂N(H)-, (halo)alkyl-N(H)-S(O)₀₋₂N(H)-, C₁₋₄ (halo)alkyl-C(=O)N(H)-,
 C₁₋₄ (halo)alkyl-N(H)-C(=O)-, ((halo)alkyl)₂N-C(=O)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, C₁₋₄
 (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)₂N-C(=O)O-, C₁₋₄
 alkylthio, C₁₋₄ alkylamino and C₁₋₄ dialkylamino.

2220. A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17;
 25 or 18, 19 or 21, wherein Cy is optionally substituted with from 1 to 5 R^{Cy} substituents
 selected from the group consisting of F, Cl, Br, I, -OH, -CN, -NO₂, -SF₅, C₁₋₈ alkyl, C₁₋₈
 haloalkyl, C₁₋₈ heteroalkyl, -(L^{Cy})₀₋₁₋₃₋₈ membered cycloalkyl, -(L^{Cy})₀₋₁₋₃₋₈ membered
 heterocycloalkyl, -(L^{Cy})₀₋₁₋₅ to 6 membered heteroaryl, -(L^{Cy})₀₋₁-C₆ aryl, wherein L^{Cy} is
 selected from the group consisting of -C(O)-, -C(O)CH₂-, -OCH₂-, -CH₂O-, -CH₂-, -
 30 CH₂CH₂-, -CH₂OCH₂-, -N(H)CH₂-, -N(C₁₋₃ alkyl)CH₂-, CH₂N(H)-, -CH₂N(C₁₋₃ alkyl)-;
 wherein said 3-8 membered cycloalkyl is selected from the group consisting of propane,
 butane, pentane and hexane; wherein said 3 to 8 membered heterocycloalkyl is selected
 from the group consisting of oxetane, tetrahydrofuran, tetrahydropyran, oxepane, azetidine,
 pyrrolidine, piperidine and

azepane; wherein said 5 to 6 membered heteroaryl is selected from the group consisting of pyrrole, pyrazole, imidazole, thiophene, thiazole, oxazole, triazole, pyridine, pyrimidine, pyrazine, pyridazine; wherein said C₆ aryl is phenyl; and wherein R^{Cy} is optionally substituted with from 1 to 5 R^{RCy} substituents selected from, F, Cl, Br, I, -NH₂, -OH, -CN, -NO₂, =O, -SF₅, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ (halo)alkyl-C(=O)-, C₁₋₄ (halo)alkyl-S(O)₀₋₂-, C₁₋₄ (halo)alkyl-N(H)S(O)₀₋₂-, C₁₋₄ (halo)alkyl-S(O)₀₋₂N(H)-, (halo)alkyl-N(H)-S(O)₀₋₂N(H)-, C₁₋₄ (halo)alkyl-C(=O)N(H)-, C₁₋₄ (halo)alkyl-N(H)-C(=O)-, ((halo)alkyl)₂N-C(=O)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, C₁₋₄ (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)₂N-C(=O)O-, C₁₋₄ alkylthio, C₁₋₄ alkylamino and C₁₋₄ dialkylamino.

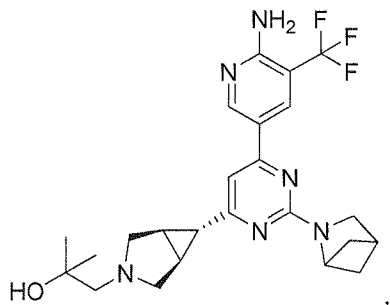
2321. A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 19, or 20, 21 or 22, wherein A is optionally substituted with 1 to 5 R^A substituents selected from the group consisting of F, Cl, Br, I, CN, CH₃O-, CH₃, cyclopropylmethyl, CF₃ and butyl.

2422. A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21, 22 or 23, wherein said compound is selected from the subformula consisting of

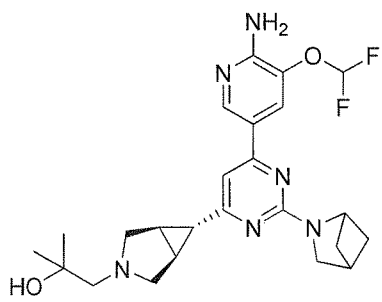


2523. A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21, 22 or 23, wherein said compound is selected from the subformula consisting of

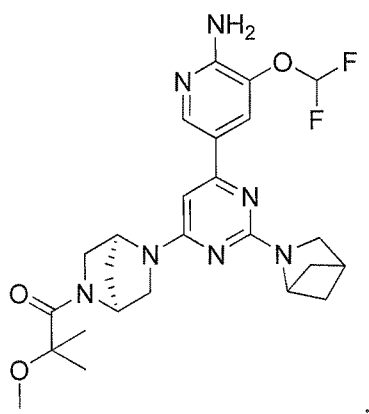
27. A compound according to any one of claims 1-24 that is 1-[(1R,5S)-6-[6-[6-amino-5-(trifluoromethyl)-3-pyridyl]-2-(3-azabicyclo[2.1.1]hexan-3-yl)pyrimidin-4-yl]-3-azabicyclo[3.1.0]hexan-3-yl]-2-methyl-propan-2-ol



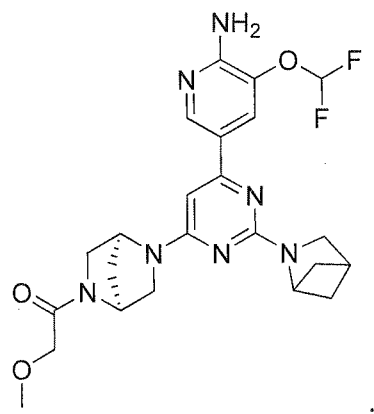
5 28. A compound according to any one of claims 1-24 that is [6-amino-5-(difluoromethoxy)-3-pyridyl]-2-(3-azabicyclo[2.1.1]hexan-3-yl)pyrimidin-4-yl]-3-azabicyclo[3.1.0]hexan-3-yl]-2-methyl-propan-2-ol



10 29. A compound according to any one of claims 1-24 that is 1-[(1S,4S)-5-[6-[6-amino-5-(difluoromethoxy)-3-pyridyl]-2-(3-azabicyclo[2.1.1]hexan-3-yl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]heptan-2-yl]-2-methoxy-2-methyl-propan-1-one

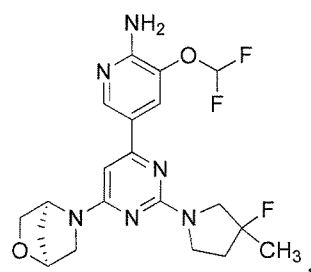


15 30. A compound according to any one of claims 1-24 that is [6-amino-5-(difluoromethoxy)-3-pyridyl]-2-(3-azabicyclo[2.1.1]hexan-3-yl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]heptan-2-yl]-2-methoxy-ethanone

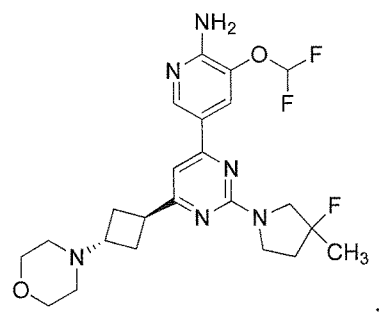


31. A compound according to any one of claims 1-24 that is 3-(difluoromethoxy)-5-[2-(3-fluoro-3-methyl-pyrrolidin-1-yl)-6-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrimidin-4-yl]pyridin-2-amine

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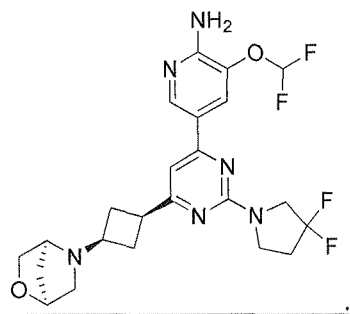


32. A compound according to any one of claims 1-24 that is (±)-3-(difluoromethoxy)-5-[2-(3-fluoro-3-methyl-pyrrolidin-1-yl)-6-(3-morpholino-*trans*-cyclobutyl)pyrimidin-4-yl]pyridin-2-amine

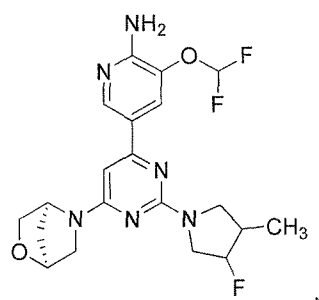


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33. A compound according to any one of claims 1-24 that is 3-(difluoromethoxy)-5-[2-(3,3-difluoropyrrolidin-1-yl)-6-[3-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-*cis*-cyclobutyl]pyrimidin-4-yl]pyridin-2-amine



34. A compound according to any one of claims 1-24 that is 3-(difluoromethoxy)-5-[2-[*cis*-3-fluoro-4-methyl-pyrrolidin-1-yl]-6-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrimidin-4-yl]pyridin-2-amine



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2735. A pharmaceutical composition comprising a compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, ~~or 26~~, ~~27, 28, 29, 30, 31, 32, 33 or 34~~, and a pharmaceutically acceptable carrier, diluent or excipient.

28. A compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or 26 for use in therapy.

29. Use of a compound of Formula I-I or Formula I in the manufacture of a medicament for the inhibition or prevention of degeneration of a central nervous system (CNS) neuron or a portion thereof.

30. The use of claim 29, wherein said compound of Formula I-I or Formula I is administered to the CNS neuron in vitro.

31. The use of claim 30, wherein the CNS neuron is to be grafted or implanted into a human patient after administration of the compound of Formula I-I or Formula I.

32. The use of claim 30, wherein the CNS neuron is present in a human patient.

33. — The use of claim 29, wherein said compound of Formula I-I or Formula I is administered in a pharmaceutically acceptable carrier, diluent or excipient.

34. — The use of claim 29, wherein said compound of Formula I-I or Formula I is to be administered to the CNS neuron by an administration route selected from the group consisting of parenteral, subcutaneous, intravenous, intraperitoneal, intracerebral, intralesional, intramuscular, intraocular, intraarterial interstitial infusion and implanted delivery device.

35. — The use of claim 29, further comprising use of one or more additional pharmaceutical agents.

36. — The use of claim 29, wherein the use of said compound of Formula I-I or Formula I results in a decrease in JNK phosphorylation, JNK activity and/or JNK expression.

37. — The use of claim 36, wherein the use of said compound of Formula I-I or Formula I results in a decrease of cJun phosphorylation, cJun activity, and/or cJun expression.

38. — The use of claim 36, wherein the use of said compound of Formula I-I or Formula I results in a decrease in p38 phosphorylation, p38 activity, and/or p38 expression.

39. Use of a compound of Formula I-I or Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the inhibition or prevention of degeneration of a central nervous system (CNS) neuron in a patient having or at risk of developing a neurodegenerative disease or condition, wherein said neurodegenerative disease or condition is selected from the group consisting of: Alzheimer's disease, Huntington's disease, Parkinson's disease, Parkinson's-plus diseases, amyotrophic lateral sclerosis (ALS), ischemia, stroke, intracranial hemorrhage, cerebral hemorrhage, trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, progressive muscular atrophy, primary lateral sclerosis (PLS), pseudobulbar palsy, progressive bulbar palsy, spinal muscular atrophy, inherited muscular atrophy, invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, porphyria, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies, frontotemporal dementia, demyelinating diseases, Guillain-Barré syndrome, multiple sclerosis, Charcot-Marie-Tooth disease, prion disease, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), bovine spongiform encephalopathy, Pick's disease, epilepsy, AIDS demential complex, nerve

damage caused by exposure to toxic compounds selected from the group consisting of heavy metals, industrial solvents, drugs and chemotherapeutic agents; injury to the nervous system caused by physical, mechanical or chemical trauma, glaucoma, lattice dystrophy, retinitis pigmentosa, age-related macular degeneration (AMD), photoreceptor degeneration associated with wet or dry AMD, other retinal degeneration, optic nerve drusen, optic neuropthy and optic neuritis.

4037. Use of a compound of Formula I-I or Formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for decreasing or preventing one or more symptoms of a neurodegenerative disease or condition in a patient suffering therefrom, wherein said neurodegenerative disease or condition is selected from the group consisting of: Alzheimer's disease, Huntington's disease, Parkinson's disease, Parkinson's-plus diseases, amyotrophic lateral sclerosis (ALS), ischemia, stroke, intracranial hemorrhage, cerebral hemorrhage, trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, progressive muscular atrophy, primary lateral sclerosis (PLS), pseudobulbar palsy, progressive bulbar palsy, spinal muscular atrophy, inherited muscular atrophy, invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, prophyria, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies, frontotemporal dementia, demyelinating diseases, Guillain-Barré syndrome, multiple sclerosis, Charcot-Marie-Tooth disease, prion disease, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), bovine spongiform encephalopathy, Pick's disease, epilepsy, AIDS demential complex, nerve damage caused by exposure to toxic compounds selected from the group consisting of heavy metals, industrial solvents, drugs and chemotherapeutic agents; injury to the nervous system caused by physical, mechanical or chemical trauma, glaucoma, lattice dystrophy, retinitis pigmentosa, age-related macular degeneration (AMD), photoreceptor degeneration associated with wet or dry AMD, other retinal degeneration, optic nerve drusen, optic neuropthy and optic neuritis.

4138. Use of a compound of Formula I-I or Formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for decreasing the progression of a neurodegenerative disease or condition in a patient suffering therefrom.

42. ~~The use of claim 41,~~ wherein said neurodegenerative disease ~~of or~~ condition is selected from the group consisting of: Alzheimer's disease, Huntington's disease, Parkinson's disease, Parkinson's-plus diseases, amyotrophic lateral sclerosis (ALS), ischemia, stroke, intracranial hemorrhage, cerebral hemorrhage, trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, progressive muscular atrophy, primary lateral sclerosis (PLS), pseudobulbar palsy, progressive bulbar palsy, spinal muscular atrophy, inherited muscular atrophy, invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, porphyria, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies, frontotemporal dementia, demyelinating diseases, Guillain-Barré syndrome, multiple sclerosis, Charcot-Marie-Tooth disease, prion disease, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), bovine spongiform encephalopathy, Pick's disease, epilepsy, AIDS demential complex, nerve damage caused by exposure to toxic compounds selected from the group consisting of heavy metals, industrial solvents, drugs and chemotherapeutic agents; injury to the nervous system caused by physical, mechanical or chemical trauma, glaucoma, lattice dystrophy, retinitis pigmentosa, age-related macular degeneration (AMD), photoreceptor degeneration associated with wet or dry AMD, other retinal degeneration, optic nerve drusen, optic neuropathy and optic neuritis.

4339. The use of claim 4138, wherein the compound of Formula I-I or Formula I is in combination with one or more additional pharmaceutical agents.