

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

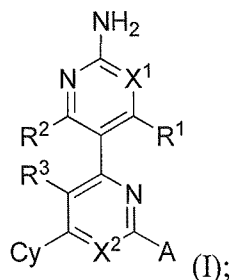
10 Neuron or axon degeneration plays a central role in the proper development of the nervous system and is a hall mark of many neurodegenerative diseases including for example, amyotrophic lateral sclerosis (ALS), glaucoma, Alzheimer's disease, and Parkinson's disease, as well a traumatic injury to the 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 In one aspect the present ~~invention~~ 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~~ ~~inventions~~ 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;

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;

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 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 ~~invention-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 ~~In another aspect,~~ The present disclosure invention 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
15 of 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%.

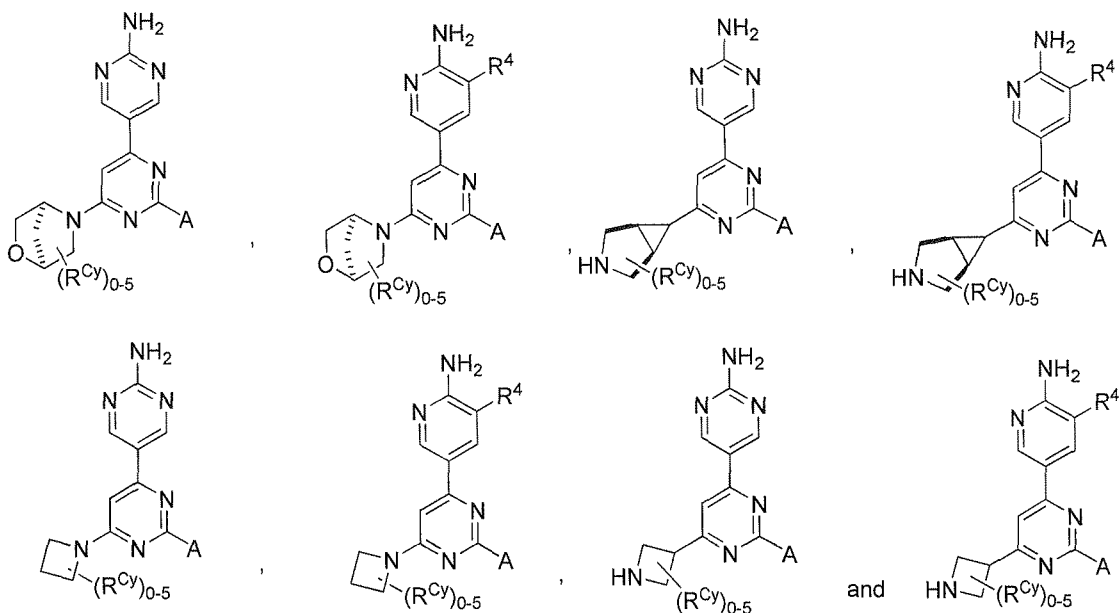
~~In another aspect,~~ The present invention-disclosure provides for a method for inhibiting or preventing degeneration of a central nervous system (CNS) neuron in a patient having or at risk of developing a neurodegenerative disease or condition comprising administering to said

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 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.

~~In another aspect, the present invention~~ 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.

~~In another aspect, the present invention~~ disclosure provides for a method for decreasing the progression 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, 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 a neurodegenerative disease or condition in a patient suffering therefrom. In certain embodiments, 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. 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.



wherein R^{Cy} if present replaces a hydrogen atom attached to a carbon or nitrogen atom of the Cy ring.

26. A compound of claim 1 selected from the group as set forth in Table 1.

5 27. 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, 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.

10 ~~2829.~~ Use of a compound of Formula I-I or Formula I in the manufacture of a medicament for the inhibition or prevention of 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.

15 ~~2930.~~ The method use of claim 2829, wherein said compound of Formula I-I or Formula I is administered administering to the CNS neuron is performed in vitro.

~~3031.~~ The method use of claim 2930, wherein the method further comprises grafting or implanting the CNS neuron is to be grafted or implanted into a human patient after administration of the agent compound of Formula I-I or Formula I.

20 ~~3132.~~ The method use of claim 2930, wherein the CNS neuron is present in a human patient.

3233. The ~~method-use~~ of claim ~~2829~~, wherein ~~administering to the CNS neuron~~ comprises ~~administration of said compound of Formula I-I or Formula I~~ is administered in a pharmaceutically acceptable carrier, diluent or excipient.

5 3334. The ~~method-use~~ of claim ~~2829~~, wherein said compound of Formula I-I or Formula I is to be administered ~~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 delivery device.

10 3435. The ~~method-use~~ of claim ~~2829~~, further comprising use of administering one or more additional pharmaceutical agents.

3536. The ~~method-use~~ of claim ~~2829~~, wherein the ~~administering-use~~ of a said compound of Formula I-I or Formula I results in a decrease in JNK phosphorylation, JNK activity and/or JNK expression.

15 3637. The ~~method-use~~ of claim ~~3536~~, wherein the ~~administering-use~~ of a said compound of Formula I-I or Formula I results in a decrease of cJun phosphorylation, cJun activity, and/or cJun expression.

3738. The ~~method-use~~ of claim ~~3536~~, wherein the ~~administering-use~~ of a said compound of Formula I-I or Formula I results in a decrease in p38 phosphorylation, p38 activity, and/or p38 expression.

20 3839. 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 A method for inhibiting or preventing degeneration of a central nervous system (CNS) neuron in a patient having or at risk of developing a neurodegenerative disease or condition comprising administering to said patient a therapeutically effective amount of a compound
25 of Formula I-I or Formula I, or a pharmaceutically acceptable salt thereof.

3940. Use of a compound of Formula I-I or Formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament ~~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~~
30 ~~amount of a compound of Formula I-I or Formula I or a pharmaceutically acceptable salt thereof.~~

~~40. A method for decreasing the progression of a neurodegenerative disease or condition in a patient suffering therefrom comprising administering to said patient a~~

41. 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 therefromtherapeutically effective amount of a compound of Formula I-I or Formula I or a pharmaceutically acceptable salt thereof.

4142. The method-use of claim 4041, wherein 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 neuropthy and optic neuritis.

4243. The method-use of claim 4041, wherein the compound of Formula I-I or Formula I is administered in combination with one or more additional pharmaceutical agents.