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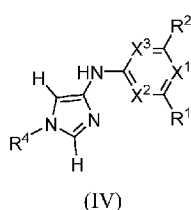
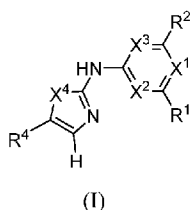
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(54) Title: HETEROCYCLIC AZOLES FOR THE TREATMENT OF DEMYELINATING DISEASES



(57) Abstract: The invention relates to heterocyclic compounds of formula (I) and (IV) or pharmaceutically acceptable salts thereof, useful as modulators of demyelinating diseases. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention, methods of using the compositions and kits thereof in the treatment of various demyelinating and neurodegenerative diseases, including multiple sclerosis.



HETEROCYCLIC AZOLES FOR THE TREATMENT OF DEMYELINATING DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

5 **[0001]** This application claims the benefit of U.S. Provisional Patent Application No. 62/430,822, filed December 6, 2016, the entire contents of which are hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

10 **[0002]** Multiple sclerosis (MS) is an inflammatory neurodegenerative disease of the central nervous system, characterized by myelin loss and degeneration of axons (see, Blakemore, et al., *J. of Neuroimmunology*, 98, 69-76, 1999). Activation and CNS infiltration of the peripheral immune system is typical in early stages of the disease, but can become less prevalent as disease progresses.

15 **[0003]** A hallmark of MS is loss of myelin, accompanied by the death of associated oligodendrocytes (see, Merrill, J.E. et al., *Neuropathology and Applied Neurobiology*, 25, 435-458, 1999). Myelin, which is produced by oligodendrocytes, ensheathes axons and dramatically increases conduction velocity of neural impulses while providing trophic support to the neuron. Myelin is thought to regenerate early in disease, as oligodendrocyte progenitor cells (OPCs) proliferate and generate new
20 myelinating oligodendrocytes in response to demyelination events. As the disease progresses the regenerative capacity of the OPCs becomes less robust, and axons remain chronically demyelinated. Chronic demyelination is thought to underlie axon loss, as loss of trophic support combined with the metabolic stress of transmitting impulses along a demyelinated membrane can lead to a breakdown of axonal integrity
25 and permanent damage to the demyelinated circuit. In addition, exposure of a demyelinated axon to an inflammatory milieu, including infiltrating immune cells and activated microglial cells, is also thought to produce permanent damage and axonal loss. Axon loss as a result of demyelination is thought to underlie long term disease progression and disability in MS patients (see, Compston, et al., *The Lancet*, Vol. 359, 1221-1231, 2002 and D. Kremer et al, *Trends in Neurosciences*, Vol. 39, No. 4, 246-
30 263, 2016).

[0004] The loss of remyelinating capacity in MS is not well understood, but is thought to involve a block in the differentiation capacity of OPCs, or the absence of a

necessary signal present in the cell environment of the demyelinating lesion or in the demyelinated axons (see, R. Franklin et al., *Nature Reviews/Neuroscience*, Vol. 9, 839-855, 2008). The OPC cell population is prevalent in MS patients, but fails to generate new myelin in response to demyelination. Thus, a compound that can
5 promote differentiation and myelination of OPCs should function to restore this regenerative capacity and blunt or reverse the degenerative effects of MS (see, Stangel, M. et al., *Progress in Neurobiology*, 68, 361-376, 2002, Nalm, F. J. et al., *Nature* (Letter), published online 20 April 2015, doi:10.1038/nature14335). Such an agent could both increase the function of neurons and provide trophic support to
10 enhance their survival (see, Mei, F. et al. *Nature Medicine*, Vol. 20, No. 8, 954-961, 2014).

[0005] Leukodystrophies are degenerative white matter diseases characterized by dysmyelination or demyelination. Multiple genetic or metabolic disorders can lead to progressive white matter damage in pediatric or adult populations resulting in severe
15 motor or cognitive deficits, mental retardation or death. A compound that can delay myelin damage or promote repair of demyelinated axons could significantly alter the course of leukodystrophies and improve their outcome. Such a compound could be also useful in combination with other therapies that can correct the disease-specific defect, metabolic, genetic or other, responsible for initiating or maintaining the
20 disease in order to accelerate repair, restore function or prevent further damage.

[0006] Hypoxic-ischemic insults leading to reduced oxygenation and blood supply into the brain can cause severe damage to OPCs, and demyelination. Periventricular leukomalacia is a condition characterized by toxic death of OPCs in the periventricular region and leading to severe dysmyelination and demyelination. This
25 pathology has been proposed as the root cause of cerebral palsy, a life-long debilitating CNS disorder characterized by various motor and/or cognitive deficits of variable intensity. A compound promoting differentiation of surviving OPCs and remyelination of damaged areas could be used for the treatment or prevention of cerebral palsy in vulnerable infant populations.

[0007] Current therapies for MS are immunomodulatory in nature and do not
30 directly promote repair. In addition, some of these immunomodulatory agents can leave patients vulnerable to opportunistic infection or neoplasia. Thus, there remains a need for compounds, such as those of the present invention, that can promote

differentiation and myelination of OPCs and lead to the repair of demyelinated axons. Such a compound could also be useful in combination with existing or experimental immunomodulating and other relevant therapies to treat MS and other neurological and demyelinating diseases.

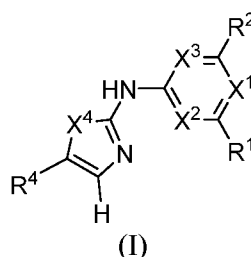
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SUMMARY OF THE INVENTION

[0008] The present invention provides compounds or a pharmaceutically acceptable salt thereof and the methods, compositions and kits disclosed herein for treating or lessening the severity of, in a subject, a disease or disorder selected from a demyelinating disease, central pontine myelinolysis, a nerve injury disease or disorder, a leukoencephalopathy or a leukodystrophy.

10

[0009] In a first aspect are compounds having the general formula (I):



15 **[0010]** or a pharmaceutically acceptable salt thereof,

[0011] wherein:

[0012] X^1 is CR^{X1} or N;

[0013] X^2 is CR^{X2} or N;

[0014] X^3 is CR^{X3} or N;

20 **[0015]** X^4 is O or S;

[0016] provided that X^1 is not N simultaneously with X^2 and X^3 ;

[0017] R^1 is selected from the group consisting of $-OC_{1-6}alkyl$, $-OC_{1-6}haloalkyl$, $-O-C_{2-6}alkylene-OC_{1-4}alkyl$, $-O-C_{2-6}alkylene-OH$, $-NHC(O)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl)$, $-C(O)NH_2$, $-C(O)NH(C_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-C(O)NH(C_{1-4}haloalkyl)$, $-C(O)NH(-C_{2-6}alkylene-OC_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)(-C_{2-6}alkylene-OC_{1-4}alkyl)$, $-C(O)NH(-C_{2-6}alkylene-OH)$, $-C(O)N(C_{1-4}alkyl)(-C_{2-6}alkylene-OH)$, $-L^1-G^1-R^6$, $-L^1-G^2$, $-L^1-G^3$, and $-L^2-G^4$;

25

[0018] R^2 is selected from the group consisting of hydrogen, $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, halogen, and $-OC_{1-4}alkyl$;

[0019] R^{X1} is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, C₁₋₄haloalkyl, and -O-C₁₋₄alkyl;

[0020] R^{X2} is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, and C₁₋₄haloalkyl;

5 **[0021]** R^{X3} is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, C₁₋₄haloalkyl, and -O-C₁₋₄alkyl;

[0022] L¹ is a bond, -O-, -O-C₁₋₄alkylene-, -NR⁵-, -NR⁵-C₁₋₄alkylene-, or -C(O)-, wherein R⁵ is hydrogen or C₁₋₄alkyl;

[0023] L² is -O-C₁₋₄alkylene-;

10 **[0024]** G¹ is a 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C₁₋₃alkylene bridge between two non-adjacent ring atoms, G¹ being optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁-

15 4haloalkyl, halogen, hydroxyl, and oxo;

[0025] R⁶ is (a) a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the heterocycle being optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, -CH₂S(O)₂phenyl, halogen, hydroxyl, oxo, -OC₁₋₄alkyl, -C₁₋₆alkylene-OC₁₋₄alkyl, and -C₁₋₆alkylene-OH; or (b) a 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, -C(O)OC₁₋₄alkyl, -C(O)OH, oxo, -OC₁₋₄alkyl, -C₁₋₆alkylene-OC₁₋₄alkyl, and -C₁₋₆alkylene-OH;

[0026] G² is a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, G² being optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, oxo, cyano, -C₁₋₆alkylene-cyano, -C(O)C₁₋₄alkyl, -C(O)-C₁₋₆alkylene-OC₁₋₄alkyl, -C(O)-C₁₋₆alkylene-OH, -C(O)C₃₋₆cycloalkyl, -C(O)OC₁₋₄alkyl, -C(O)OC₁₋₄haloalkyl, -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -N(C₁₋

30 ₆cycloalkyl, -C(O)OC₁₋₄alkyl, -C(O)OC₁₋₄haloalkyl, -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -N(C₁₋

- 4alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -NH(-C₁₋₆alkylene-OH), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -C(O)C₁₋₄haloalkyl, -OC₁₋₄alkyl, -OC₁₋₄haloalkyl, -C₁₋₆alkylene-OC₁₋₄alkyl, -C₁₋₆alkylene-OH, -C₁₋₆alkylene-NH₂, -C₁₋₆alkylene-NH(C₁₋₄alkyl), -C₁₋₆alkylene-N(C₁₋₄alkyl)(C₁₋₄alkyl), -O-C₁₋₆alkylene-NH₂, -O-C₁₋₆alkylene-NH(C₁₋₄alkyl), -O-C₁₋₆alkylene-N(C₁₋₄alkyl)(C₁₋₄alkyl), -O-C₁₋₆alkylene-OC₁₋₄alkyl, -O-C₁₋₆alkylene-OH, -C₁₋₄alkylene-O-C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₄alkylene-O-C₁₋₄alkylene-OH, -C₁₋₄alkylene-C(O)OC₁₋₄alkyl, -C₁₋₄alkylene-C(O)OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)(C₁₋₄alkyl), -S(O)₁₋₂C₁₋₄alkyl, -C₁₋₆alkylene-S(O)₁₋₂C₁₋₄alkyl, and a -C₁₋₆alkylene substituted by 2 groups independently selected from hydroxyl, halogen, -OC(O)C₁₋₄alkyl, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)(C₁₋₄alkyl);
- [0027]** G³ is 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, oxo, cyano, -C(O)C₁₋₄alkyl, -C(O)C₃₋₆cycloalkyl, -C(O)OC₁₋₄alkyl, -C(O)OC₁₋₄haloalkyl, -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -NH(-C₁₋₆alkylene-OH), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -C(O)C₁₋₄haloalkyl, -OC₁₋₄alkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₆alkylene-OH, -C₁₋₆alkylene substituted by 2 groups independently selected from hydroxyl and -OC(O)C₁₋₄alkyl, -C₁₋₄alkylene-C(O)OC₁₋₄alkyl, -C₁₋₄alkylene-C(O)OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)(C₁₋₄alkyl);
- [0028]** G⁴ is phenyl optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, cyano, phenyl, -C(O)C₁₋₄alkyl, -C(O)C₃₋₆cycloalkyl, -C(O)OC₁₋₄alkyl, -C(O)OC₁₋₄haloalkyl, -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -NH(-C₁₋₆alkylene-OH), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -C(O)C₁₋₄haloalkyl, -OC₁₋₄alkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₆alkylene-OH, -C₁₋₆alkylene substituted by 2 groups independently selected from hydroxyl and -OC(O)C₁₋₄alkyl, -C₁₋₄alkylene-C(O)OC₁₋

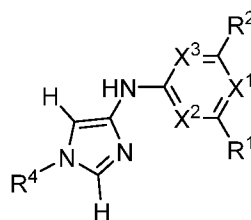
alkyl, $-C_{1-4}alkylene-C(O)OH$, $-NHC(O)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl)$, $-NH_2$, $-NH(C_{1-4}alkyl)$, and $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$; and

- [0029]** R^4 is phenyl or a 5- or 6-membered heteroaryl containing 1-3 heteroatoms independently selected from oxygen, nitrogen and sulfur, R^4 being optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, $-S(O)_2C_{1-4}alkyl$, $-S(O)C_{1-4}alkyl$, $-SC_{1-4}alkyl$, $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, $-OC_{1-4}alkyl$, $-OC_{1-4}haloalkyl$, $-C_{1-4}alkylene-OC_{1-4}alkyl$, $-C_{1-4}alkylene-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-NH(C_{1-4}alkylene-OC_{1-4}alkyl)$, $-NH(C_{1-4}alkylene-OH)$, $-N(C_{1-4}alkyl)(C_{1-4}alkylene-OC_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(C_{1-4}alkylene-OH)$, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $C_{3-6}cycloalkyl$, $C_{5-6}cycloalkenyl$, or a 4- to 8-membered monocyclic heterocycle containing 1-2 nitrogen atoms, the $C_{3-6}cycloalkyl$, the $C_{5-6}cycloalkenyl$, and the 4- to 8-membered monocyclic heterocycle being independently optionally substituted with 1-2 substituents independently selected from the group consisting of pyridyl, halogen, hydroxyl, $-OC_{1-4}alkyl$, $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, $-C_{1-4}alkylene-OC_{1-4}alkyl$, and $-C_{1-4}alkylene-OH$;

- [0030]** provided that when X^4 is S then (i) R^1 is not $-O-C_{2-6}alkylene-OC_{1-4}alkyl$, $-O-C_{2-6}alkylene-OH$, G^2 , $-O-G^2$, or $-O-C_{1-4}alkylene-G^2$, where G^2 is an optionally substituted monocyclic heterocycle containing at least one nitrogen atom, when X^1 is N, X^3 is N, X^2 is CH, and R^4 is optionally substituted phenyl; (ii) R^1 is not $-OC_{1-4}alkyl$ when R^4 is optionally substituted phenyl or thiophene, and X^1 is CR^{X^1} ; (iii) R^2 is other than H, when R^1 is G^2 or $-O-G^2$, G^2 is an optionally substituted monocyclic heterocycle containing at least one nitrogen atom, X^1 is CH, X^2 is CH and X^3 is N; (iv) R^2 is other than H, when R^1 is G^2 or $-NR^5-C_{1-4}alkylene-G^2$, G^2 is an optionally substituted monocyclic heterocycle containing at least one nitrogen atom, X^1 is CH, X^3 is CH and X^2 is N; or (v) the compound of formula (II) is not N-(4-chloro-6-(4-methylpiperazin-1-yl)pyridin-2-yl)-5-(pyridin-4-yl)thiazol-2-amine; and

- [0031]** provided that when X^4 is O then (i) G^2 is not morpholino when R^4 is phenyl substituted with cyano; (ii) R^1 is not $-O-C_{1-4}alkyl$ when R^4 is optionally substituted phenyl; or (iii) R^1 is not $-NHC(O)(C_{1-4}alkyl)$ when R^4 is pyridinyl.

- [0032]** In another aspect are compounds of formula (IV)



(IV)

- [0033] or a pharmaceutically acceptable salt thereof,
- [0034] wherein:
- 5 [0035] X^1 is CR^{X1} or N;
- [0036] X^2 is CR^{X2} or N;
- [0037] X^3 is CR^{X3} or N;
- [0038] provided that X^1 is not N simultaneously with X^2 or X^3 ;
- [0039] R^1 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, $-O-C_{1-4}$ alkyl, OH, $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-NH_2$, $-L^1-G^1-R^6$, $-L^1-G^2$, $-L^1-G^3$, $-L^2-G^4$, $-L^2-G^5$, and G^5 ;
- 10 [0040] R^2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;
- [0041] R^{X1} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, $-O-C_{1-4}$ alkyl, and G^2 ;
- 15 [0042] provided that R^1 and R^{X1} do not simultaneously contain G^2 ;
- [0043] R^{X2} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, and $-OC_{1-4}alkyl$;
- [0044] R^{X3} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl;
- 20 [0045] L^1 is a bond, $-O-$, or $-O-C_{1-4}alkylene-$;
- [0046] L^2 is $-O-$ or $-O-C_{1-4}alkylene-$;
- [0047] G^1 is a 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a $C_{1-3}alkylene$ bridge between two non-adjacent ring atoms, G^1 being optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, and oxo;
- 25

- [0048]** R^6 is (a) a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the heterocycle being optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, $-CH_2S(O)_2$ phenyl, halogen, hydroxyl, oxo, $-OC_{1-4}$ alkyl, $-C_{1-6}$ alkylene- OC_{1-4} alkyl, and $-C_{1-6}$ alkylene-OH; or (b) a 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, $-C(O)OC_{1-4}$ alkyl, $-C(O)OH$, oxo, $-OC_{1-4}$ alkyl, $-C_{1-6}$ alkylene- OC_{1-4} alkyl, and $-C_{1-6}$ alkylene-OH;
- [0049]** G^2 is a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, G^2 being optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, oxo, cyano, $-C_{1-6}$ alkylene-cyano, $-C(O)C_{1-4}$ alkyl, $-C(O)-C_{1-6}$ alkylene- OC_{1-4} alkyl, $-C(O)-C_{1-6}$ alkylene-OH, $-C(O)C_{3-6}$ cycloalkyl, $-C(O)OC_{1-4}$ alkyl, $-C(O)OC_{1-4}$ haloalkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-4}$ alkyl), $-C(O)N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $-C(O)NH(-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-C(O)N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-C(O)NH(-C_{1-6}$ alkylene-OH), $-C(O)N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene-OH), $-NH(-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-NH(-C_{1-6}$ alkylene-OH), $-N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene-OH), $-C(O)C_{1-4}$ haloalkyl, $-OC_{1-4}$ alkyl, $-OC_{1-4}$ haloalkyl, $-C_{1-6}$ alkylene- OC_{1-4} alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ alkylene- NH_2 , $-C_{1-6}$ alkylene- $NH(C_{1-4}$ alkyl), $-C_{1-6}$ alkylene- $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $-O-C_{1-6}$ alkylene- NH_2 , $-O-C_{1-6}$ alkylene- $NH(C_{1-4}$ alkyl), $-O-C_{1-6}$ alkylene- $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $-O-C_{1-6}$ alkylene- OC_{1-4} alkyl, $-O-C_{1-6}$ alkylene-OH, $-C_{1-4}$ alkylene- $O-C_{1-4}$ alkylene- OC_{1-4} alkyl, $-C_{1-4}$ alkylene- $O-C_{1-4}$ alkylene-OH, $-C_{1-4}$ alkylene- $C(O)OC_{1-4}$ alkyl, $-C_{1-4}$ alkylene- $C(O)OH$, $-NHC(O)(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl) $C(O)(C_{1-4}$ alkyl), $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $-S(O)_{1-2}C_{1-4}$ alkyl, $-C_{1-6}$ alkylene- $S(O)_{1-2}C_{1-4}$ alkyl, and a $-C_{1-6}$ alkylene substituted by 2 groups independently selected from hydroxyl, $-OC(O)C_{1-4}$ alkyl, $-OC_{1-4}$ alkyl, $-NH_2$, $-NH(C_{1-4}$ alkyl), and $-N(C_{1-4}$ alkyl)(C_{1-4} alkyl);
- [0050]** G^3 is 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, oxo, cyano, $-C(O)C_{1-4}$ alkyl, $-C(O)C_{3-6}$ cycloalkyl, $-C(O)OC_{1-4}$ alkyl, $-C(O)OC_{1-4}$ haloalkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-4}$ alkyl), $-C(O)N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $-C(O)NH(-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-C(O)N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-C(O)NH(-C_{1-6}$ alkylene-OH), $-C(O)N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene-OH), $-NH(-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-NH(-C_{1-6}$ alkylene-OH), $-N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene-OH), $-C(O)C_{1-4}$ haloalkyl, $-OC_{1-4}$ alkyl, $-OC_{1-4}$ haloalkyl, $-C_{1-6}$ alkylene- OC_{1-4} alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ alkylene- NH_2 , $-C_{1-6}$ alkylene- $NH(C_{1-4}$ alkyl), $-C_{1-6}$ alkylene- $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $-O-C_{1-6}$ alkylene- NH_2 , $-O-C_{1-6}$ alkylene- $NH(C_{1-4}$ alkyl), $-O-C_{1-6}$ alkylene- $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $-O-C_{1-6}$ alkylene- OC_{1-4} alkyl, $-O-C_{1-6}$ alkylene-OH, $-C_{1-4}$ alkylene- $O-C_{1-4}$ alkylene- OC_{1-4} alkyl, $-C_{1-4}$ alkylene- $O-C_{1-4}$ alkylene-OH, $-C_{1-4}$ alkylene- $C(O)OC_{1-4}$ alkyl, $-C_{1-4}$ alkylene- $C(O)OH$, $-NHC(O)(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl) $C(O)(C_{1-4}$ alkyl), $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $-S(O)_{1-2}C_{1-4}$ alkyl, $-C_{1-6}$ alkylene- $S(O)_{1-2}C_{1-4}$ alkyl, and a $-C_{1-6}$ alkylene substituted by 2 groups independently selected from hydroxyl, $-OC(O)C_{1-4}$ alkyl, $-OC_{1-4}$ alkyl, $-NH_2$, $-NH(C_{1-4}$ alkyl), and $-N(C_{1-4}$ alkyl)(C_{1-4} alkyl);

- 4alkyl)(C₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -NH(-C₁₋₆alkylene-OH), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -C(O)C₁₋₄haloalkyl, -OC₁₋₄alkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₆alkylene-OH, -C₁₋₆alkylene substituted by 2 groups independently selected from hydroxyl and -OC(O)C₁₋₄alkyl, -C₁₋₄alkylene-C(O)OC₁₋₄alkyl, -C₁₋₄alkylene-C(O)OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)(C₁₋₄alkyl);
- [0051]** G⁴ is phenyl optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, cyano, phenyl, -C(O)C₁₋₄alkyl, -C(O)C₃₋₆cycloalkyl, -C(O)OC₁₋₄alkyl, -C(O)OC₁₋₄haloalkyl, -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -NH(-C₁₋₆alkylene-OH), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -C(O)C₁₋₄haloalkyl, -OC₁₋₄alkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₆alkylene-OH, -C₁₋₆alkylene substituted by 2 groups independently selected from hydroxyl and -OC(O)C₁₋₄alkyl, -C₁₋₄alkylene-C(O)OC₁₋₄alkyl, -C₁₋₄alkylene-C(O)OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)(C₁₋₄alkyl);
- [0052]** G⁵ is a monocyclic 5- or 6-membered heteroaryl containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, G⁵ being optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, cyano, phenyl, -C(O)C₁₋₄alkyl, -C(O)C₃₋₆cycloalkyl, -C(O)OC₁₋₄alkyl, -C(O)OC₁₋₄haloalkyl, -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -NH(-C₁₋₆alkylene-OH), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -C(O)C₁₋₄haloalkyl, -OC₁₋₄alkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₆alkylene-OH, -C₁₋₆alkylene substituted by 2 groups independently selected from hydroxyl and -OC(O)C₁₋₄alkyl, -C₁₋₄alkylene-C(O)OC₁₋₄alkyl, -C₁₋₄alkylene-

C(O)OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)(C₁₋₄alkyl); and

[0053] R⁴ is phenyl or a 5- or 6-membered heteroaryl containing 1-3 heteroatoms independently selected from oxygen, nitrogen and sulfur, R⁴ being optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, -S(O)₂C₁₋₄alkyl, -S(O)C₁₋₄alkyl, -SC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄haloalkyl, -OC₁₋₄alkyl, -OC₁₋₄haloalkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₄alkylene-N(C₁₋₄alkyl)(C₁₋₄alkyl), -NH(C₁₋₄alkylene-OC₁₋₄alkyl), -NH(C₁₋₄alkylene-OH), -N(C₁₋₄alkyl)(C₁₋₄alkylene-OC₁₋₄alkyl), -N(C₁₋₄alkyl)(C₁₋₄alkylene-OH), -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)(C₁₋₄alkyl), C₃₋₆cycloalkyl, C₅₋₆cycloalkenyl, or a 4- to 8-membered monocyclic heterocycle containing 1-2 nitrogen atoms, the C₃₋₆cycloalkyl, the C₅₋₆cycloalkenyl, and the 4- to 8-membered monocyclic heterocycle being independently optionally substituted with 1-2 substituents independently selected from the group consisting of pyridyl, halogen, hydroxyl, -OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄haloalkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, and -C₁₋₄alkylene-OH.

[0054] In another aspect, the present invention provides compounds of formula (I) or (IV).

[0055] Another aspect of the present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and therapeutically effective amounts of a compound of formula (I) or (IV), or a pharmaceutically acceptable salt thereof.

[0056] In another aspect, the invention provides compounds of formula (I) or (IV), or a pharmaceutically acceptable salt thereof, which promote remyelination of demyelinated axons.

[0057] In another aspect, the invention provides compounds of formula (I) or (IV), or a pharmaceutically acceptable salt thereof, which differentiate endogenous oligodendrocyte precursor cells.

[0058] In another aspect, the invention provides methods of treating multiple sclerosis by administering to a patient in need thereof a therapeutically effective amount of a compound or composition of formula (I) or (IV), or a pharmaceutically acceptable salt thereof.

[0059] In another aspect, the present invention provides a method of treating, preventing or ameliorating one or more symptoms of a subject with multiple sclerosis or another neurological disease.

5 [0060] In another aspect, the invention provides the use of a compound of formula (I) or (IV), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of multiple sclerosis, the promotion of remyelination of demyelinated axons, or the differentiation of endogenous oligodendrocyte precursor cells.

10 [0061] In another aspect, the invention provides compounds of formula (I) or (IV), or a pharmaceutically acceptable salt thereof, for use in treating multiple sclerosis, promoting remyelination of demyelinated axons, or differentiating endogenous oligodendrocyte precursor cells.

15 [0062] In another aspect, the invention provides compounds of formula (I) or (IV), or a pharmaceutically acceptable salt thereof for treating or lessening the severity of, in a subject, a disease or disorder selected from a demyelinating disease, central pontine myelinolysis, a nerve injury disease or disorder, a leukoencephalopathy or a leukodystrophyin.

[0063] In another aspect, the invention provides compounds of formula (I) or (IV), or a pharmaceutically acceptable salt thereof

20 [0064] In another aspect, the invention provides compounds of formula (I) or (IV), or a pharmaceutically acceptable salt thereof can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures.

25 [0065] The present invention also features kits comprising compounds of formula (I) or (IV).

DETAILED DESCRIPTION OF THE INVENTION

[0066] 1. Definitions

30 [0067] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry," Thomas Sorrell, University Science Books,

Sausalito: 1999, and "March's Advanced Organic Chemistry," 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0068] As described herein, compounds of the invention can optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. As described herein, the variables in formula I encompass specific groups, such as, for example, alkyl and cycloalkyl. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0069] The phrase "optionally substituted" may be used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted," whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group can have a substituent at each substitutable position of the group, and when more than one position in any given structure can be substituted with more than one substituent selected from a specified group, the substituent can be either the same or different at every position. A ring substituent, such as a heterocycloalkyl, can be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, e.g., both rings share one common atom. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds.

[0070] The compounds of the invention are defined according to the terms in the claims and the embodiments. The following definitions are provided as a general

guide to understanding the claims and embodiments and are applicable where specific definitions are absent.

[0071] The term "alkyl" as used herein, means a straight or branched chain saturated hydrocarbon. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

[0072] The term "alkylene," as used herein, means a divalent group derived from a straight or branched chain saturated hydrocarbon. Representative examples of alkylene include, but are not limited to, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, and $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}_2-$.

[0073] The term "alkoxy" as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, and hexyloxy.

[0074] The term "aryl," as used herein, means phenyl or a bicyclic aryl. The bicyclic aryl is naphthyl, dihydronaphthalenyl, tetrahydronaphthalenyl, indanyl, or indenyl. The phenyl and bicyclic aryls are attached to the parent molecular moiety through any carbon atom contained within the phenyl or bicyclic aryl.

[0075] The term "halogen" means a chlorine, bromine, iodine, or fluorine atom.

[0076] The term "haloalkyl," as used herein, means an alkyl, as defined herein, in which one, two, three, four, five, six, or seven hydrogen atoms are replaced by halogen. For example, representative examples of haloalkyl include, but are not limited to, 2-fluoroethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trifluoro-1,1-dimethylethyl, and the like.

[0077] The term "haloalkoxy," as used herein, means an alkoxy group, as defined herein, in which one, two, three, four, five, or six hydrogen atoms are replaced by halogen. Representative examples of haloalkoxy include, but are not limited to, trifluoromethoxy, difluoromethoxy, 2,2,2-trifluoroethoxy, 2,2-difluoroethoxy, 2-fluoroethoxy, and pentafluoroethoxy.

[0078] The term "heteroaryl," as used herein, means an aromatic heterocycle, i.e., an aromatic ring that contains at least one heteroatom. A heteroaryl may contain from 5 to 12 ring atoms. A heteroaryl may be a 5- to 6-membered monocyclic heteroaryl

or an 8- to 12-membered bicyclic heteroaryl. A 5-membered monocyclic heteroaryl ring contains two double bonds, and one, two, three, or four heteroatoms as ring atoms. Representative examples of 5-membered monocyclic heteroaryls include, but are not limited to, furanyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, and triazolyl. A 6-membered heteroaryl ring contains three double bonds, and one, two, three or four heteroatoms as ring atoms. Representative examples of 6-membered monocyclic heteroaryls include, but are not limited to, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. The bicyclic heteroaryl is an 8- to 12-membered ring system having a monocyclic heteroaryl fused to an aromatic, saturated, or partially saturated carbocyclic ring, or fused to a second monocyclic heteroaryl ring. Representative examples of bicyclic heteroaryl include, but are not limited to, benzofuranyl, benzoxadiazolyl, 1,3-benzothiazolyl, benzimidazolyl, benzothieryl, indolyl, indazolyl, isoquinolinyl, naphthyridinyl, oxazolopyridine, quinolinyl, thienopyridinyl, 5,6,7,8-tetrahydroquinolinyl, and 6,7-dihydro-5H-cyclopenta[b]pyridinyl. The heteroaryl groups are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the groups.

[0079] The term "cycloalkyl" as used herein, means a monocyclic all-carbon ring containing zero heteroatoms as ring atoms, and zero double bonds. Examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The cycloalkyl groups described herein can be appended to the parent molecular moiety through any substitutable carbon atom.

[0080] The term "cycloalkenyl" as used herein, means a monocyclic non-aromatic all-carbon 5- to 6-membered ring containing zero heteroatoms as ring atoms and one double bond. Examples of cycloalkenyl include cyclopentenyl and cyclohexenyl. The cycloalkenyl groups described herein can be appended to the parent molecular moiety through any substitutable carbon atom.

[0081] The terms "heterocycle" or "heterocyclic" refer generally to ring systems containing at least one heteroatom as a ring atom where the heteroatom is selected from oxygen, nitrogen, and sulfur. In some embodiments, a nitrogen or sulfur atom of the heterocycle is optionally substituted with oxo. Heterocycles may be a monocyclic heterocycle, a fused bicyclic heterocycle, or a spiro heterocycle. The monocyclic

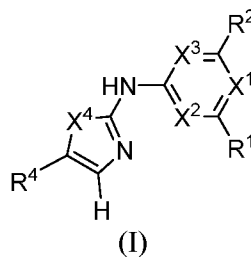
heterocycle is generally a 4, 5, 6, 7, or 8-membered non-aromatic ring containing at least one heteroatom selected from O, N, or S. The 4-membered ring contains one heteroatom and optionally one double bond. The 5-membered ring contains zero or one double bond and one, two or three heteroatoms. The 6, 7, or 8-membered ring contains zero, one, or two double bonds, and one, two, or three heteroatoms. Representative examples of monocyclic heterocycle include, but are not limited to, azetidiny, azepany, diazepany, 1,3-dioxany, 1,4-dioxany, 1,3-dioxolany, 4,5-dihydroisoxazol-5-yl, 3,4-dihydropyrany, 1,3-dithiolany, 1,3-dithiany, imidazoliny, imidazolidiny, isothiazoliny, isothiazolidiny, isoxazoliny, isoxazolidiny, morpholiny, oxadiazoliny, oxadiazolidiny, oxazoliny, oxazolidiny, oxetany, piperaziny, piperidiny, pyrany, pyrazoliny, pyrazolidiny, pyrroliny, pyrrolidiny, tetrahydrofurany, tetrahydropyrany, tetrahydrothieny, thiadiazoliny, thiadiazolidiny, thiazoliny, thiazolidiny, thiomorpholiny, 1,1-dioxidothiomorpholiny, thiopyrany, and trithiany. The fused bicyclic heterocycle is a 7-12-membered ring system having a monocyclic heterocycle fused to a phenyl, to a saturated or partially saturated carbocyclic ring, or to another monocyclic heterocyclic ring, or to a monocyclic heteroaryl ring. Representative examples of fused bicyclic heterocycle include, but are not limited to, 1,3-benzodioxol-4-yl, 1,3-benzodithiolyl, 3-azabicyclo[3.1.0]hexany, hexahydro-1H-furo[3,4-c]pyrroly, 2,3-dihydro-1,4-benzodioxiny, 2,3-dihydro-1-benzofurany, 2,3-dihydro-1-benzothiény, 2,3-dihydro-1H-indolyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyraziny, and 1,2,3,4-tetrahydroquinoliny. Spiro heterocycle means a 4, 5-, 6-, 7-, or 8-membered monocyclic heterocycle ring wherein two of the substituents on the same carbon atom form a second ring having 3, 4, 5, 6, 7, or 8- members. Examples of a spiro heterocycle include, but are not limited to, 1,4-dioxa-8-azaspiro[4.5]decany, 2-oxa-7-azaspiro[3.5]nonany, 2-oxa-6-azaspiro[3.3]heptany, and 8-azaspiro[4.5]decane. The monocyclic heterocycle groups of the present invention may contain an alkylene bridge of 1, 2, or 3 carbon atoms, linking two non-adjacent atoms of the group. Examples of such a bridged heterocycle include, but are not limited to, 2,5-diazabicyclo[2.2.1]heptany, 2-azabicyclo[2.2.1]heptany, 2-azabicyclo[2.2.2]octany, and oxabicyclo[2.2.1]heptany. The monocyclic, fused bicyclic, and spiro heterocycle groups are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the group.

[0082] The term "oxo" as used herein refers to an oxygen atom bonded to the parent molecular moiety. An oxo may be attached to a carbon atom or a sulfur atom by a double bond. Alternatively, an oxo may be attached to a nitrogen atom by a single bond, i.e., an N-oxide.

- 5 **[0083]** Terms such as "alkyl," "cycloalkyl," "alkylene," etc. may be preceded by a designation indicating the number of atoms present in the group in a particular instance (e.g., "C₁₋₄alkyl," "C₃₋₆cycloalkyl," "C₁₋₄alkylene"). These designations are used as generally understood by those skilled in the art. For example, the representation "C" followed by a subscripted number indicates the number of carbon
- 10 atoms present in the group that follows. Thus, "C₃alkyl" is an alkyl group with three carbon atoms (i.e., n-propyl, isopropyl). Where a range is given, as in "C₁₋₄," the members of the group that follows may have any number of carbon atoms falling within the recited range. A "C₁₋₄alkyl," for example, is an alkyl group having from 1 to 4 carbon atoms, however arranged (i.e., straight chain or branched).
- 15 **[0084]** Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and
- 20 geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Thus, included within the scope of the invention are tautomers of compounds of formula (I) or (IV). The structures also include zwitterionic forms of the compounds or salts of formula I
- 25 where appropriate.

[0085] 2. Compounds

[0086] In a first aspect of the invention are provided compounds of formula (I)



[0087] or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^4 , X^1 , X^2 , X^3 , and X^4 are as defined herein.

[0088] In some embodiments, R^1 is selected from the group consisting of $-OC_{1-6}alkyl$, $-O-C_{1-6}alkylene-OC_{1-4}alkyl$, $-O-C_{1-6}alkylene-OH$, $-NHC(O)(C_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-C(O)NH(C_{1-4}haloalkyl)$, $-C(O)NH(-C_{1-6}alkylene-OC_{1-4}alkyl)$, $-L^1-G^1-R^6$, $-L^1-G^2$, $-L^1-G^3$, and $-L^2-G^4$;

R^2 is selected from the group consisting of hydrogen, $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, halogen, and $-OC_{1-4}alkyl$;

R^{X1} is selected from the group consisting of hydrogen and $-O-C_{1-4}alkyl$;

10 R^{X2} is selected from the group consisting of hydrogen, halogen, and $C_{1-4}alkyl$;

R^{X3} is selected from the group consisting of hydrogen, $C_{1-4}alkyl$, and $-O-C_{1-4}alkyl$;

L^1 is a bond, $-O-$, $-O-C_{1-4}alkylene-$, $-NR^5-$, or $-C(O)-$, wherein R^5 is hydrogen or $C_{1-4}alkyl$;

L^2 is $-O-C_{1-4}alkylene-$;

15 G^1 is a 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from nitrogen;

R^6 is a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, the heterocycle being optionally substituted with 1-4 substituents independently selected from the group consisting of $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, $-CH_2S(O)_2phenyl$, halogen, hydroxyl, oxo, $-OC_{1-4}alkyl$, $-C_{1-6}alkylene-OC_{1-4}alkyl$, and $-C_{1-6}alkylene-OH$;

20 G^2 is a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, G^2 being optionally substituted with 1-4 substituents independently selected from the group consisting of $C_{1-4}alkyl$, $-C(O)OC_{1-4}alkyl$, and a $-C_{1-6}alkylene$ substituted by 2 groups independently selected from hydroxyl and halogen;

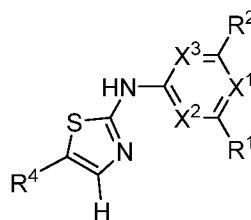
25 G^2 is a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, G^2 being optionally substituted with 1-4 substituents independently selected from the group consisting of $C_{1-4}alkyl$, $-C(O)OC_{1-4}alkyl$, and a $-C_{1-6}alkylene$ substituted by 2 groups independently selected from hydroxyl and halogen;

G^3 is 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl and $-OC_{1-4}$ alkyl;

G^4 is phenyl optionally substituted with 1-4 substituents independently selected from the group consisting of $-OC_{1-4}$ alkyl; and

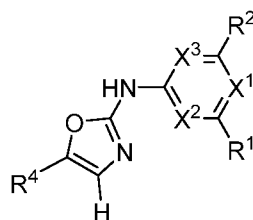
- 5 R^4 is phenyl or a 6-membered heteroaryl containing 1-3 nitrogen, R^4 being optionally substituted with 1-3 substituents independently selected from the group consisting of halogen.

- [0089] In some embodiments X^4 is S (i.e., formula (II)). In the embodiments according to formula (II) and corresponding sub-formulas are further embodiments
- 10 wherein X^2 is N, X^1 is CR^{X1} (e.g., CH), and X^3 is CR^{X3} (e.g., CH). In other embodiments, X^3 is N, X^1 is CR^{X1} (e.g., CH), and X^2 is CR^{X2} (e.g., CH, C-halogen, C- C_{1-4} alkyl). In other embodiments, X^1 is N, X^2 is CR^{X2} (e.g., C- C_{1-4} alkyl), and X^3 is CR^{X3} (e.g., CH). In other embodiments, X^3 is N, X^1 is N, and X^2 is CR^{X2} (e.g., CH, C-halogen, C- C_{1-4} alkyl). In other embodiments, X^1 is N, X^2 is N, and X^3 is CR^{X3}
- 15 (e.g., CH, C- C_{1-4} alkyl). In other embodiments, X^1 is CR^{X1} (e.g., CH), X^2 is CR^{X2} (e.g., CH, C-halogen), and X^3 is CR^{X3} (e.g., CH).



(II)

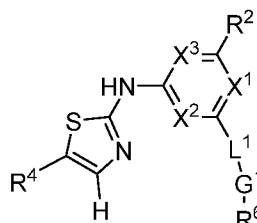
- [0090] In some embodiments, X^4 is O (i.e., formula (III)). In the embodiments according to formula (III) and corresponding sub-formulas are further embodiments
- 20 wherein X^1 is CR^{X1} (e.g., CH, C- OC_{1-4} alkyl), X^2 is CR^{X2} (e.g., CH, C-halogen), and X^3 is CR^{X3} (e.g., CH). In other embodiments, X^2 is N, X^1 is CR^{X1} (e.g., CH), and X^3 is CR^{X3} (e.g., CH). In other embodiments, X^3 is N, X^1 is CR^{X1} (e.g., CH), and X^2 is CR^{X2} (e.g., CH, C-halogen, C- C_{1-4} alkyl). In other embodiments, X^1 is N, X^2 is CR^{X2} (e.g., C- C_{1-4} alkyl), and X^3 is CR^{X3} (e.g., CH). In other embodiments, X^3 is N, X^1 is N, and X^2 is CR^{X2} (e.g., CH, C-halogen, C- C_{1-4} alkyl). In other embodiments, X^1 is N, X^2 is N, and X^3 is CR^{X3} (e.g., CH, C- C_{1-4} alkyl).
- 25



(III)

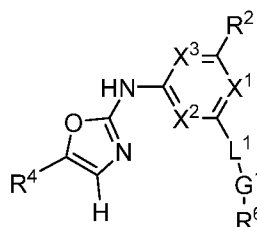
- [0091]** In the embodiments according to formula (IV) and corresponding sub-formulas are further embodiments wherein X^1 is CR^{X1} (e.g., CH, C-OC₁₋₄alkyl), X^2 is CR^{X2} (e.g., CH, C-halogen), and X^3 is CR^{X3} (e.g., CH, C-OC₁₋₄alkyl). In other
- 5 embodiments, X^2 is N, X^1 is CR^{X1} (e.g., CH, C-C₁₋₄alkyl, C-halogen, C-OC₁₋₄alkyl, C-G²), and X^3 is CR^{X3} (e.g., CH). In other embodiments, X^3 is N, X^1 is CR^{X1} (e.g., CH), and X^2 is CR^{X2} (e.g., CH, C-halogen, C-C₁₋₄alkyl). In other embodiments, X^1 is N, X^2 is CR^{X2} (e.g., C-C₁₋₄alkyl), and X^3 is CR^{X3} (e.g., CH). In other embodiments, X^3 is N, X^1 is N, and X^2 is CR^{X2} (e.g., CH, C-halogen, C-C₁₋₄alkyl). In other embodiments, X^1
- 10 is N, X^2 is N, and X^3 is CR^{X3} (e.g., CH, C-C₁₋₄alkyl). In other embodiments, X^2 is N, X^3 is N, and X^1 is CR^{X1} (e.g., CH).

[0092] Further according to formula (II) are embodiments wherein R^1 is $-L^1-G^1-R^6$ (i.e., (II-1)), wherein G^1 , L^1 , and R^6 are as defined herein.



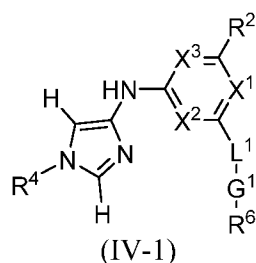
(II-1)

- 15 **[0093]** Further according to formula (III) are embodiments wherein R^1 is $-L^1-G^1-R^6$ (i.e., (III-1)), wherein G^1 , L^1 , and R^6 are as defined herein.



(III-1)

[0094] In some embodiments of formula (IV), R^1 is $-L^1-G^1-R^6$ (i.e., (IV-1)), wherein G^1 , L^1 , and R^6 are as defined herein.



[0095] G^1 is a 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms, G^1 being optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, and oxo. In further embodiments, G^1 is a 4- to 8-membered optionally substituted monocyclic heterocycle containing a first nitrogen atom and optionally a second heteroatom independently selected from oxygen and nitrogen, and optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms. In some embodiments, G^1 is connected to the parent molecular moiety (i.e., at L^1) through the first nitrogen atom. In other embodiments, G^1 is attached to L^1 at a ring carbon atom of G^1 . In further embodiments, G^1 is a 4- to 6-membered optionally substituted monocyclic heterocycle containing a first nitrogen atom and optionally a second heteroatom independently selected from oxygen and nitrogen, and optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms, G^1 being connected to the parent molecular moiety through the first nitrogen atom. In some embodiments, G^1 is a 4- to 8-membered monocyclic heterocycle containing 1 or 2 nitrogen atoms, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms, G^1 being optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, and oxo. In some embodiments, G^1 contains one nitrogen atom. In other embodiments, G^1 contains two nitrogen atoms. The heterocycles at G^1 may be unsubstituted or substituted. For example, in some embodiments, G^1 may be piperazinyl, homopiperazinyl, azetidiny, pyrrolidiny, piperidiny, azepany, 2,5-diazabicyclo[2.2.1]heptany, 2,5-dihydro-1H-pyrroly, oxetany, morpholino, tetrahydropyrany, or 1,2,3,6-tetrahydropyridiny,

each unsubstituted or substituted as described herein. In other embodiments, the piperazinyl, homopiperazinyl, azetidiny, pyrrolidinyl, piperidinyl, azepanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2,5-dihydro-1H-pyrrolyl, oxetanyl, morpholino, tetrahydropyranyl, or 1,2,3,6-tetrahydropyridinyl are optionally substituted with 1-4 substituents independently selected from 1 hydroxyl, 1-2 halogen, 1 oxo, and 1-4 C₁₋₄alkyl groups. In some embodiments, a pyrrolidinyl and/or piperidinyl is optionally substituted with halogen, 1 hydroxyl, or 1 oxo and the piperazinyl is optionally substituted with oxo. In some embodiments, G¹ is piperazin-1-yl optionally substituted with oxo. In some embodiments, G¹ may have a C₁₋₃alkylene bridge between two non-adjacent ring atoms (e.g., 2,5-diazabicyclo[2.2.1]heptanyl). In other embodiments, G¹ is without a C₁₋₃alkylene bridge between two non-adjacent ring atoms. The heterocycles of G¹ may be appended to the parent molecule (i.e., at L¹) by any substitutable carbon or nitrogen atom. In some embodiments, L¹ is –O– and G¹ is attached to L¹ at a ring carbon atom of G¹. In some embodiments, L¹ is a bond and G¹ is attached to L¹ at a ring nitrogen atom of G¹. For example, non-limiting examples of G¹ include piperazin-1-yl, 2-oxo-piperazin-1-yl, homopiperazin-1-yl, azetidin-1-yl, azetidin-3-yl, pyrrolidin-3-yl, 3-hydroxy-pyrrolidin-3-yl, 3-fluoro-pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, 3-hydroxypiperidin-4-yl, 4-hydroxypiperidin-4-yl, 3-fluoropiperidin-4-yl, 4-fluoropiperidin-4-yl, 3,3-difluoropiperidin-4-yl, azepan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 2,5-dihydro-1H-pyrrol-3-yl, or 1,2,3,6-tetrahydropyridin-4-yl.

[0096] R⁶ is a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the heterocycle being optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, –CH₂S(O)₂phenyl, halogen, hydroxyl, oxo, –OC₁₋₄alkyl, –C₁₋₆alkylene–OC₁₋₄alkyl, and –C₁₋₆alkylene–OH.

[0097] In embodiments containing R⁶, the 4- to 12-membered heterocycle at R⁶ may be a 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C₁₋₃alkylene bridge between two non-adjacent ring atoms and being optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, –CH₂S(O)₂phenyl, halogen, hydroxyl, oxo, –OC₁₋₄alkyl, –C₁₋₆alkylene–OC₁₋₄alkyl,

and $-C_{1-6}alkylene-OH$. In some embodiments, R^6 is a 4- to 6-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from oxygen and nitrogen, and sulfur, the heterocycle being optionally substituted with 1-4 substituents independently selected from the group consisting of $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, halogen, hydroxyl, oxo, and $-OC_{1-4}alkyl$. For example, in some embodiments, R^6 is an oxetanyl, a tetrahydrofuranyl, a tetrahydropyranyl, a morpholinyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 6-oxa-3-azabicyclo[3.1.1]heptanyl, 1,4-oxazepanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, a pyrrolidinyl, piperidinyl, thiomorpholinyl, a thietanyl, piperazinyl, or azetidiny, each being optionally substituted as described herein. In other embodiments, R^6 is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, pyrrolidinyl, or thietanyl, each being optionally substituted with 1-4 substituents independently selected from $C_{1-4}alkyl$ and oxo. In some embodiments, the oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, pyrrolidinyl, thietanyl, piperazinyl, and azetidiny, are each optionally substituted with 1-4 substituents independently selected from halogen, $C_{1-4}alkyl$ and oxo. In some embodiments, the oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, pyrrolidinyl, thietanyl, and piperazinyl are each optionally substituted with $C_{1-4}alkyl$, and the pyrrolidinyl, piperazinyl, and thietanyl further optionally substituted with 1-2 oxo groups. In other embodiments, R^6 is a 4- to 8-membered monocyclic heterocycle containing 1 oxygen atom (e.g., an oxetanyl, a tetrahydrofuranyl, a tetrahydropyranyl). In other embodiments, R^6 is a 4-membered monocyclic heterocycle containing 1 oxygen atom and optionally substituted with $C_{1-4}alkyl$ or $-CH_2S(O)_2phenyl$. In other embodiments, R^6 is a 4-membered monocyclic heterocycle containing 1 oxygen atom and optionally substituted with $C_{1-4}alkyl$. In other embodiments, R^6 is a 4- to 8-membered monocyclic heterocycle containing 1 sulfur atom (e.g., thietanyl, tetrahydrothiophenyl, tetrahydro-2H-thiopyranyl). In other embodiments, R^6 is a 4-membered monocyclic heterocycle containing 1 sulfur atom and optionally substituted with 1-2 oxo groups. In other embodiments, R^6 is a 4- to 8-membered monocyclic heterocycle containing 1 nitrogen atom and optionally 1 oxygen atom or 1 sulfur atom (e.g., azetidiny, pyrrolidinyl, morpholinyl, homomorpholinyl, thiomorpholinyl, piperazinyl) and optionally substituted with oxo (e.g., 2-oxopyrrolidin-1-yl). The heterocycles of R^6 may be appended to the parent molecule (i.e., to G^1) by any substitutable carbon atom or nitrogen atom in R^6 . Thus,

in some embodiments, the oxygen-containing heterocycle is oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl, or tetrahydropyran-4-yl. In other embodiments, the sulfur-containing heterocycle is thietan-3-yl, tetrahydrothiophen-3-yl, tetrahydro-2H-thiopyran-3-yl, or tetrahydro-2H-thiopyran-4-yl. In other

5 embodiments, the heterocycle containing 1 nitrogen atom and optionally 1 oxygen or sulfur atom is e.g., piperidin-1-yl, morpholin-4-yl, azetidin-1-yl, piperazin-1-yl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, 6-oxa-3-azabicyclo[3.1.1]heptan-3-yl, 1,4-oxazepan-4-yl, 3-oxa-8-azabicyclo[3.2.1]octan-8-yl, 8-oxa-3-azabicyclo[3.2.1]octan-3-yl, thiomorpholin-4-yl, or 2-oxopyrrolidin-1-yl. In the embodiments of the

10 invention, the oxygen- and sulfur-containing heterocycles may be unsubstituted or substituted as described herein. For example, the oxygen-containing heterocycle may be oxetan-3-yl, 3-methyloxetan-3-yl or 3-((phenylsulfonyl)methyl)oxetan-3-yl and the sulfur-containing heterocycle may be thietan-3-yl or 1,1-dioxothietan-3-yl. In some embodiments, R⁶ is oxetanyl, tetrahydrofuranyl, 1,4-dioxanyl, morpholino,

15 pyrrolidinyl, piperidinyl, or piperazinyl, each optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, oxo, and –OC₁₋₄alkyl.

[0098] In embodiments containing R⁶, the 4- to 12-membered heterocycle at R⁶ may be a 7- to 12-membered spiro heterocycle comprising a first ring and a second

20 ring, the first ring being a 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from nitrogen and oxygen and being attached to G¹, the second ring being a C₃₋₈cycloalkyl or a 4- to 8-membered monocyclic heterocycle containing 1-2 oxygen atoms wherein two atoms of the second ring are attached to one carbon of the first ring to form a spirocycle optionally substituted with

25 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, and oxo. In some embodiments, the spirocyclic R⁶ is optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, –CH₂S(O)₂phenyl, halogen, hydroxyl, oxo, –OC₁₋₄alkyl, –C₁₋₆alkylene–OC₁₋₄alkyl, and –C₁₋₆alkylene–OH. In some

30 embodiments, R⁶ is a 7- to 12-membered spiro heterocycle consisting of the first ring and a second ring, as described herein. The first ring is attached to G¹ through any substitutable carbon or nitrogen atom. In one embodiment, the first ring is attached to G¹ through a nitrogen atom. The first ring of R⁶ includes, but is not limited to,

heterocycles such as azetidine, pyrrolidine, piperidine, azepane, morpholine, azocane, piperazine, and homopiperazine. In some embodiments, the first ring of R^6 is a 4- to 8-membered monocyclic heterocycle containing 1-2 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom. For example, in some embodiments, the first ring is morpholino, piperazin-1-yl, or piperidin-1-yl. The second ring includes a C_{3-8} cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl. The second ring is formed by the attachment of two atoms of the second ring to a single carbon atom of the first ring such that the first ring and the second ring share one carbon atom in common. For example, in some embodiments, R^6 is 4-oxa-7-azaspiro[2.5]octanyl (e.g., 4-oxa-7-azaspiro[2.5]octan-7-yl).

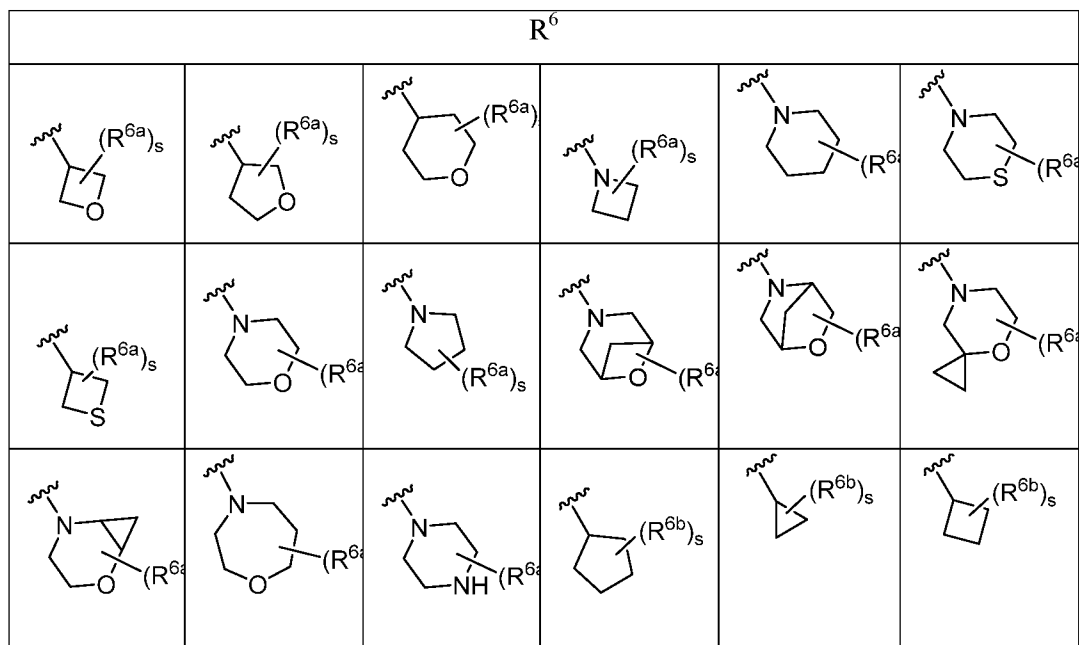
[0099] In embodiments containing R^6 , the 4- to 12-membered heterocycle at R^6 may be a 7- to 12-membered fused bicyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur and being optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, and oxo. In other embodiments, R^6 is a 7- to 12-membered fused bicyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur and being optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, oxo, $-OC_{1-4}$ alkyl, $-C_{1-6}$ alkylene- OC_{1-4} alkyl, and $-C_{1-6}$ alkylene-OH. In some embodiments, the fused bicyclic heterocycle is a 7-12-membered ring system having a monocyclic heterocycle, as defined herein, fused to another monocyclic heterocyclic ring. For example, in some embodiments, R^6 is 2-oxa-5-azabicyclo[4.1.0]heptanyl (e.g., 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl).

[00100] In embodiments containing R^6 , R^6 may be a 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, $-C(O)OC_{1-4}$ alkyl, $-C(O)OH$, and oxo. In other embodiments, R^6 is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, $-C(O)OC_{1-4}$ alkyl, $-C(O)OH$, oxo, $-OC_{1-4}$ alkyl, $-C_{1-6}$ alkylene- OC_{1-4} alkyl, and $-C_{1-6}$ alkylene-OH. For example, in some embodiments, R^6 is cyclopropyl, cyclobutyl, or cyclopentyl, each being optionally substituted with $-C(O)OC_{1-4}$ alkyl, $-C(O)OH$, hydroxyl or 1-2 halogen. In one group of compounds, R^6 is cyclopropyl. In

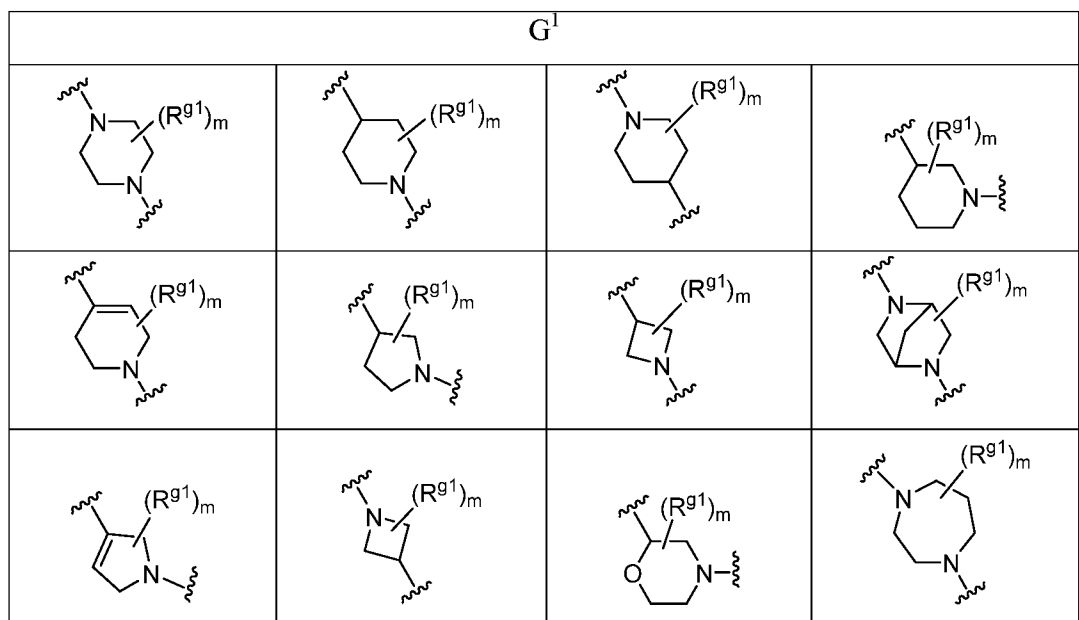
another group of compounds R^6 is cyclobutyl. In other embodiments, R^6 is 3,3-difluorocyclobutyl. In other embodiments, R^6 is a cyclobutane carboxylic acid.

[00101] For example, R^6 may be represented by the following formulas, wherein R^{6a} and R^{6b} are the optional R^6 substituents, respectively, for the 4-12 membered

5 heterocycle or C_{3-8} cycloalkyl of R^6 and s is an integer from 0-4:



[00102] In embodiments wherein R^6 is an optionally substituted oxetan-3-yl, G^1 may be represented by the following formulas, wherein R^{g1} is the optional G^1 substituent and m is an integer from 0-4:



[00103] G^1-R^6 may also be represented by the following formulas, wherein R^{g1} , R^{6a} , R^{6b} , m and s are as defined herein:

G^1-R^6			

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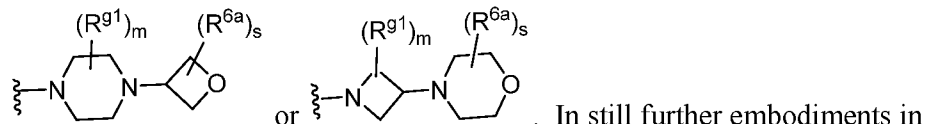
- [00104] $-G^1-R^6$ together may be 4-(oxetan-3-yl)piperazin-1-yl, 4-(3-methyloxetan-3-yl)piperazin-1-yl, 4-(tetrahydrofuran-3-yl)piperazin-1-yl, 4-(2-methyltetrahydrofuran-3-yl)piperazin-1-yl, 4-(tetrahydro-2H-pyran-3-yl)piperazin-1-yl, 4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl, 4-(oxetan-3-yl)-2-oxo-piperazin-1-yl, 4-(oxetan-3-yl)piperidin-1-yl, 1-(oxetan-3-yl)piperidin-3-yl, 1-(oxetan-3-yl)piperidin-4-yl, 1-(3-methyloxetan-3-yl)piperidin-4-yl, 3-hydroxy-1-(oxetan-3-yl)piperidin-4-yl, 3-fluoro-1-(oxetan-3-yl)piperidin-4-yl, 4-hydroxy-1-(oxetan-3-yl)piperidin-4-yl, 4-fluoro-1-(oxetan-3-yl)piperidin-4-yl, 3,3-difluoro-1-(oxetan-3-yl)piperidin-4-yl, 4-(2-oxopyrrolidin-1-yl)piperidin-1-yl, 3-(2-oxopyrrolidin-1-yl)piperidin-1-yl, 4-morpholinopiperidin-1-yl, (4-methylpiperazin-1-yl)piperidin-1-yl, 4-(3,3-difluoroazetidin-1-yl)piperidin-1-yl, 3-morpholinopyrrolidin-1-yl, 1-(oxetan-3-yl)pyrrolidin-3-yl, 5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl, 3-hydroxy-1-(oxetan-3-yl)-pyrrolidin-3-yl, 3-fluoro-1-(oxetan-3-yl)pyrrolidin-3-yl, 1-(oxetan-3-yl)azetidin-3-yl, 3-(oxetan-3-yl)azetidin-1-yl, 3-(pyrrolidin-1-yl)azetidin-1-yl, 3-(4-fluoropiperidin-1-yl)azetidin-1-yl, 3-morpholinoazetidin-1-yl, 3-methyl-3-morpholinoazetidin-1-yl, 3-(2-methylmorpholino)azetidin-1-yl, 3-(3-methylmorpholino)azetidin-1-yl, dimethylmorpholino)azetidin-1-yl, 3-(2,6-dimethylmorpholino)azetidin-1-yl, 3-(1,4-oxazepan-4-yl)azetidin-1-yl, 3-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)azetidin-1-yl, 3-(3-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)azetidin-1-yl, 3-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)azetidin-1-yl, 3-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)azetidin-1-yl, 3-(4-oxa-7-azaspiro[2.5]octan-7-yl)azetidin-1-yl, 3-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)azetidin-1-yl, 3-(morpholinomethyl)azetidin-1-yl, 3-(1,1-dioxidothiomorpholino)azetidin-1-yl, 4-(thietan-3-yl)piperazin-1-yl, 4-(piperazin-1-yl)thietane 1,1-dioxide, 4-(oxetan-3-yl)-4-(λ^1 -oxidanyl)-4 λ^4 -piperazin-1-yl, 4-(oxetan-3-yl)morpholin-2-yl, 6-methyl-4-(oxetan-3-yl)morpholin-2-yl, 5-methyl-

4-(oxetan-3-yl)morpholin-2-yl, 2-methyl-4-(oxetan-3-yl)morpholin-2-yl, or 4-(oxetan-3-yl)-1,4-diazepan-1-yl.

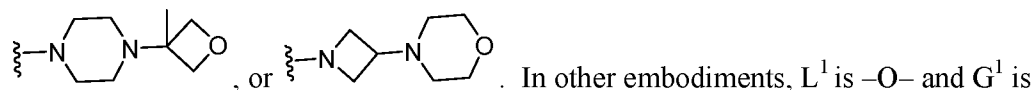
[00105] In other embodiments, $-G^1-R^6$ together may represent 3-(1-hydroxycyclobutyl)piperazin-1-yl; 4-cyclopropylpiperazin-1-yl; 4-cyclobutylpiperazin-1-yl; 4-cyclopentylpiperazin-1-yl; 1-cyclopropylpiperidin-4-yl; 1-cyclopropylpiperidin-3-yl; 1-cyclobutylpiperidin-4-yl, 1-cyclopentylpiperidin-4-yl, 4-(3,3-difluorocyclobutyl)piperazin-1-yl; or 5-cyclopropyl-2,5-diazabicyclo[2.2.1]heptan-2-yl.

[00106] Further according to formulas (I), (II), (II-1), (III), and (III-1), and the foregoing description are embodiments wherein L^1 is a bond or $-O-$. In further embodiments, R^2 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl. In further embodiments, R^{X1} is hydrogen. In further embodiments, R^{X2} is hydrogen or halogen. In still further embodiments, R^{X3} is hydrogen or $-OC_{1-4}$ alkyl. In further embodiments, G^1 is a 4- to 8-membered or 4- to 6-membered optionally substituted monocyclic heterocycle as described above. In further embodiments, R^6 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms. In still further embodiments, L^1 is a bond or $-O-$; R^2 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl; R^{X1} is hydrogen; R^{X2} is hydrogen or halogen; R^{X3} is hydrogen or $-OC_{1-4}$ alkyl; G^1 is a 4- to 8-membered optionally substituted monocyclic heterocycle containing a first nitrogen atom and optionally a second heteroatom independently selected from oxygen and nitrogen, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms; and R^6 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms. In further embodiments, L^1 is a bond and G^1 is a 4- to 8-membered optionally substituted monocyclic heterocycle containing a first nitrogen atom and optionally a second heteroatom independently selected from oxygen and nitrogen, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms, G^1 being connected to the parent molecular moiety through the first nitrogen atom. In

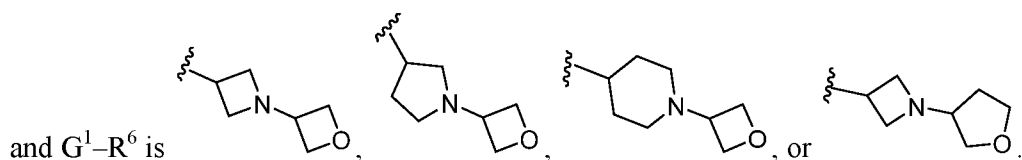
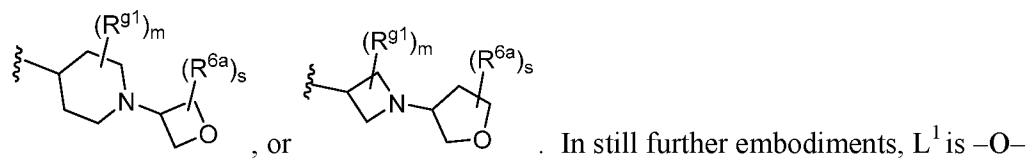
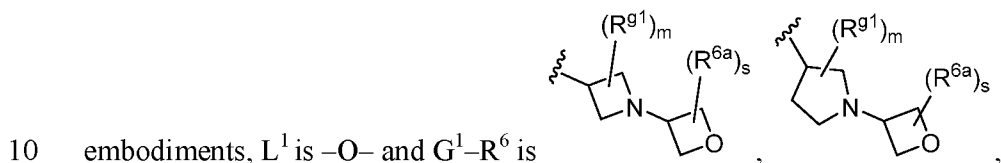
further embodiments according to the foregoing, L^1 is a bond and G^1-R^6 is



combination with the foregoing, L^1 is a bond and G^1-R^6 is

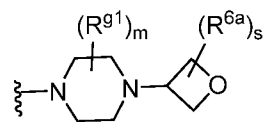


- 5 a 4- to 8-membered optionally substituted monocyclic heterocycle containing a first nitrogen atom and optionally a second heteroatom independently selected from oxygen and nitrogen, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms, wherein G^1 is connected to the parent molecular moiety through a carbon atom of G^1 . In further

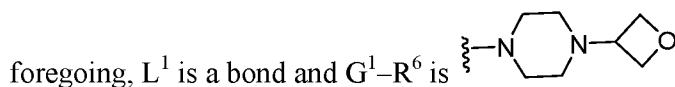


- [00107]** Further according to formulas (IV) and (IV-1), and the foregoing description, are embodiments wherein L^1 is a bond. In further embodiments, R^2 is
- 15 hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl. In further embodiments, R^{X1} is hydrogen. In further embodiments, R^{X2} is hydrogen or halogen. In still further embodiments, R^{X3} is hydrogen. In further embodiments, G^1 is a 4- to 8-membered or 4- to 6-membered optionally substituted monocyclic heterocycle as described above. In further
- embodiments, R^6 is an optionally substituted 4- to 8-membered monocyclic
- 20 heterocycle containing 1-2 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms. In still

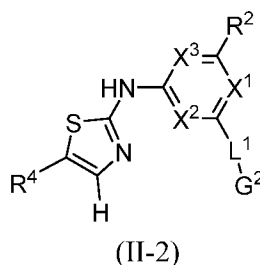
- further embodiments, L^1 is a bond; R^2 is C_{1-4} alkyl; R^{X1} is hydrogen; R^{X2} is hydrogen; R^{X3} is hydrogen; G^1 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing a first nitrogen atom and optionally a second heteroatom independently selected from oxygen and nitrogen, the monocyclic heterocycle
- 5 optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms, G^1 being connected to the parent molecular moiety through the first nitrogen atom; and R^6 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double
- 10 bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms. In further embodiments according to the foregoing, L^1 is a bond and G^1-R^6 is



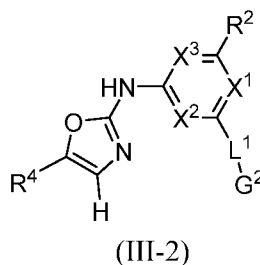
. In still further embodiments in combination with the



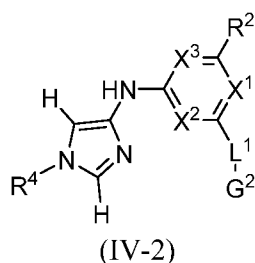
- [00108]** Further according to formula (II) are embodiments wherein R^1 is $-L^1-G^2$
- 15 (i.e., (II-2)), wherein G^2 and L^1 are as defined herein.



- [00109]** Further according to formula (III) are embodiments wherein R^1 is $-L^1-G^2$
- (i.e., (III-2)), wherein G^2 and L^1 are as defined herein.



- 20 **[00110]** Further according to formula (IV) are embodiments wherein R^1 is $-L^1-G^2$
- (i.e., (IV-2)), wherein G^2 and L^1 are as defined herein.



- [00111]** G^2 is a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, G^2 being optionally substituted with 1-4 substituents independently selected from the group consisting of
- 5 C_{1-4} alkyl (e.g., methyl, ethyl, isopropyl), C_{1-4} haloalkyl (e.g., $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$), halogen (e.g., fluoro), hydroxyl, oxo, cyano, $-C_{1-6}$ alkylene-cyano, $-C(O)C_{1-4}$ alkyl (e.g., $-C(O)CH_3$), $-C(O)-C_{1-6}$ alkylene- OC_{1-4} alkyl, $-C(O)-C_{1-6}$ alkylene-OH, $-C(O)C_{3-6}$ cycloalkyl, $-C(O)OC_{1-4}$ alkyl (e.g., $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-C(O)OC(CH_3)_3$), $-C(O)OC_{1-4}$ haloalkyl (e.g., $-C(O)OCH_2CF_3$), $-$
 - 10 $C(O)NH_2$, $-C(O)NH(C_{1-4}alkyl)$ (e.g., $-C(O)NHCH_2CH_3$), $-C(O)N(C_{1-4}alkyl)(C_{1-4}alkyl)$ (e.g., $-C(O)N(CH_3)_2$), $-C(O)NH(-C_{1-6}alkylene-OC_{1-4}alkyl)$ (e.g., $-C(O)NH(CH_2CH_2OCH_3)$), $-C(O)N(C_{1-4}alkyl)(-C_{1-6}alkylene-OC_{1-4}alkyl)$ (e.g., $-C(O)NCH_3(CH_2CH_2OCH_3)$), $-C(O)NH(-C_{1-6}alkylene-OH)$ (e.g., $-C(O)NH(CH_2CH_2OH)$), $-C(O)N(C_{1-4}alkyl)(-C_{1-6}alkylene-OH)$ (e.g., $-$
 - 15 $C(O)NCH_3(CH_2CH_2OH)$), $-NH(-C_{1-6}alkylene-OC_{1-4}alkyl)$ (e.g., $-NH(CH_2CH_2OCH_3)$), $-N(C_{1-4}alkyl)(-C_{1-6}alkylene-OC_{1-4}alkyl)$ (e.g., $-NCH_3(CH_2CH_2OCH_3)$), $-NH(-C_{1-6}alkylene-OH)$ (e.g., $-NH(CH_2CH_2OH)$), $-N(C_{1-4}alkyl)(-C_{1-6}alkylene-OH)$ (e.g., $-NCH_3(CH_2CH_2OH)$), $-C(O)C_{1-4}$ haloalkyl (e.g., $-C(O)CF_3$), $-OC_{1-4}alkyl$ (e.g., $-OCH_3$), $-OC_{1-4}haloalkyl$, $-C_{1-6}alkylene-OC_{1-4}alkyl$
 - 20 (e.g., $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$), $-C_{1-6}alkylene-OH$ (e.g., $-CH_2OH$, $-C(OH)(CH_3)_2$, $-CH_2C(OH)(CH_3)_2$, $-C(OH)(CH_3)CH(CH_3)_2$), $-C_{1-6}alkylene-NH_2$, $-C_{1-6}alkylene-NH(C_{1-4}alkyl)$, $-C_{1-6}alkylene-N(C_{1-4}alkyl)(C_{1-4}alkyl)$ (e.g., $-CH_2CH_2-N(CH_3)_2$), $-O-C_{1-6}alkylene-NH_2$, $-O-C_{1-6}alkylene-NH(C_{1-4}alkyl)$, $-O-C_{1-6}alkylene-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-O-C_{1-6}alkylene-OC_{1-4}alkyl$, $-O-C_{1-6}alkylene-OH$, $-C_{1-4}alkylene-O-C_{1-4}alkylene-OC_{1-4}alkyl$, $-C_{1-4}alkylene-O-C_{1-4}alkylene-OH$, $-C_{1-4}alkylene-C(O)OC_{1-4}alkyl$ (e.g., $-CH(CH_3)C(O)OCH_3$, $-CH_2C(O)OCH_2CH_3$, $-CH_2C(O)OCH_2CH_3$), $-C_{1-4}alkylene-C(O)OH$, $-NHC(O)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl)$, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$
 - 25

(e.g., $-\text{N}(\text{CH}_3)_2$), $-\text{S}(\text{O})_{1-2}\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{1-6}\text{alkylene}-\text{S}(\text{O})_{1-2}\text{C}_{1-4}\text{alkyl}$, and a $-\text{C}_{1-6}\text{alkylene}$ substituted by 2 groups independently selected from hydroxyl, halogen, $-\text{OC}(\text{O})\text{C}_{1-4}\text{alkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-4}\text{alkyl})$, and $-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$ (e.g., $-\text{CH}(\text{CH}_2\text{OH})(\text{CH}_2\text{Cl})$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{OCH}_2\text{CH}_3$). In some embodiments, G^2 is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, $\text{C}_{1-4}\text{alkyl}$, $-\text{C}(\text{O})\text{OC}_{1-4}\text{alkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$, $-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl}$, and $-\text{C}_{1-6}\text{alkylene}$ substituted by 2 groups independently selected from hydroxyl and halogen. In some embodiments, G^2 may be substituted with one substituent selected from the foregoing group and further optionally substituted with 1-3 substituents selected from the group consisting of $\text{C}_{1-4}\text{alkyl}$ and halogen.

[00112] The heterocycles of G^2 may be appended to the parent molecule (i.e., at L^1) by any substitutable carbon or nitrogen atom. In some embodiments, L^1 is $-\text{O}-$, $-\text{O}-\text{C}_{1-4}\text{alkylene}-$, or $-\text{NR}^5-$ and G^2 is attached to L^1 at a ring carbon atom of G^2 . In some embodiments, L^1 is a bond or $-\text{C}(\text{O})-$ and G^2 is attached to L^1 at a ring nitrogen atom of G^2 .

[00113] In some embodiments, the 4- to 12-membered heterocycle at G^2 is a 4- to 8-membered monocyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a $\text{C}_{1-3}\text{alkylene}$ bridge between two non-adjacent ring atoms, G^2 being optionally substituted with 1-4 substituents as described herein. In some embodiments, G^2 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing a first nitrogen atom and optionally a second nitrogen atom, an oxygen or sulfur atom, and optionally containing one double bond and/or a $\text{C}_{1-3}\text{alkylene}$ bridge between two non-adjacent ring atoms, G^2 being connected to L^1 through the first nitrogen atom. In some embodiments, G^2 is an optionally substituted 4- to 6-membered monocyclic heterocycle containing a first nitrogen atom and optionally a second heteroatom independently selected from oxygen and nitrogen, and optionally containing one double bond and/or a $\text{C}_{1-3}\text{alkylene}$ bridge between two non-adjacent ring atoms, G^2 being connected to the parent molecular moiety through a nitrogen atom. In further embodiments, G^2 is an optionally substituted 4- to 6-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from oxygen and nitrogen, G^2 being connected to the parent molecular moiety through

ring carbon atom of G^2 . In some embodiments, G^2 is a 6-membered monocyclic heterocycle containing 1 or 2 nitrogen atoms and substituted with C_{1-4} alkyl. In some embodiments, G^2 is piperazin-1-yl optionally substituted with C_{1-4} alkyl. For example, G^2 may be 4- C_{1-4} alkyl-piperazin-1-yl. In other embodiments, G^2 may be

5 unsubstituted. In some embodiments, G^2 may be an optionally substituted 4- to 8-membered monocyclic heterocycle containing one oxygen atom and optionally one double bond (e.g., oxetanyl, tetrahydrofuranyl, 2,5-dihydrofuranyl). In other embodiments, G^2 may be an optionally substituted 4- to 8-membered monocyclic heterocycle containing one nitrogen and optionally a second nitrogen atom, an oxygen

10 or sulfur atom, and optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms (e.g., azetidiny, piperidiny, piperaziny, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 6-oxa-3-azabicyclo[3.1.1]heptanyl, 2,5-dihydro-1H-pyrroly, morpholinyl). For example, G^2

15 may be morpholinyl, homomorpholinyl, thiomorpholinyl, piperaziny, homopiperaziny, azetidiny, pyrrolidiny, piperidiny, azepanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2,5-dihydro-1H-pyrroly, 6-oxa-3-azabicyclo[3.1.1]heptanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 1,2,3,6-

20 tetrahydropyridiny, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 2,5-dihydrofuranyl, or 3,6-dihydro-2H-pyranyl. In some embodiments, G^2 may have a C_{1-3} alkylene bridge between two non-adjacent ring atoms (e.g., 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 8-oxa-3-azabicyclo[3.2.1]octanyl). In other embodiments,

25 G^2 is without a C_{1-3} alkylene bridge between two non-adjacent ring atoms. The heterocycles of G^2 may be appended to the parent molecule (i.e., at L^1) by any substitutable carbon or nitrogen atom (e.g., morpholin-4-yl, homomorpholin-4-yl, thiomorpholin-4-yl, 4-thiomorpholine 1,1-dioxide, piperazin-1-yl, homopiperazin-1-yl, azetidin-1-yl, azetidin-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, 2-oxooxazolidin-3-yl,

30 2-oxooxazolidin-5-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, azepan-1-yl, azepan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 6-oxa-3-azabicyclo[3.1.1]heptan-3-yl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, 3-oxa-8-azabicyclo[3.2.1]octan-8-yl, 8-oxa-3-azabicyclo[3.2.1]octan-3-yl, 2,5-dihydro-1H-pyrrol-3-yl, 1,2,3,6-tetrahydropyridin-

4-yl, oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, 2,5-dihydrofuran-3-yl, and 3,6-dihydro-2H-pyran-4-yl).

[00114] In some embodiments, G^2 may be represented by the following formulas, wherein R^{g2a} is the optional G^2 substituent and m is an integer between 0 and 4.

5

G^2			

[00115] In other embodiments, the 4- to 12-membered heterocycle at G^2 is a 7- to 12-membered spiro heterocycle comprising a first ring and a second ring, the first ring being a 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from nitrogen and oxygen and being attached to L^1 , the second ring being a C_{3-8} cycloalkyl or a 4- to 8-membered monocyclic heterocycle containing 1-2 oxygen atoms wherein two atoms of the second ring are attached to one carbon of the first ring to form a spirocycle, and wherein G^2 is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, and oxo. In some embodiments, G^2 is connected to the parent molecular moiety through a nitrogen atom of the first ring (e.g., when L^1 is a bond). In some embodiments, G^2 is a 7- to 12-membered spiro heterocycle consisting of the first ring and a second ring, as described herein. The first ring of the spiro heterocycle includes, but is not limited to, heterocycles such as azetidine, pyrrolidine, piperidine, azepane, morpholine, azocane, piperazine, and homopiperazine. In another embodiment, the first ring is a 4- to 8-membered monocyclic heterocycle

containing 1-2 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom. In another embodiment, the first ring is a 4- to 6-membered monocyclic heterocycle containing 1-2 nitrogen atoms. The first ring may be attached to the parent molecule through a nitrogen atom (e.g., azetidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, or piperidin-1-yl).

5 The second ring includes, but is not limited to, heterocycles such as oxetane, tetrahydrofuran, tetrahydropyran, dioxolane, etc. In some embodiments, the second ring has one oxygen atom. In other embodiments, the second ring has two oxygen atoms. In other embodiments, the second ring is a C₃₋₈cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl. The second ring is formed by the attachment of two atoms of

10 the second ring to a single carbon atom of the first ring such that the first ring and the second ring share one carbon atom in common. For example, the second ring may be joined with the first ring at the 4-position of a first ring piperidin-1-yl or the 3-position of a first ring azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, or piperazin-1-yl. In certain embodiments, G² is 1,4-dioxo-8-azaspiro[4.5]decanyl, 2-oxa-6-

15 azaspiro[3.5]nonanyl, 2-oxa-7-azaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,5-dioxo-8-azaspiro[3.5]nonanyl, 1-oxa-8-azaspiro[4.5]decanyl, 5-oxa-8-azaspiro[3.5]nonanyl, 2-oxa-6-azaspiro[3.4]octanyl, 6-oxa-2-azaspiro[3.4]octanyl, 1-oxa-6-azaspiro[3.3]heptanyl, or 2-oxa-6-azaspiro[3.3]heptanyl, 2-oxa-8-azaspiro[4.5]decanyl, 2,6-diazaspiro[3.3]heptanyl, 2-

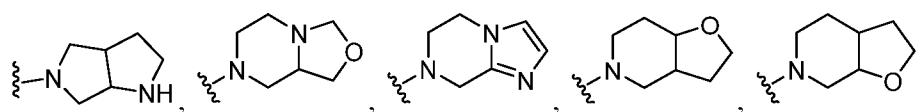
20 oxa-7-azaspiro[4.4]nonanyl, 2-oxa-5-azaspiro[3.4]octanyl, 1-oxa-9-azaspiro[5.5]undecanyl, where the 2,6-diazaspiro[3.3]heptanyl and 2-oxa-5,8-diazaspiro[3.5]nonanyl are optionally substituted with C₁₋₄alkyl and/or oxo. Other embodiments include 1,4-dioxo-8-azaspiro[4.5]decan-8-yl, 2-oxa-7-

25 azaspiro[3.5]nonan-7-yl, 2-oxa-7-azaspiro[4.4]nonan-7-yl, 5-methyl-2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 2-oxa-5-azaspiro[3.4]octan-5-yl, 1-oxa-6-azaspiro[3.3]heptan-6-yl, 2-oxa-6-azaspiro[3.5]nonan-6-yl, 2,5-dioxo-8-azaspiro[3.5]nonan-8-yl, 1-oxa-8-azaspiro[4.5]decan-8-yl, 5-oxa-8-azaspiro[3.5]nonan-8-yl, 6-oxa-2-azaspiro[3.4]octan-2-yl, 2-oxa-6-azaspiro[3.3]heptan-6-yl, 2-oxa-8-

30 azaspiro[4.5]decan-8-yl, 1-oxa-9-azaspiro[5.5]undecan-9-yl, 6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl, or 2,6-diazaspiro[3.3]heptan-2-yl. In further embodiments, G² is selected from the group consisting of 2,6-diazaspiro[3.3]heptan-2-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, and 2-oxa-8-azaspiro[4.5]decan-8-yl.

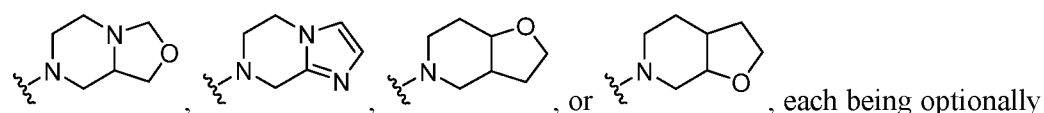
[00116] In other embodiments, the 4- to 12-membered heterocycle at G² is a 7- to 12-membered fused bicyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, -OC₁₋₄alkyl, and oxo. In some embodiments, the fused bicyclic heterocycle is a 7-12-membered ring system having a monocyclic heterocycle, as defined herein, fused to another monocyclic heterocyclic ring. For

example, in some embodiments, G^2 may be  , 



10 , each being optionally substituted with 1-4 substituents selected from the group consisting of C₁₋₄alkyl (e.g., methyl, ethyl, isobutyl), C₁₋₄haloalkyl (e.g., -CF₃, -CH₂CF₃), halogen (e.g., fluoro), hydroxyl, and

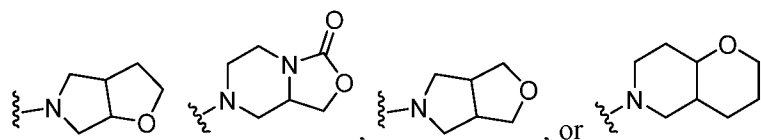
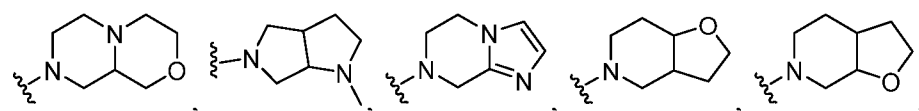
oxo. In other embodiments G^2 may be



15 substituted with one C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, or oxo. In some embodiments, G² may be substituted with one substituent selected from the foregoing group. For

example, in some embodiments, G^2 is

The image shows three chemical structures of G^2 substituents, separated by commas. Each structure consists of a bicyclic indole-like core. The first structure has an isobutyl group attached to the 2-position of the indole ring, and a wavy line is attached to the nitrogen atom. The second structure is a 2,3-dihydro-1H-indole ring system with a wavy line attached to the nitrogen atom. The third structure is a 2,3-dihydro-1H-indole-1-one ring system with a wavy line attached to the nitrogen atom.



- [00117] Further according to formulas (I), (II), (II-2), (III), and (III-2), and the foregoing description are embodiments wherein L^1 is a bond, $-O-$, $-O-C_{1-4}alkylene-$, $-NR^5-$, or $-C(O)-$. In further embodiments, R^2 is hydrogen, $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, or halogen. In further embodiments, R^{X1} is hydrogen. In further embodiments, R^{X2} is hydrogen or halogen. In still further embodiments, R^{X3} is hydrogen. In some embodiments, G^2 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a $C_{1-3}alkylene$ bridge between two non-adjacent ring atoms. In still further embodiments, L^1 is a bond, $-O-$, $-O-C_{1-4}alkylene-$, $-NR^5-$, or $-C(O)-$; R^2 is hydrogen, $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, or halogen; R^{X1} is hydrogen; R^{X2} is hydrogen or halogen; R^{X3} is hydrogen or $-OC_{1-4}alkyl$; and G^2 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a $C_{1-3}alkylene$ bridge between two non-adjacent ring atoms.
- [00118] In still other embodiments of formula (II-2), L^1 is a bond, $-O-$, $-O-C_{1-4}alkylene-$, $-NR^5-$, or $-C(O)-$; R^2 is $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, or halogen; R^{X1} is hydrogen; R^{X2} is hydrogen or halogen; R^{X3} is hydrogen or $-OC_{1-4}alkyl$; and G^2 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a $C_{1-3}alkylene$ bridge between two non-adjacent ring atoms.
- [00119] In still other embodiments of formula (II-2), L^1 is a bond, $-O-$, $-O-C_{1-4}alkylene-$, $-NR^5-$, or $-C(O)-$; R^2 is hydrogen, $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, or halogen; R^{X1} is hydrogen; R^{X2} is hydrogen or halogen; R^{X3} is hydrogen or $-OC_{1-4}alkyl$; G^2 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a $C_{1-3}alkylene$ bridge between two non-adjacent ring atoms; and X^3 is R^{X3} .
- [00120] In still other embodiments of formula (II-2), L^1 is a bond, $-O-$, $-O-C_{1-4}alkylene-$, $-NR^5-$, or $-C(O)-$; R^2 is hydrogen, $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, or halogen; R^{X1} is hydrogen; R^{X2} is hydrogen or halogen; R^{X3} is hydrogen or $-OC_{1-4}alkyl$; G^2 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-3

heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C₁₋₃alkylene bridge between two non-adjacent ring atoms; and R⁴ is optionally substituted pyridinyl.

- 5 **[00121]** In still other embodiments of formula (II-2), L¹ is a bond, -O-, -O-C₁₋₄alkylene-, -NR⁵-, or -C(O)-; R² is hydrogen, C₁₋₄alkyl, C₁₋₄haloalkyl, or halogen; R^{X1} is hydrogen; R^{X2} is hydrogen or halogen; R^{X3} is hydrogen or -OC₁₋₄alkyl; G² is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the
10 monocyclic heterocycle optionally containing one double bond and/or a C₁₋₃alkylene bridge between two non-adjacent ring atoms; and X¹ is R^{X1}.

- [00122]** In still other embodiments of formula (II-2), L¹ is a bond, -O-, -O-C₁₋₄alkylene-, -NR⁵-, or -C(O)-; R² is hydrogen, C₁₋₄alkyl, C₁₋₄haloalkyl, or halogen; R^{X1} is hydrogen; R^{X2} is hydrogen or halogen; R^{X3} is hydrogen or -OC₁₋₄alkyl; G² is
15 an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C₁₋₃alkylene bridge between two non-adjacent ring atoms; and X² is R^{X2}.

- [00123]** In still other embodiments of formula (II-2), X¹ is CR^{X1}; X³ is CR^{X3}; X² is N; R^{X1} is hydrogen; R^{X3} is hydrogen; R² is C₁₋₄alkyl, C₁₋₄haloalkyl, or halogen; L¹ is a bond, -O-, -O-C₁₋₄alkylene-, -NR⁵-, or -C(O)-; G² is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C₁₋₃alkylene bridge between two non-adjacent
20 ring atoms; and R⁴ is optionally substituted phenyl or pyridinyl. In one subembodiment, R⁴ is phenyl substituted with phenyl (e.g., 3,5-difluorophenyl). In another subembodiment, R⁴ is pyridin-2-yl.

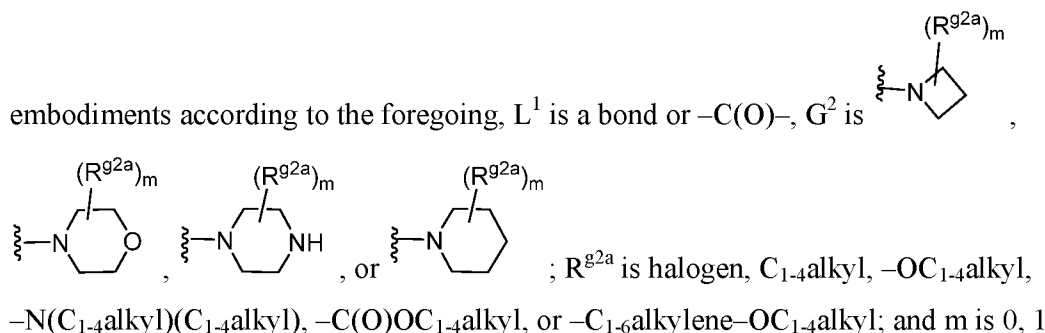
- [00124]** In still other embodiments of formula (II-2), X¹ is CR^{X1}; X² is CR^{X2}; X³ is N; R^{X1} is hydrogen; R^{X2} is hydrogen; R² is C₁₋₄alkyl, C₁₋₄haloalkyl, or halogen; L¹ is a
30 bond, -O-, -O-C₁₋₄alkylene-, -NR⁵-, or -C(O)-; G² is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C₁₋₃alkylene bridge between two non-adjacent

ring atoms; and R^4 is optionally substituted pyridinyl. In one subembodiment, R^4 is pyridin-2-yl.

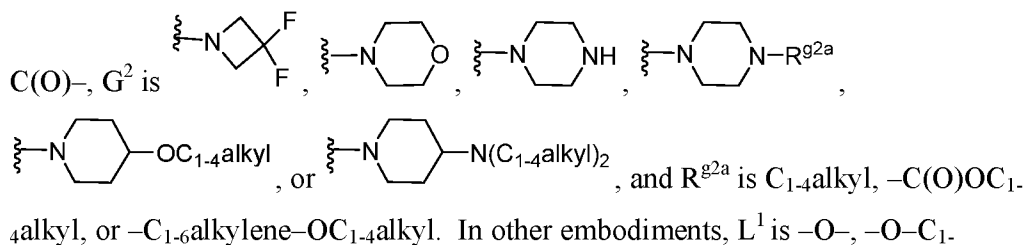
- [00125]** In still other embodiments of formula (II-2), X^1 is N; X^2 is CR^{X2} ; X^3 is N; R^{X2} is hydrogen or halogen; R^2 is C_{1-4} alkyl, C_{1-4} haloalkyl, or halogen; L^1 is a bond, –O–, –O– C_{1-4} alkylene–, –NR⁵–, or –C(O)–; G^2 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms; and R^4 is optionally substituted pyridinyl. In one subembodiment, R^4 is pyridin-2-yl.
- [00126]** In still other embodiments of formula (III-2), L^1 is a bond, –O–, –O– C_{1-4} alkylene–, –NR⁵–, or –C(O)–; R^2 is hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, or halogen; R^{X1} is hydrogen; R^{X2} is hydrogen or halogen; R^{X3} is hydrogen or –OC₁₋₄alkyl; G^2 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms; and R^4 is optionally substituted pyridinyl.

- [00127]** In still other embodiments of formula (III-2), L^1 is a bond, –O–, –O– C_{1-4} alkylene–, –NR⁵–, or –C(O)–; R^2 is hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, or halogen; R^{X1} is hydrogen; R^{X2} is hydrogen or halogen; R^{X3} is hydrogen or –OC₁₋₄alkyl; G^2 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing 1-3 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms; and R^4 is phenyl or pyridinyl.

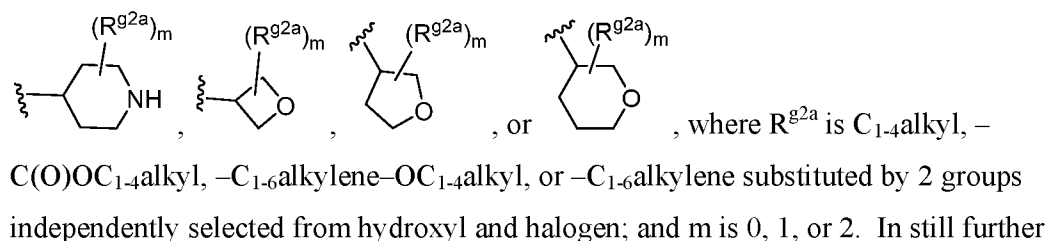
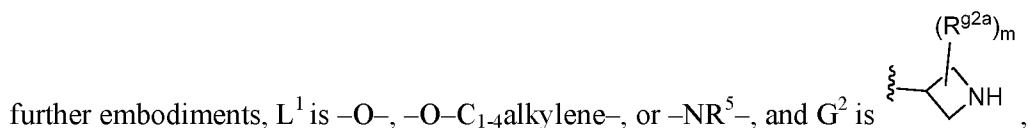
- [00128]** In further embodiments of formulas (I), (II), (II-2), (III), and (III-2), L^1 is a bond or –C(O)–, and G^2 is connected to L^1 through a nitrogen atom of G^2 . In further

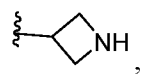


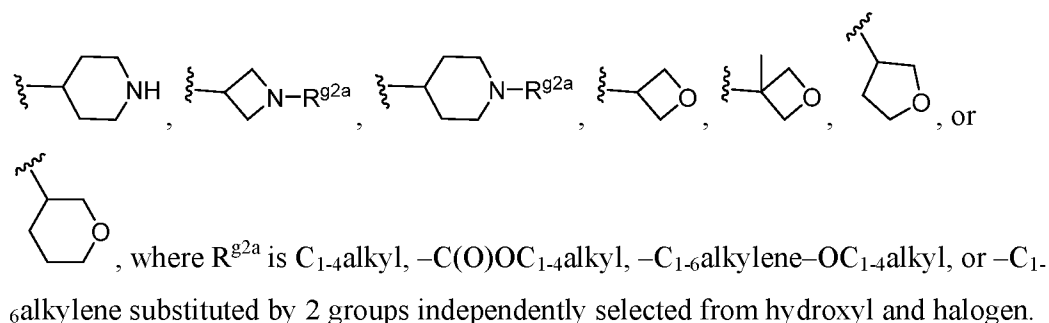
or 2. In still further embodiments in combination with the foregoing, L^1 is a bond or –



5 4 alkylene-, or $-NR^5-$, and G^2 is connected to L^1 through a carbon atom of G^2 . In

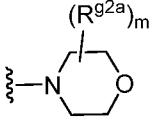
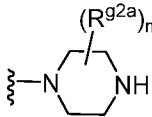
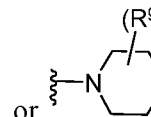


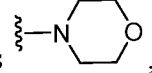
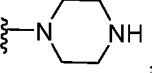
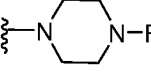
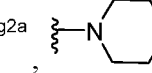
10 embodiments, L^1 is $-O-$, $-O-C_{1-4}$ alkylene-, or $-NR^5-$, and G^2 is ,

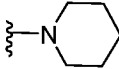


[00129] Further according to formulas (IV) and (IV-2), and the foregoing description are embodiments wherein L^1 is a bond. In further embodiments, R^2 is hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, or halogen. In further embodiments, R^2 is hydrogen. In further embodiments, R^{X1} is hydrogen. In further embodiments, R^{X2} is hydrogen or halogen. In further embodiments, R^{X2} is hydrogen. In still further embodiments, R^{X3} is hydrogen. In still further embodiments, L^1 is a bond; R^2 is hydrogen; R^{X1} is hydrogen; R^{X2} is hydrogen; R^{X3} is hydrogen; and G^2 is an optionally substituted 4- to 8-membered monocyclic heterocycle containing a first nitrogen atom and optionally a second nitrogen atom, an oxygen or sulfur atom, and optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms, G^2 being

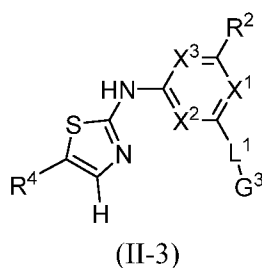
connected to L^1 through the first nitrogen atom. In further embodiments according to

the foregoing, L^1 is a bond; G^2 is , , or ; R^{g2a} is C_{1-4} alkyl; and m is 0 or 1. In further embodiments according to the foregoing, L^1 is a

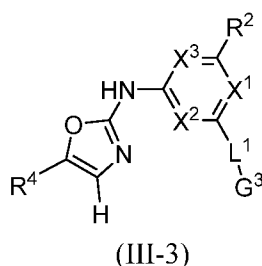
bond; G^2 is , , , , or

5 ; and R^{g2a} is C_{1-4} alkyl.

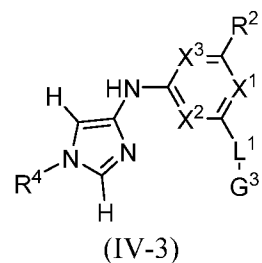
[00130] Further according to formula (II) are embodiments wherein R^1 is $-L^1-G^3$ (i.e., (II-3)), wherein G^3 and L^1 are as defined herein.



10 **[00131]** Further according to formula (III) are embodiments wherein R^1 is $-L^1-G^3$ (i.e., (III-3)), wherein G^3 and L^1 are as defined herein.

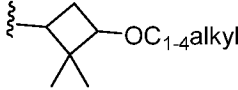


[00132] Further according to formula (IV) are embodiments wherein R^1 is $-L^1-G^3$ (i.e., (IV-3)), wherein G^3 and L^1 are as defined herein.



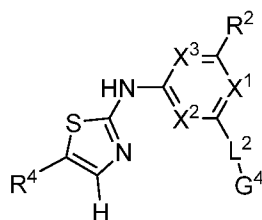
15 **[00133]** G^3 is a 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-}

- 4haloalkyl, halogen, hydroxyl, oxo, cyano, $-\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$, $-\text{C}(\text{O})\text{C}_{3-6}\text{cycloalkyl}$, $-\text{C}(\text{O})\text{OC}_{1-4}\text{alkyl}$, $-\text{C}(\text{O})\text{OC}_{1-4}\text{haloalkyl}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}(\text{C}_{1-4}\text{alkyl})$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$, $-\text{C}(\text{O})\text{NH}(-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{alkyl})(-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{C}(\text{O})\text{NH}(-\text{C}_{1-6}\text{alkylene}-\text{OH})$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{alkyl})(-\text{C}_{1-6}\text{alkylene}-\text{OH})$, $-\text{NH}(-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{NH}(-\text{C}_{1-6}\text{alkylene}-\text{OH})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(-\text{C}_{1-6}\text{alkylene}-\text{OH})$, $-\text{C}(\text{O})\text{C}_{1-4}\text{haloalkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-6}\text{alkylene}-\text{OH}$, $-\text{C}_{1-6}\text{alkylene}$ substituted by 2 groups independently selected from hydroxyl and $-\text{OC}(\text{O})\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{C}(\text{O})\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{C}(\text{O})\text{OH}$, $-\text{NHC}(\text{O})(\text{C}_{1-4}\text{alkyl})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})\text{C}(\text{O})(\text{C}_{1-4}\text{alkyl})$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-4}\text{alkyl})$, and $-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$. In some embodiments, G^3 is optionally substituted with 1-4 substituents independently selected from the group consisting of $\text{C}_{1-4}\text{alkyl}$, and $-\text{OC}_{1-4}\text{alkyl}$. In some embodiments, G^3 is optionally substituted $\text{C}_{3-5}\text{cycloalkyl}$. In some embodiments, G^3 is optionally substituted cyclopropyl or cyclobutyl.
- 15 **[00134]** Further according to formulas (I), (II), (II-3), (III), and (III-3), and the foregoing description are embodiments wherein L^1 is $-\text{O}-$ or $-\text{O}-\text{C}_{1-4}\text{alkylene}-$. In further embodiments, R^2 is $\text{C}_{1-4}\text{alkyl}$. In further embodiments, $\text{R}^{\text{X}1}$ is hydrogen. In further embodiments, $\text{R}^{\text{X}2}$ is hydrogen. In still further embodiments, $\text{R}^{\text{X}3}$ is hydrogen. In still further embodiments, L^1 is $-\text{O}-$ or $-\text{O}-\text{C}_{1-4}\text{alkylene}-$; R^2 is $\text{C}_{1-4}\text{alkyl}$; $\text{R}^{\text{X}1}$ is hydrogen; $\text{R}^{\text{X}2}$ is hydrogen; $\text{R}^{\text{X}3}$ is hydrogen; and G^3 is optionally substituted C_3 .

20 $\text{C}_3\text{cycloalkyl}$. In still further embodiments G^3 is cyclopropyl or .

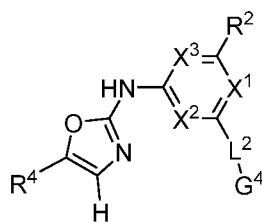
- [00135]** Further according to formulas (IV) and (IV-3) and the foregoing description are embodiments wherein L^1 is a bond or $-\text{O}-$. In further embodiments, R^2 is hydrogen. In further embodiments, $\text{R}^{\text{X}1}$ is hydrogen. In further embodiments, $\text{R}^{\text{X}2}$ is hydrogen. In still further embodiments, $\text{R}^{\text{X}3}$ is hydrogen. In still further embodiments, L^1 is a bond or $-\text{O}-$; R^2 is hydrogen; $\text{R}^{\text{X}1}$ is hydrogen; $\text{R}^{\text{X}2}$ is hydrogen; $\text{R}^{\text{X}3}$ is hydrogen; and G^3 is optionally substituted $\text{C}_{3-6}\text{cycloalkyl}$.

[00136] Further according to formula (II) are embodiments wherein R^1 is $-\text{L}^2-\text{G}^4$ (i.e., (II-4)), wherein G^4 and L^2 are as defined herein.



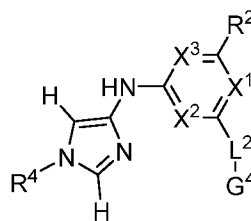
(II-4)

[00137] Further according to formula (III) are embodiments wherein R^1 is $-L^2-G^4$ (i.e., (III-4)), wherein G^4 and L^2 are as defined herein.



(III-4)

- 5 **[00138]** Further according to formula (IV) are embodiments wherein R^1 is $-L^2-G^4$ (i.e., (IV-4)), wherein G^4 and L^2 are as defined herein.

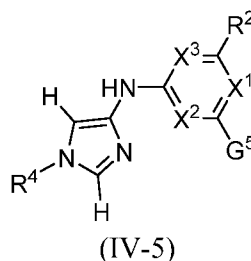


(IV-4)

- [00139]** G^4 is phenyl optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, cyano, phenyl, $-C(O)C_{1-4}$ alkyl, $-C(O)C_{3-6}$ cycloalkyl, $-C(O)OC_{1-4}$ alkyl, $-C(O)OC_{1-4}$ haloalkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-4}$ alkyl), $-C(O)N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $-C(O)NH(-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-C(O)N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-C(O)NH(-C_{1-6}$ alkylene-OH), $-C(O)N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene-OH), $-NH(-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-NH(-C_{1-6}$ alkylene-OH), $-N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene-OH), $-C(O)C_{1-4}$ haloalkyl, $-OC_{1-4}$ alkyl, $-C_{1-4}$ alkylene- OC_{1-4} alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ alkylene substituted by 2 groups independently selected from hydroxyl and $-OC(O)C_{1-4}$ alkyl, $-C_{1-4}$ alkylene- $C(O)OC_{1-4}$ alkyl, $-C_{1-4}$ alkylene- $C(O)OH$, $-NHC(O)(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl) $C(O)(C_{1-4}$ alkyl), $-NH_2$, $-NH(C_{1-4}$ alkyl), and $-N(C_{1-4}$ alkyl)(C_{1-4} alkyl). In some embodiments, G^4 is

phenyl optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, cyano, –or OC₁₋₄alkyl. In further embodiments, G⁴ is phenyl optionally substituted with OC₁₋₄alkyl.

- [00140] Further according to formulas (I), (II), (II-4), (III), and (III-4), and the foregoing description are embodiments wherein L¹ is –O–C₁₋₄alkylene–. In further embodiments, R² is C₁₋₄alkyl. In further embodiments, R^{X1} is hydrogen. In further embodiments, R^{X2} is C₁₋₄alkyl. In still further embodiments, R^{X3} is hydrogen. In still further embodiments, L¹ is –O–C₁₋₄alkylene–; R² is C₁₋₄alkyl; R^{X1} is hydrogen; R^{X2} is C₁₋₄alkyl; R^{X3} is hydrogen; and G⁴ is phenyl optionally substituted with OC₁₋₄alkyl.
- 10 [00141] Further according to formulas (IV) and (IV-4), and the foregoing description are embodiments wherein L¹ is –O–C₁₋₄alkylene–. In further embodiments, R² is hydrogen. In further embodiments, R^{X1} is hydrogen. In further embodiments, R^{X2} is hydrogen. In still further embodiments, R^{X3} is hydrogen. In still further embodiments, L¹ is –O–C₁₋₄alkylene–; R² is hydrogen; R^{X1} is hydrogen; R^{X2} is hydrogen; R^{X3} is hydrogen; and G⁴ is phenyl.
- 15 [00142] Further according to formula (IV) are embodiments wherein R¹ is –G⁵ (i.e., (IV-5)), wherein G⁵ is as defined herein.



- [00143] G⁵ is a monocyclic 5- or 6-membered heteroaryl containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, G⁵ being optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, cyano, phenyl, –C(O)C₁₋₄alkyl, –C(O)C₃₋₆cycloalkyl, –C(O)OC₁₋₄alkyl, –C(O)OC₁₋₄haloalkyl, –C(O)NH₂, –C(O)NH(C₁₋₄alkyl), –C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), –C(O)NH(–C₁₋₆alkylene–OC₁₋₄alkyl), –C(O)N(C₁₋₄alkyl)(–C₁₋₆alkylene–OC₁₋₄alkyl), –C(O)NH(–C₁₋₆alkylene–OH), –C(O)N(C₁₋₄alkyl)(–C₁₋₆alkylene–OH), –NH(–C₁₋₆alkylene–OC₁₋₄alkyl), –N(C₁₋₄alkyl)(–C₁₋₆alkylene–OC₁₋₄alkyl), –NH(–C₁₋₆alkylene–OH), –N(C₁₋₄alkyl)(–C₁₋₆alkylene–OH), –C(O)C₁₋₄haloalkyl, –OC₁₋₄alkyl, –C₁₋₄alkylene–OC₁₋₄alkyl, –C₁₋
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- ₆alkylene-OH, -C₁₋₆alkylene substituted by 2 groups independently selected from hydroxyl and -OC(O)C₁₋₄alkyl, -C₁₋₄alkylene-C(O)OC₁₋₄alkyl, -C₁₋₄alkylene-C(O)OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)(C₁₋₄alkyl). In some embodiments, G⁵ is optionally substituted with
- 5 C₁₋₄alkyl. In some embodiments, G⁵ is an optionally substituted monocyclic 5-membered heteroaryl containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, G⁵ is an optionally substituted monocyclic 5-membered heteroaryl containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur (e.g., thiazole, oxazole, imidazole).
- 10 **[00144]** Further according to formulas (I)-(III) are embodiments wherein R¹ is selected from the group consisting of -OC₁₋₆alkyl, -OC₁₋₆haloalkyl, -O-C₂₋₆alkylene-OC₁₋₄alkyl, -O-C₂₋₆alkylene-OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(C₁₋₄haloalkyl), -C(O)NH(-C₂₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₂₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₂₋₆alkylene-OH), and -C(O)N(C₁₋₄alkyl)(-C₂₋₆alkylene-OH); and R², R⁸, X¹, X², X³, and X⁴ are as defined herein. In some embodiments, R⁴ is optionally substituted phenyl. In some embodiments, R⁴ is optionally substituted pyridinyl.
- 15 **[00145]** Further according to formula (II) are embodiments wherein R¹ is selected from the group consisting of -OC₁₋₆alkyl, -OC₁₋₆haloalkyl, -O-C₂₋₆alkylene-OC₁₋₄alkyl, -O-C₂₋₆alkylene-OH, -NHC(O)(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(C₁₋₄haloalkyl), and -C(O)NH(-C₂₋₆alkylene-OC₁₋₄alkyl); R² is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, and -OC₁₋₄alkyl; X¹ is CH or N; X² is CR^{X2} or N; X³ is CR^{X3} or N; R^{X2} is hydrogen or C₁₋₄alkyl;
- 20 and R^{X3} is hydrogen or C₁₋₄alkyl. In some embodiments, R⁴ is optionally substituted phenyl. In some embodiments, R⁴ is optionally substituted pyridinyl.
- 25 **[00146]** Further according to formula (II) are embodiments wherein R¹ is selected from the group consisting of -OC₁₋₆haloalkyl, -NHC(O)(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(C₁₋₄haloalkyl), and -C(O)NH(-C₂₋₆alkylene-OC₁₋₄alkyl); R² is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, and -OC₁₋₄alkyl; X¹ is CH or N; X² is CR^{X2} or N; X³ is CR^{X3} or N; R^{X2} is hydrogen or C₁₋₄alkyl; and R^{X3} is hydrogen or C₁₋₄alkyl. In some embodiments, R⁴ is
- 30

optionally substituted phenyl. In some embodiments, R⁴ is optionally substituted pyridinyl.

[00147] Further according to formula (III) are embodiments wherein R¹ is selected from the group consisting of –OC₁₋₆alkyl or –NHC(O)(C₁₋₄alkyl); R² is C₁₋₄alkyl; X¹ is CH; X² is CH; X³ is CH; and R⁴ is optionally substituted phenyl.

[00148] Further according to formula (III) are embodiments wherein R¹ is –OC₁₋₆alkyl; R² is hydrogen; X¹ is CH; X² is CH; X³ is CH; and R⁴ is optionally substituted pyridinyl.

[00149] Further according to formula (III) are embodiments wherein R¹ is selected from the group consisting of –OC₁₋₆haloalkyl, –O–C₂₋₆alkylene–OC₁₋₄alkyl, –O–C₂₋₆alkylene–OH, –NHC(O)(C₁₋₄alkyl), –C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), –C(O)NH(C₁₋₄haloalkyl), and –C(O)NH(–C₂₋₆alkylene–OC₁₋₄alkyl); R² is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, and –OC₁₋₄alkyl; X¹ is CH or N; X² is CR^{X2} or N; X³ is CR^{X3} or N; R^{X2} is hydrogen or C₁₋₄alkyl; and R^{X3} is hydrogen or C₁₋₄alkyl.

[00150] Further according to formula (IV) are embodiments wherein R¹ is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄haloalkyl, –O–C₁₋₄alkyl, OH, –NH–C₁₋₄alkyl, –N(C₁₋₄alkyl)(C₁₋₄alkyl), and –NH₂; and R², R⁸, X¹, X², X³, and X⁴ are as defined herein.

[00151] Further according to formula (IV) are embodiments wherein R¹ is selected from the group consisting of hydrogen, C₁₋₄alkyl, and –O–C₁₋₄alkyl; R² is hydrogen or C₁₋₄alkyl; X¹ is CR^{X1} or N; X² is CH or N; X³ is CH or N; and CR^{X1} is hydrogen, halogen, or –OC₁₋₄alkyl.

[00152] R⁴ is phenyl or a 5- or 6-membered heteroaryl containing 1-3 heteroatoms independently selected from oxygen, nitrogen and sulfur, R⁴ being optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, –S(O)₂C₁₋₄alkyl, –S(O)C₁₋₄alkyl, –SC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄haloalkyl, –OC₁₋₄alkyl, –OC₁₋₄haloalkyl, –C₁₋₄alkylene–OC₁₋₄alkyl, –C₁₋₄alkylene–N(C₁₋₄alkyl)(C₁₋₄alkyl), –NH(C₁₋₄alkylene–OC₁₋₄alkyl), –NH(C₁₋₄alkylene–OH), –N(C₁₋₄alkyl)(C₁₋₄alkylene–OC₁₋₄alkyl), –N(C₁₋₄alkyl)(C₁₋₄alkylene–OH), –NH₂, –NH(C₁₋₄alkyl), –N(C₁₋₄alkyl)(C₁₋₄alkyl), C₃₋₆cycloalkyl, C₅₋₆cycloalkenyl, or a 4- to 8-membered monocyclic heterocycle containing 1-2 nitrogen atoms, the C₃₋₆cycloalkyl, the C₅₋₆cycloalkenyl, and the 4- to 8-membered monocyclic heterocycle

being independently optionally substituted with 1-2 substituents independently selected from the group consisting of pyridyl, halogen, hydroxyl, $-OC_{1-4}alkyl$, $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, $-C_{1-4}alkylene-OC_{1-4}alkyl$, and $-C_{1-4}alkylene-OH$. In further embodiments, R^4 is phenyl, a 5-membered heteroaryl such as thiazolyl, or a 6-membered heteroaryl such as pyrazinyl, pyrimidinyl, pyridazinyl, or pyridinyl, each optionally substituted as defined above. The 6-membered heteroaryl at R^4 includes a pyridone ring, which is defined herein by the tautomeric hydroxypyridine form, whether or not the pyridone or the hydroxypyridine tautomer predominates. In some embodiments, R^4 is phenyl, the phenyl being optionally substituted with one substituent selected from the foregoing list of substituents and optionally substituted with 1-2 substituents independently selected from the group consisting of halogen and $C_{1-4}alkyl$. Alternatively, R^4 is pyrazinyl, the pyrazinyl being optionally substituted with 1-3 $C_{1-4}alkyl$ groups. In another alternative, R^4 is pyridinyl (e.g., pyridin-2-yl, pyridin-3-yl, pyridin-4-yl), the pyridinyl being optionally substituted with one substituent selected from the group consisting of halogen, hydroxyl, $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, $-OC_{1-4}alkyl$, $C_{3-6}cycloalkyl$, and a 4- to 8-membered monocyclic heterocycle containing 1-2 nitrogen atoms, the 4- to 8-membered monocyclic heterocycle being independently optionally substituted with 1-2 substituents independently selected from the group consisting of pyridyl, the R^4 pyridinyl being further optionally substituted with 1-2 substituents selected from halogen and $C_{1-4}alkyl$. In further embodiments according to the foregoing, R^4 is phenyl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen and $C_{1-4}alkyl$. For example, in certain embodiments, R^4 is phenyl optionally substituted with 1-2 fluoro atoms or 1 fluoro and 1 methyl group. In certain embodiments, R^4 is independently any of phenyl, 3,5-difluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 2,5-difluorophenyl, or 3-fluoro-5-methylphenyl. In further embodiments according to the foregoing, R^4 is pyrazine, which is unsubstituted.

[00153] In some embodiments according to formulas (I), (II), (II-1)-(II-4), (III), and (III-1)-(III-4), and the foregoing description, R^4 is phenyl or a 6-membered heteroaryl containing 1-3 nitrogen atoms and optionally substituted with 1-3 halogen. In some embodiments, R^4 is optionally substituted pyridinyl.

[00154] In some embodiments according to formulas (IV) and (IV-1)-(IV-5), and the foregoing description, R^4 is phenyl or a 5- or 6-membered heteroaryl containing 1-3

heteroatoms independently selected from nitrogen and sulfur, R⁴ being optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, cyano, C₁₋₄alkyl, C₁₋₄haloalkyl, -OC₁₋₄alkyl, C₃₋₆cycloalkyl, or a 4- to 8-membered monocyclic heterocycle containing 1-2 nitrogen atoms, the 4- to 8-membered monocyclic heterocycle being independently optionally substituted with pyridyl.

[00155] In other embodiments of the present invention, the compound is 6-isopropoxy-N-(1-thiazol-4-ylimidazol-4-yl)pyridin-2-amine; 6-isopropoxy-N-[1-(2-pyridyl)imidazol-4-yl]pyridin-2-amine; 6-(cyclobutoxy)-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine; N-[1-(3,5-difluorophenyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine; 6-ethoxy-N-(1-phenylimidazol-4-yl)pyridin-2-amine; N-[1-(3,4-difluorophenyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine; 6-isopropoxy-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine; 6-(cyclohexoxy)-N-[1-(2-pyridyl)imidazol-4-yl]pyridin-2-amine; or 4-[4-[(6-ethoxy-2-pyridyl)amino]imidazol-1-yl]benzonitrile; 6-ethoxy-N-[1-(2-pyridyl)imidazol-4-yl]pyridin-2-amine.

[00156] In other embodiments of the present invention, the compound is N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine; N-(4-methyl-6-tetrahydropyran-3-yloxy-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine; N-[2-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrimidin-4-yl]-5-(2-pyridyl)thiazol-2-amine; N-(6-ethoxy-4-methyl-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine; N-[4-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine; N-(6-isopropoxy-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine; N-[6-methyl-4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine; N-(6-isobutoxy-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine; N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3-pyridyl)thiazol-2-amine; N-[6-[(1S)-2-methoxy-1-methyl-ethoxy]-4-methyl-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine; or N-(2-isopropoxy-3,6-dimethyl-4-pyridyl)-5-(2-pyridyl)thiazol-2-amine.

[00157] In other embodiments of the present invention, the compound is N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3-fluorophenyl)oxazol-2-amine; N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-phenyl-oxazol-2-amine; N-(3-isopropoxy-5-methyl-phenyl)-5-phenyl-oxazol-2-amine; N-[3-methyl-5-[4-(3-methyloxetan-3-yl)piperazin-1-yl]phenyl]-5-phenyl-oxazol-2-amine; N-[3-ethyl-5-[5-(3-fluorophenyl)oxazol-2-

yl]amino]phenyl]acetamide; 5-(3-chlorophenyl)-N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]oxazol-2-amine; N-(3-methyl-5-morpholino-phenyl)-5-phenyl-oxazol-2-amine; N-[3-methyl-5-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]-5-phenyl-oxazol-2-amine; 5-(3-fluorophenyl)-N-(3-isopropoxy-5-methyl-phenyl)oxazol-2-amine; or 5-(4-fluorophenyl)-N-(3-isopropoxy-5-methyl-phenyl)oxazol-2-amine.

[00158] In another embodiment, the compounds of formula (I) or (IV) include isotope-labelled forms thereof. An isotope-labelled form of a compound of formula (I) or (IV) is identical to this compound apart from the fact that one or more atoms of the compound have been replaced by an atom or atoms having an atomic mass or mass number which differs from the atomic mass or mass number of the atom which usually occurs in greater natural abundance. Examples of isotopes which are readily commercially available and which can be incorporated into a compound of formula (I) or (IV) by well-known methods include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, for example ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively.

[00159] In another embodiment, a compound of formula (I) or (IV) or a pharmaceutically acceptable salt thereof which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is intended to be part of the present invention.

[00160] In another embodiment, the present invention features a compound of formula I or I' and the attendant definitions, wherein one or more hydrogen atoms are replaced by a deuterium atom.

[00161] In another embodiment, an isotope-labelled compound of formula (I) or (IV) can be used in a number of beneficial ways. In one embodiment, an isotope-labelled compound of formula (I) or (IV) into which, for example, a radioisotope, such as ^3H or ^{14}C , has been incorporated is suitable for a medicament and/or for substrate tissue distribution assays. In one embodiment, tritium (^3H) and carbon-14 (^{14}C) are particularly preferred owing to simple preparation and excellent detectability.

[00162] In yet another embodiment, incorporation of heavier isotopes, for example deuterium (^2H), into a compound of formula (I) or (IV) have therapeutic advantages owing to the higher metabolic stability of this isotope-labelled compound. Higher metabolic stability translates directly into an increased in vivo half-life or lower

dosages, which under most circumstances would represent a preferred embodiment of the present invention. An isotope-labelled compound of formula I or I' can usually be prepared by carrying out the procedures disclosed in the synthesis schemes and the related description, in the example part and in the preparation part in the present text,
5 replacing a non-isotope-labelled reactant by a readily available isotope-labelled reactant.

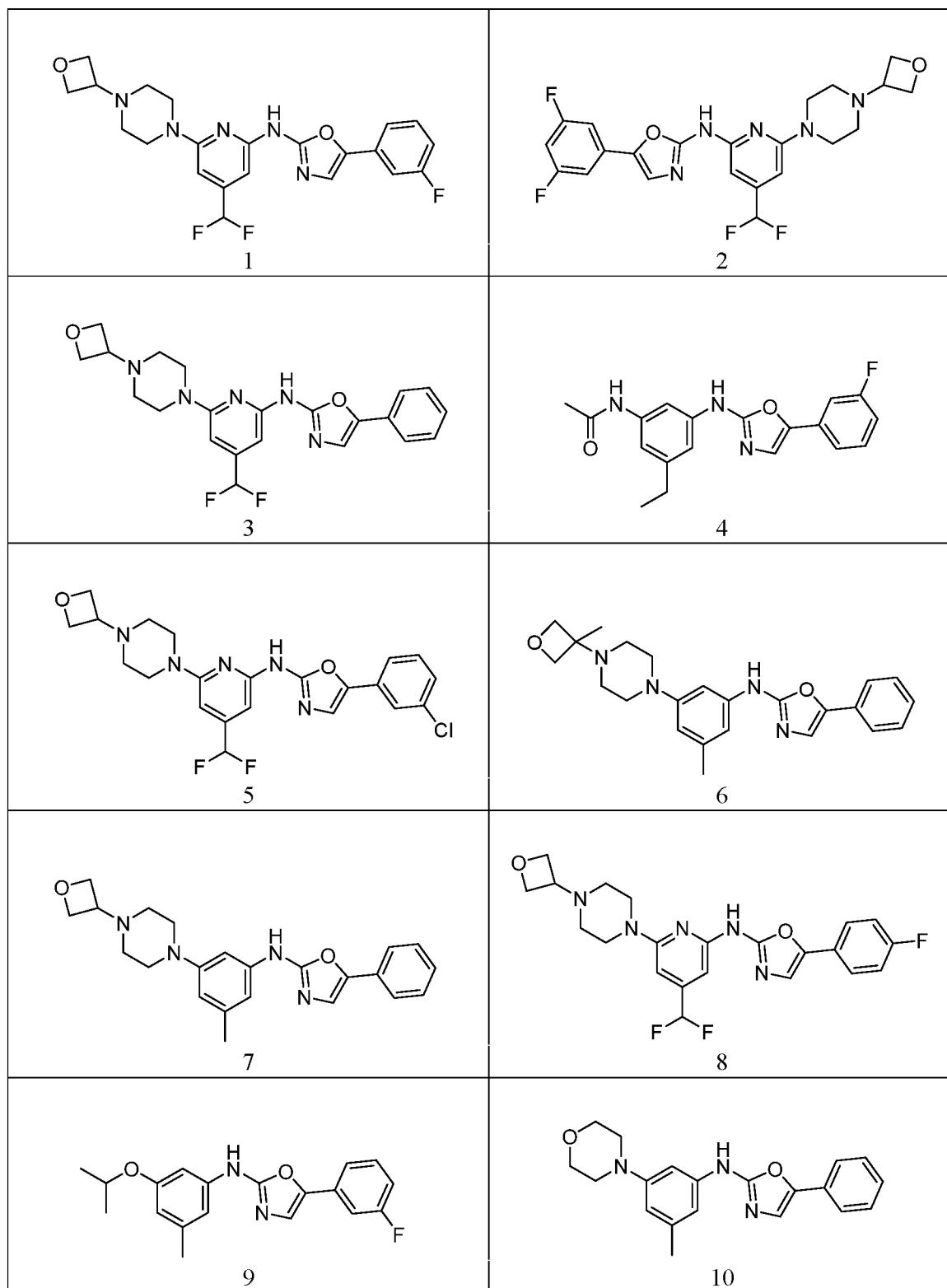
[00163] In another embodiment, Deuterium (^2H) can also be incorporated into a compound of formula (I) or (IV) for the purpose of manipulating the oxidative metabolism of the compound by way of the primary kinetic isotope effect. The
10 primary kinetic isotope effect is a change of the rate for a chemical reaction that results from exchange of isotopic nuclei, which in turn is caused by the change in ground state energies necessary for covalent bond formation after this isotopic exchange. Exchange of a heavier isotope usually results in a lowering of the ground state energy for a chemical bond and thus causes a reduction in the rate-limiting bond
15 breakage. If the bond breakage occurs in or in the vicinity of a saddle-point region along the coordinate of a multi-product reaction, the product distribution ratios can be altered substantially. For explanation: if deuterium is bonded to a carbon atom at a non-exchangeable position, rate differences of $k_{\text{M}}/k_{\text{D}} = 2-7$ are typical. If this rate difference is successfully applied to a compound of formula (I) or (IV) that is
20 susceptible to oxidation, the profile of this compound in vivo can be drastically modified and result in improved pharmacokinetic properties. For a further discussion, see S. L. Harbeson and R. D. Tung, *Deuterium In Drug Discovery and Development*, Ann. Rep. Med. Chem. 2011, 46, 403-417, incorporated in its entirety herein by reference.

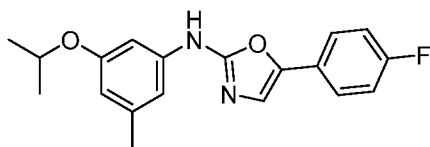
[00164] When discovering and developing therapeutic agents, the person skilled in the art attempts to optimise pharmacokinetic parameters while retaining desirable in vitro properties. It is reasonable to assume that many compounds with poor pharmacokinetic profiles are susceptible to oxidative metabolism. In vitro liver microsomal assays currently available provide valuable information on the course of
30 oxidative metabolism of this type, which in turn permits the rational design of deuterated compounds of formula (I) or (IV) with improved stability through resistance to such oxidative metabolism. Significant improvements in the pharmacokinetic profiles of compounds of formula (I) or (IV) are thereby obtained,

and can be expressed quantitatively in terms of increases in the in vivo half-life ($t_{1/2}$), concentration at maximum therapeutic effect (C_{max}), area under the dose response curve (AUC), and bioavailability; and in terms of reduced clearance, dose and materials costs.

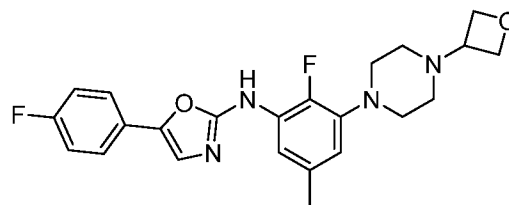
- 5 **[00165]** The following is intended to illustrate the above: a compound of formula (I) or (IV) which has multiple potential sites of attack for oxidative metabolism, for example benzylic hydrogen atoms and hydrogen atoms bonded to a nitrogen atom, is prepared as a series of analogues in which various combinations of hydrogen atoms are replaced by deuterium atoms, so that some, most or all of these hydrogen atoms
- 10 have been replaced by deuterium atoms. Half-life determinations enable favourable and accurate determination of the extent to which the improvement in resistance to oxidative metabolism has improved. In this way, it is determined that the half-life of the parent compound can be extended by up to 100% as the result of deuterium-hydrogen exchange of this type.
- 15 **[00166]** In another embodiment, deuterium-hydrogen exchange in a compound of formula (I) or (IV) can be used to achieve a favourable modification of the metabolite spectrum of the starting compound in order to diminish or eliminate undesired toxic metabolites. For example, if a toxic metabolite arises through oxidative carbon-hydrogen (C-H) bond cleavage, it can reasonably be assumed that the deuterated
- 20 analogue will greatly diminish or eliminate production of the unwanted metabolite, even if the particular oxidation is not a rate-determining step. Further information on the state of the art with respect to deuterium-hydrogen exchange may be found, for example in Hanzlik et al., J. Org. Chem. 55, 3992-3997, 1990, Reider et al., J. Org. Chem. 52, 3326-3334, 1987, Foster, Adv. Drug Res. 14, 1-40, 1985, Gillette et al,
- 25 Biochemistry 33(10) 2927-2937, 1994, and Jarman et al. Carcinogenesis 16(4), 683-688, 1993.

[00167] Table 1. Compound Table

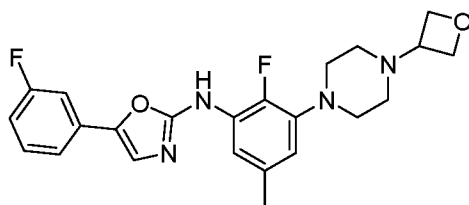




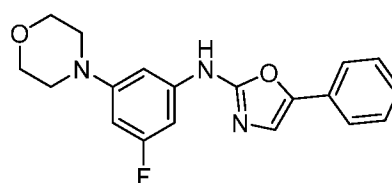
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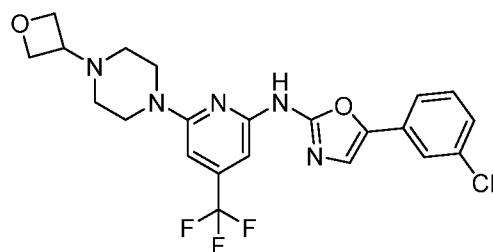
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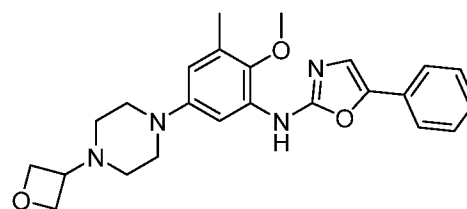
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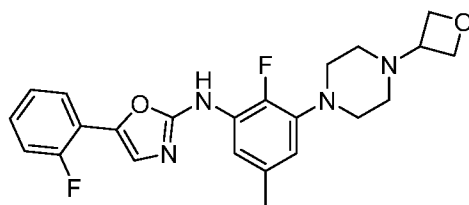
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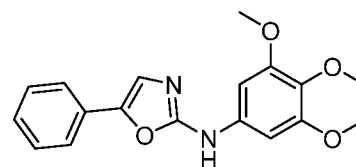
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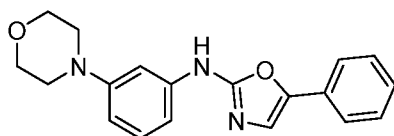
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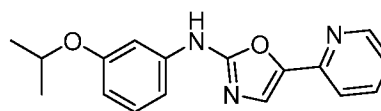
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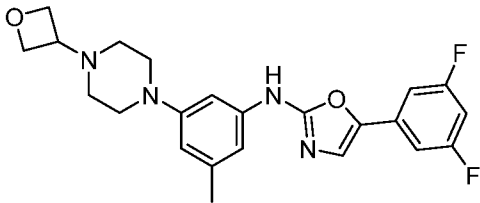
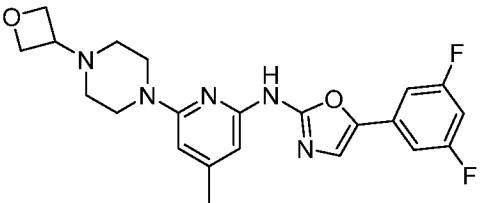
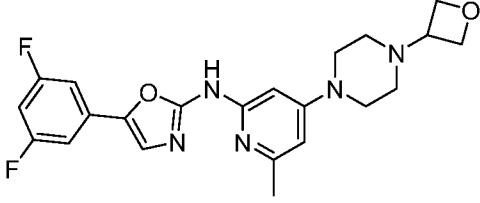
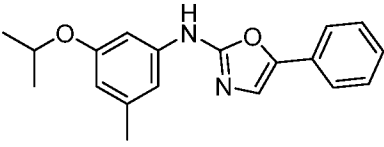
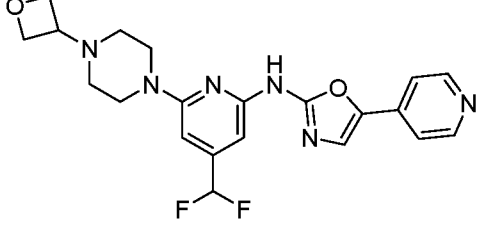
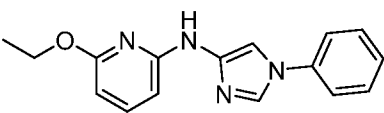
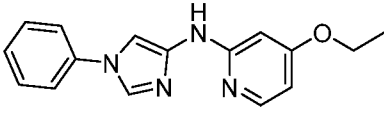
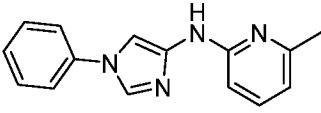
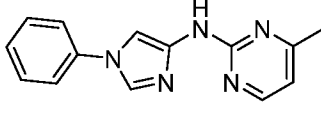
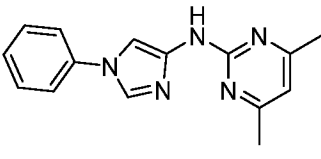
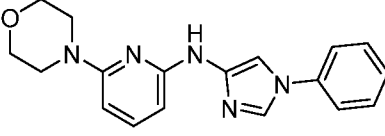
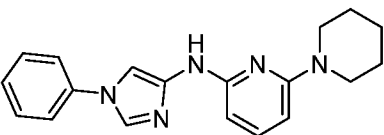
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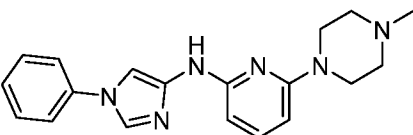
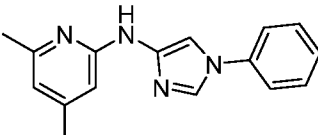
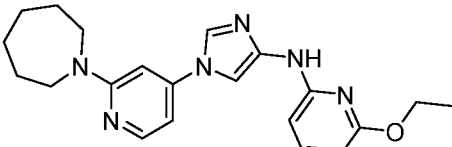
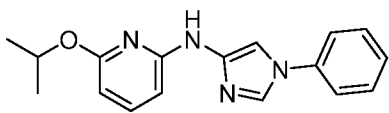
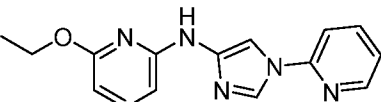
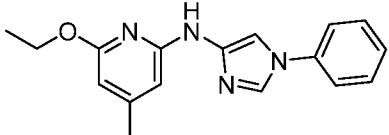
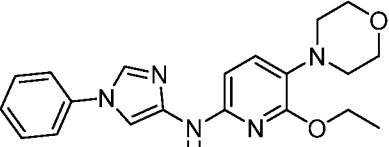
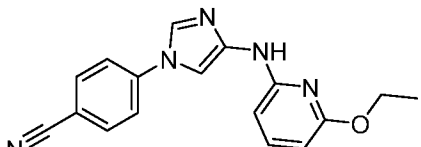
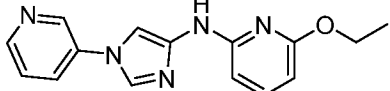
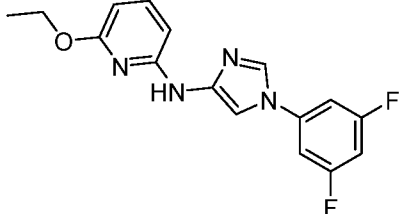
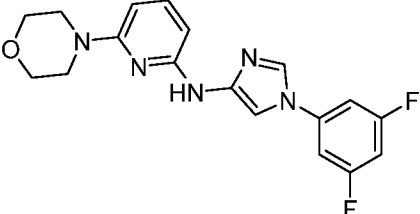
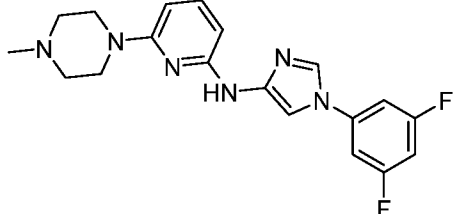


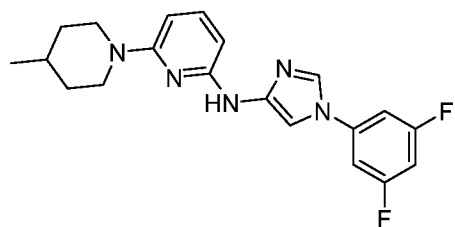
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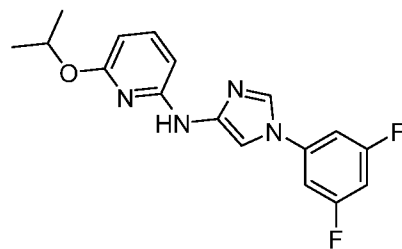
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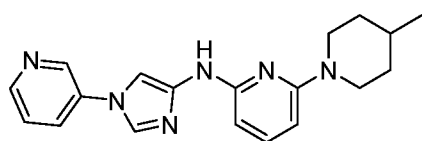
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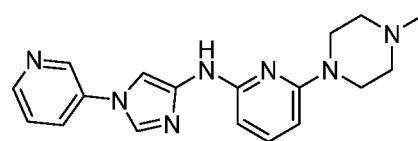
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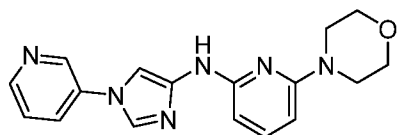
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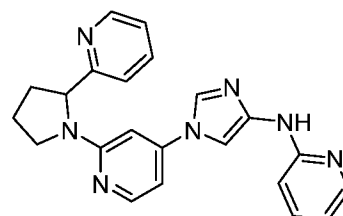
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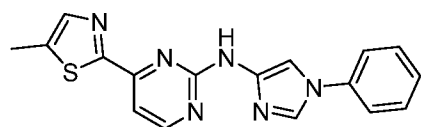
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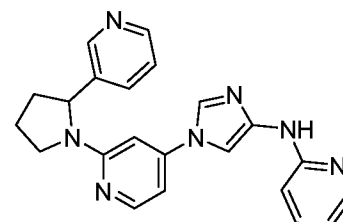
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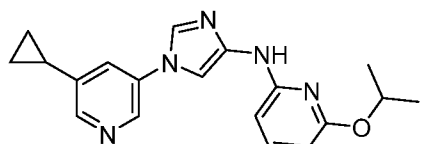
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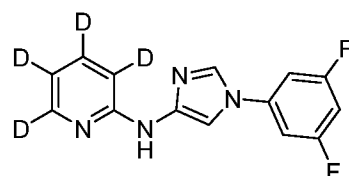
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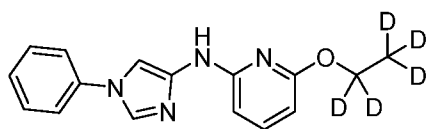
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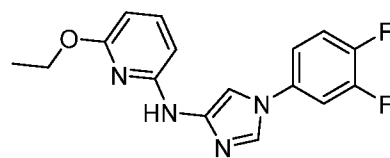
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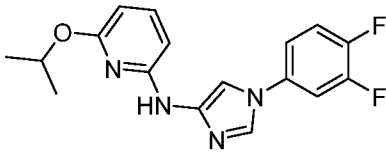
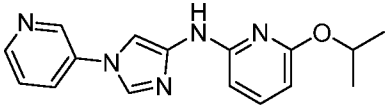
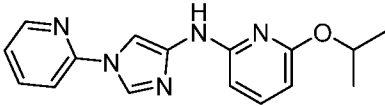
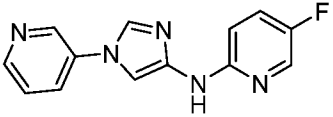
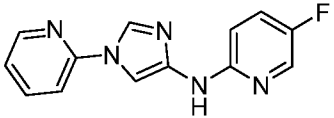
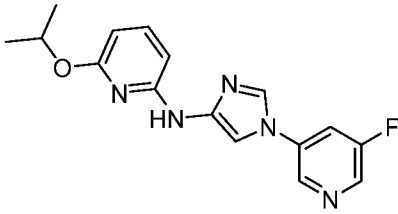
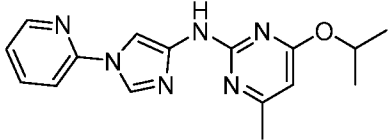
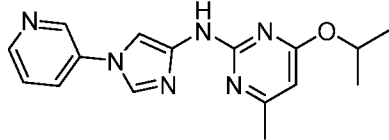
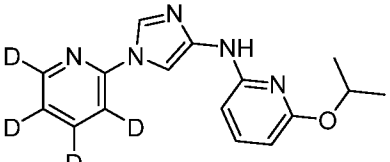
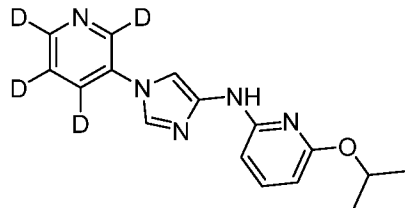
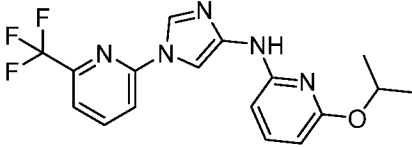
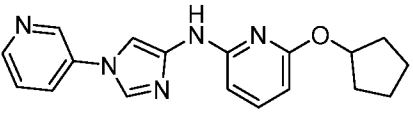
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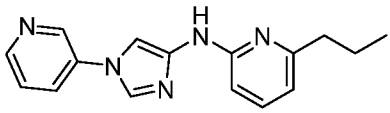
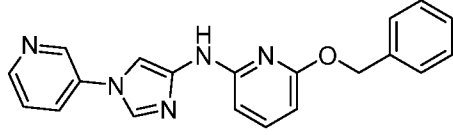
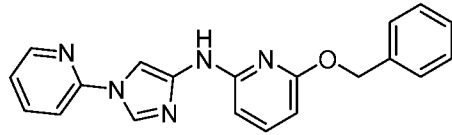
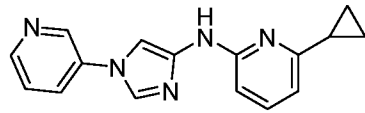
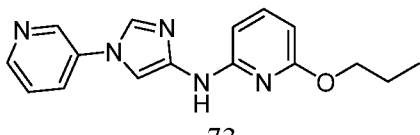
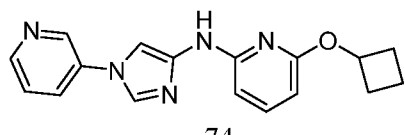
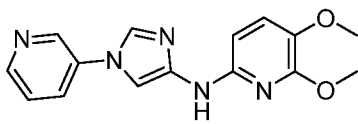
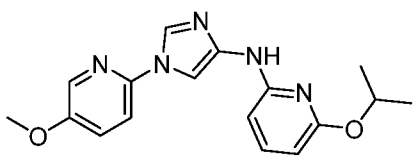
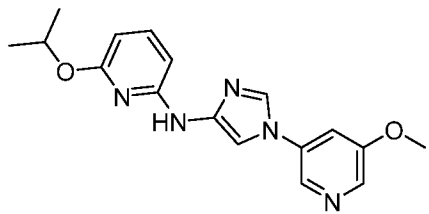
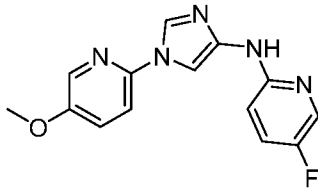
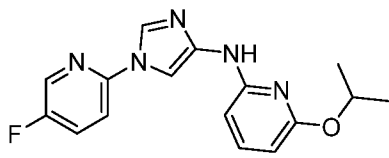
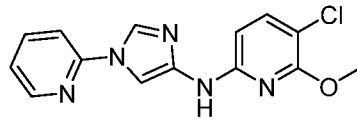
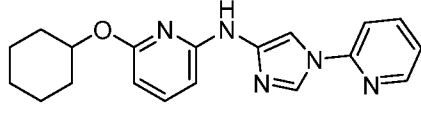
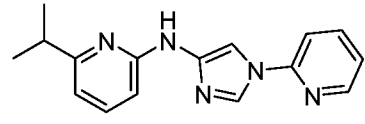


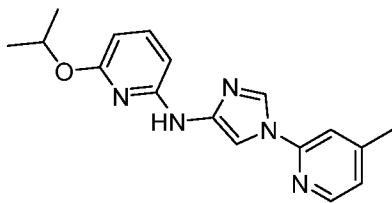
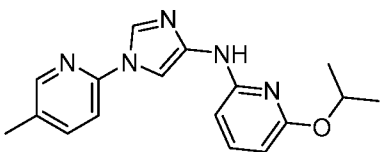
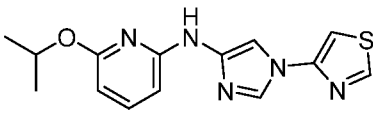
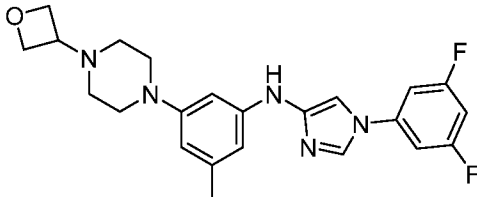
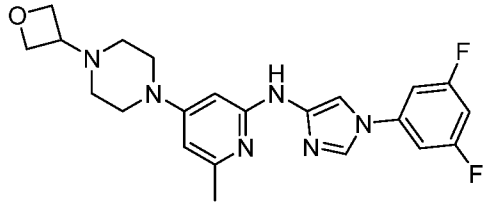
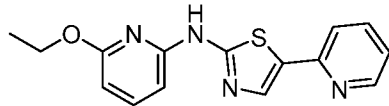
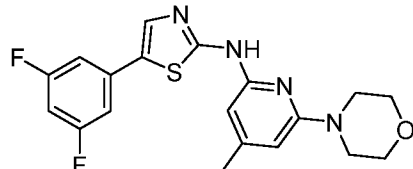
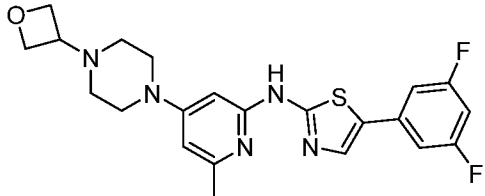
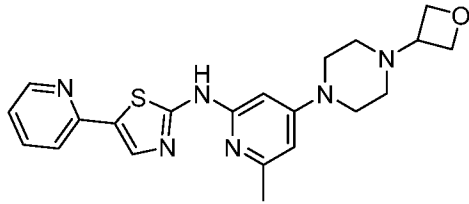
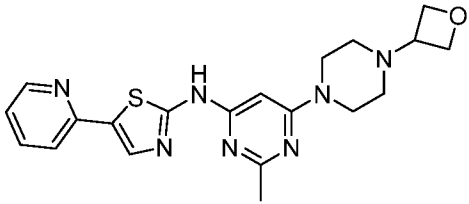
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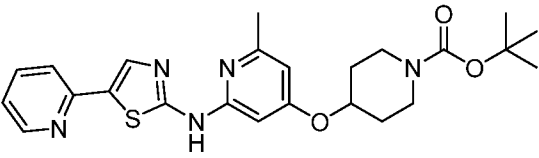
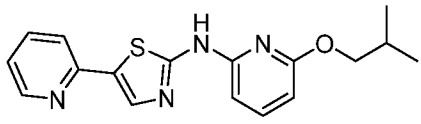
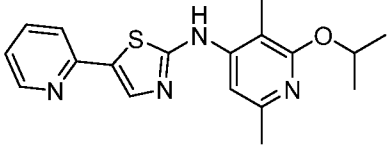
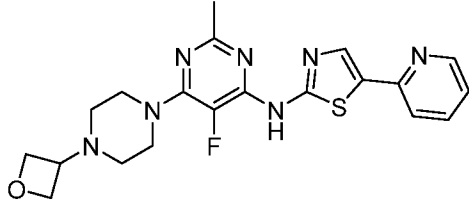
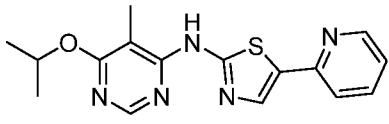
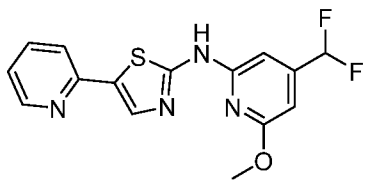
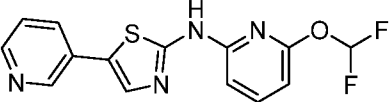
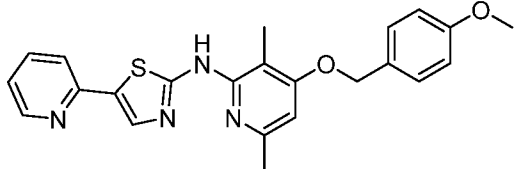
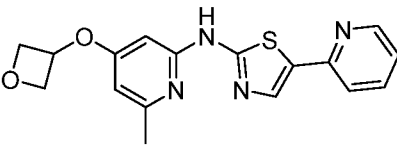
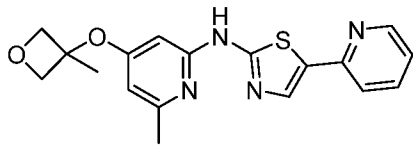
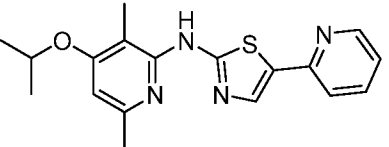
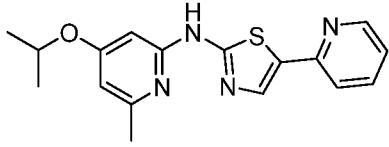
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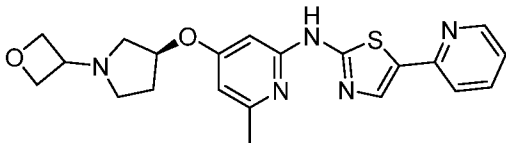
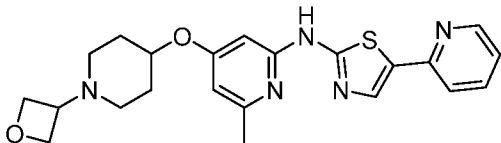
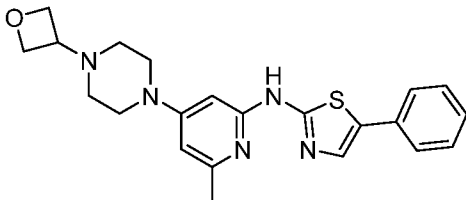
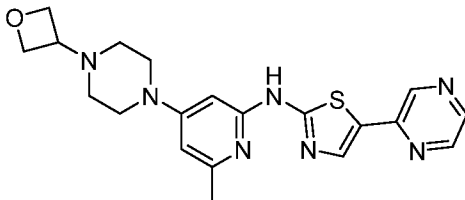
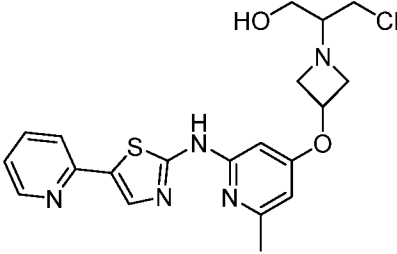
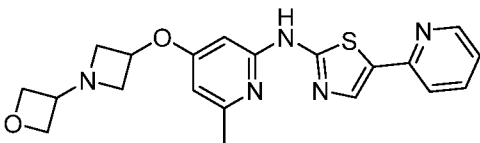
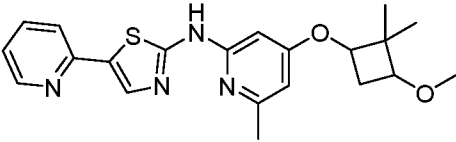
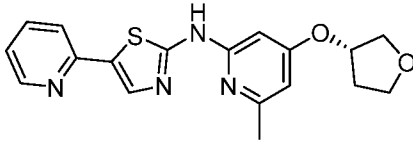
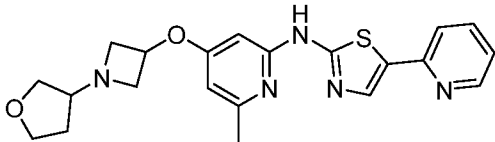
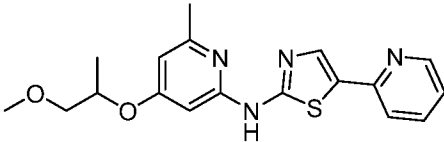
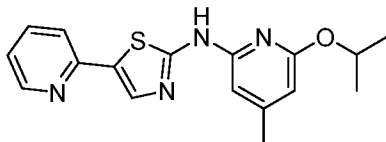
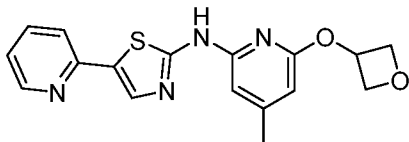
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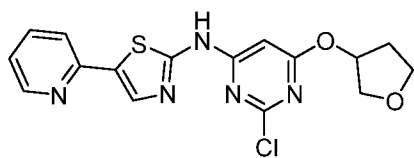
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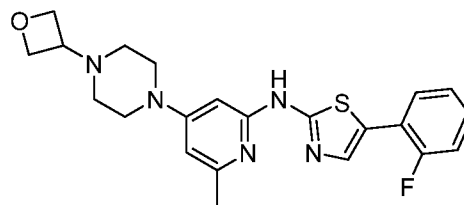
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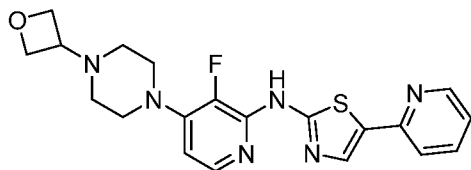
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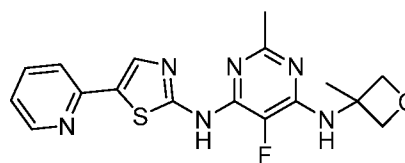
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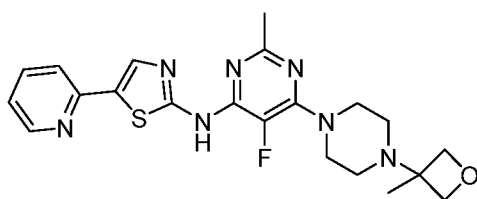
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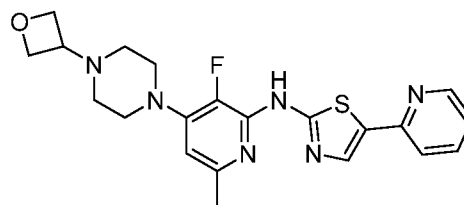
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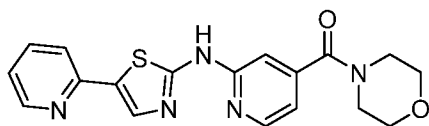
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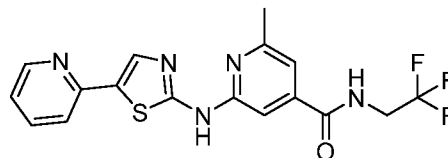
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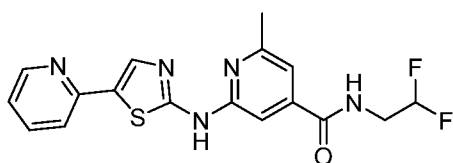
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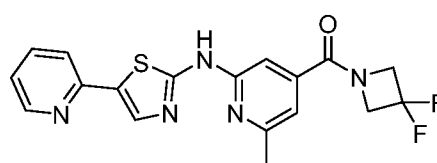
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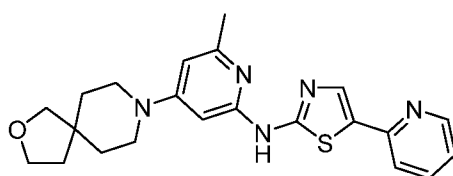
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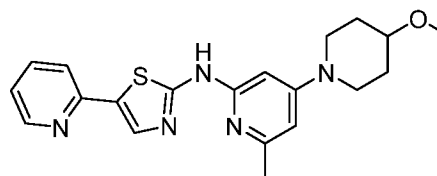
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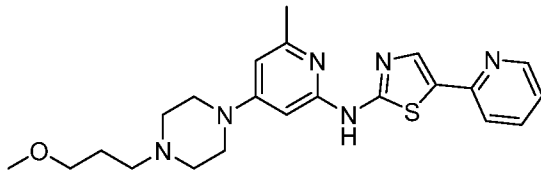
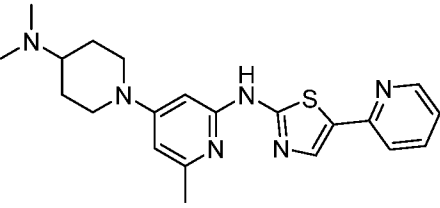
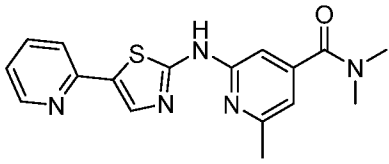
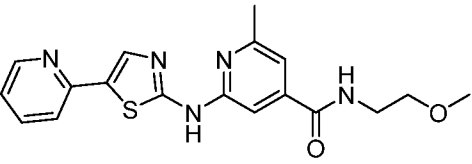
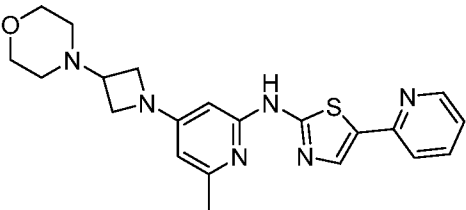
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[00168] Table 2. Compound Names (IUPAC Nomenclature)

Cmpd No.	Compound name
1	N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3-fluorophenyl)oxazol-2-amine
2	N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3,5-difluorophenyl)oxazol-2-amine
3	N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-phenyl-oxazol-2-amine
4	N-[3-ethyl-5-[[5-(3-fluorophenyl)oxazol-2-yl]amino]phenyl]acetamide
5	5-(3-chlorophenyl)-N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]oxazol-2-amine
6	N-[3-methyl-5-[4-(3-methyloxetan-3-yl)piperazin-1-yl]phenyl]-5-phenyl-oxazol-2-amine

Cmpd No.	Compound name
7	N-[3-methyl-5-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]-5-phenyl-oxazol-2-amine
8	N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(4-fluorophenyl)oxazol-2-amine
9	5-(3-fluorophenyl)-N-(3-isopropoxy-5-methyl-phenyl)oxazol-2-amine
10	N-(3-methyl-5-morpholino-phenyl)-5-phenyl-oxazol-2-amine
11	5-(4-fluorophenyl)-N-(3-isopropoxy-5-methyl-phenyl)oxazol-2-amine
12	N-[2-fluoro-5-methyl-3-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]-5-(4-fluorophenyl)oxazol-2-amine
13	N-[2-fluoro-5-methyl-3-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]-5-(3-fluorophenyl)oxazol-2-amine
14	N-(3-fluoro-5-morpholino-phenyl)-5-phenyl-oxazol-2-amine
15	5-(3-chlorophenyl)-N-[6-[4-(oxetan-3-yl)piperazin-1-yl]-4-(trifluoromethyl)-2-pyridyl]oxazol-2-amine
16	N-[2-methoxy-3-methyl-5-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]-5-phenyl-oxazol-2-amine
17	N-[2-fluoro-5-methyl-3-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]-5-(2-fluorophenyl)oxazol-2-amine
18	5-phenyl-N-(3,4,5-trimethoxyphenyl)oxazol-2-amine
19	N-(3-morpholinophenyl)-5-phenyl-oxazol-2-amine
20	N-(3-isopropoxyphenyl)-5-(2-pyridyl)oxazol-2-amine
21	5-(3,5-difluorophenyl)-N-[3-methyl-5-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]oxazol-2-amine
22	5-(3,5-difluorophenyl)-N-[4-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]oxazol-2-amine

Cmpd No.	Compound name
23	5-(3,5-difluorophenyl)-N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]oxazol-2-amine
24	N-(3-isopropoxy-5-methyl-phenyl)-5-phenyl-oxazol-2-amine
25	N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(4-pyridyl)oxazol-2-amine
26	6-ethoxy-N-(1-phenylimidazol-4-yl)pyridin-2-amine
27	4-ethoxy-N-(1-phenylimidazol-4-yl)pyridin-2-amine
28	6-methyl-N-(1-phenylimidazol-4-yl)pyridin-2-amine
29	4-methyl-N-(1-phenylimidazol-4-yl)pyrimidin-2-amine
30	4,6-dimethyl-N-(1-phenylimidazol-4-yl)pyrimidin-2-amine
31	6-morpholino-N-(1-phenylimidazol-4-yl)pyridin-2-amine
32	N-(1-phenylimidazol-4-yl)-6-(1-piperidyl)pyridin-2-amine
33	6-(4-methylpiperazin-1-yl)-N-(1-phenylimidazol-4-yl)pyridin-2-amine
34	4,6-dimethyl-N-(1-phenylimidazol-4-yl)pyridin-2-amine
35	N-[1-[2-(azepan-1-yl)-4-pyridyl]imidazol-4-yl]-6-ethoxy-pyridin-2-amine
36	6-isopropoxy-N-(1-phenylimidazol-4-yl)pyridin-2-amine
37	6-ethoxy-N-[1-(2-pyridyl)imidazol-4-yl]pyridin-2-amine
38	6-ethoxy-4-methyl-N-(1-phenylimidazol-4-yl)pyridin-2-amine
39	6-ethoxy-5-morpholino-N-(1-phenylimidazol-4-yl)pyridin-2-amine
40	4-[4-[(6-ethoxy-2-pyridyl)amino]imidazol-1-yl]benzonitrile
41	6-ethoxy-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine

Cmpd No.	Compound name
42	N-[1-(3,5-difluorophenyl)imidazol-4-yl]-6-ethoxy-pyridin-2-amine
43	N-[1-(3,5-difluorophenyl)imidazol-4-yl]-6-morpholino-pyridin-2-amine
44	N-[1-(3,5-difluorophenyl)imidazol-4-yl]-6-(4-methylpiperazin-1-yl)pyridin-2-amine
45	N-[1-(3,5-difluorophenyl)imidazol-4-yl]-6-(4-methyl-1-piperidyl)pyridin-2-amine
46	N-[1-(3,5-difluorophenyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine
47	6-(4-methyl-1-piperidyl)-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine
48	6-(4-methylpiperazin-1-yl)-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine
49	6-morpholino-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine
50	N-[1-[2-[2-(2-pyridyl)pyrrolidin-1-yl]-4-pyridyl]imidazol-4-yl]pyridin-2-amine
51	4-(5-methylthiazol-2-yl)-N-(1-phenylimidazol-4-yl)pyrimidin-2-amine
52	N-[1-[2-[2-(3-pyridyl)pyrrolidin-1-yl]-4-pyridyl]imidazol-4-yl]pyridin-2-amine
53	N-[1-(5-cyclopropyl-3-pyridyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine
54	3,4,5,6-tetradeuterio-N-[1-(3,5-difluorophenyl)imidazol-4-yl]pyridin-2-amine
55	6-(1,1,2,2,2-pentadeuterioethoxy)-N-(1-phenylimidazol-4-yl)pyridin-2-amine
56	N-[1-(3,4-difluorophenyl)imidazol-4-yl]-6-ethoxy-pyridin-2-amine
57	N-[1-(3,4-difluorophenyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine
58	6-isopropoxy-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine
59	6-isopropoxy-N-[1-(2-pyridyl)imidazol-4-yl]pyridin-2-amine
60	5-fluoro-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine
61	5-fluoro-N-[1-(2-pyridyl)imidazol-4-yl]pyridin-2-amine

Cmpd No.	Compound name
62	N-[1-(5-fluoro-3-pyridyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine
63	4-isopropoxy-6-methyl-N-[1-(2-pyridyl)imidazol-4-yl]pyrimidin-2-amine
64	4-isopropoxy-6-methyl-N-[1-(3-pyridyl)imidazol-4-yl]pyrimidin-2-amine
65	6-isopropoxy-N-[1-(3,4,5,6-tetradeuterio-2-pyridyl)imidazol-4-yl]pyridin-2-amine
66	6-isopropoxy-N-[1-(2,4,5,6-tetradeuterio-3-pyridyl)imidazol-4-yl]pyridin-2-amine
67	6-isopropoxy-N-[1-[6-(trifluoromethyl)-2-pyridyl]imidazol-4-yl]pyridin-2-amine
68	6-(cyclopentoxy)-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine
69	6-propyl-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine
70	6-benzyloxy-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine
71	6-benzyloxy-N-[1-(2-pyridyl)imidazol-4-yl]pyridin-2-amine
72	6-cyclopropyl-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine
73	6-propoxy-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine
74	6-(cyclobutoxy)-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine
75	5,6-dimethoxy-N-[1-(3-pyridyl)imidazol-4-yl]pyridin-2-amine
76	6-isopropoxy-N-[1-(5-methoxy-2-pyridyl)imidazol-4-yl]pyridin-2-amine
77	6-isopropoxy-N-[1-(5-methoxy-3-pyridyl)imidazol-4-yl]pyridin-2-amine
78	5-fluoro-N-[1-(5-methoxy-2-pyridyl)imidazol-4-yl]pyridin-2-amine
79	N-[1-(5-fluoro-2-pyridyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine
80	5-chloro-6-methoxy-N-[1-(2-pyridyl)imidazol-4-yl]pyridin-2-amine
81	6-(cyclohexoxy)-N-[1-(2-pyridyl)imidazol-4-yl]pyridin-2-amine

Cmpd No.	Compound name
82	6-isopropyl-N-[1-(2-pyridyl)imidazol-4-yl]pyridin-2-amine
83	6-isopropoxy-N-[1-(4-methyl-2-pyridyl)imidazol-4-yl]pyridin-2-amine
84	6-isopropoxy-N-[1-(5-methyl-2-pyridyl)imidazol-4-yl]pyridin-2-amine
85	6-isopropoxy-N-(1-thiazol-4-ylimidazol-4-yl)pyridin-2-amine
86	1-(3,5-difluorophenyl)-N-[3-methyl-5-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]imidazol-4-amine
87	N-[1-(3,5-difluorophenyl)imidazol-4-yl]-6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pyridin-2-amine
88	N-(6-ethoxy-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine
89	5-(3,5-difluorophenyl)-N-(4-methyl-6-morpholino-2-pyridyl)thiazol-2-amine
90	5-(3,5-difluorophenyl)-N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]thiazol-2-amine
91	N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
92	N-[2-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrimidin-4-yl]-5-(2-pyridyl)thiazol-2-amine
93	N-[6-methyl-4-(4-methylpiperazin-1-yl)-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
94	N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3-pyridyl)thiazol-2-amine
95	N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(4-pyridyl)thiazol-2-amine
96	N-(6-isobutoxy-2-pyridyl)-5-(3-pyridyl)thiazol-2-amine
97	N-(6-isopropoxy-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine
98	N-(6-ethoxy-4-methyl-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine
99	N-[5-fluoro-2-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrimidin-4-yl]-5-(3-pyridyl)thiazol-2-amine

Cmpd No.	Compound name
100	N-(2-isopropoxy-5-methyl-pyrimidin-4-yl)-5-(2-pyridyl)thiazol-2-amine
101	N-(4,6-dimethoxy-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine
102	N-(2-isopropoxy-6-methyl-pyrimidin-4-yl)-5-(2-pyridyl)thiazol-2-amine
103	N-(2-methoxy-6-methyl-pyrimidin-4-yl)-5-(2-pyridyl)thiazol-2-amine
104	tert-butyl 3-[[2-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]-4-pyridyl]oxy]azetidine-1-carboxylate
105	tert-butyl 4-[[2-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]-4-pyridyl]oxy]piperidine-1-carboxylate
106	N-(6-isobutoxy-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine
107	N-(2-isopropoxy-3,6-dimethyl-4-pyridyl)-5-(2-pyridyl)thiazol-2-amine
108	N-[5-fluoro-2-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrimidin-4-yl]-5-(2-pyridyl)thiazol-2-amine
109	N-(6-isopropoxy-5-methyl-pyrimidin-4-yl)-5-(2-pyridyl)thiazol-2-amine
110	N-[4-(difluoromethyl)-6-methoxy-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
111	N-[6-(difluoromethoxy)-2-pyridyl]-5-(3-pyridyl)thiazol-2-amine
112	N-[4-[(4-methoxyphenyl)methoxy]-3,6-dimethyl-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
113	N-[6-methyl-4-(oxetan-3-yloxy)-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
114	N-[6-methyl-4-(3-methyloxetan-3-yl)oxy-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
115	N-(4-isopropoxy-3,6-dimethyl-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine
116	N-(4-isopropoxy-6-methyl-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine
117	N-[6-methyl-4-[(3S)-1-(oxetan-3-yl)pyrrolidin-3-yl]oxy-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine

Cmpd No.	Compound name
118	N-[6-methyl-4-[[1-(oxetan-3-yl)-4-piperidyl]oxy]-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
119	N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-phenyl-thiazol-2-amine
120	N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-pyrazin-2-yl-thiazol-2-amine
121	3-chloro-2-[3-[[2-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]-4-pyridyl]oxy]azetidin-1-yl]propan-1-ol
122	N-[6-methyl-4-[1-(oxetan-3-yl)azetidin-3-yl]oxy-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
123	N-[4-(3-methoxy-2,2-dimethyl-cyclobutoxy)-6-methyl-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
124	N-[6-methyl-4-[(3S)-tetrahydrofuran-3-yl]oxy-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
125	N-[6-methyl-4-(1-tetrahydrofuran-3-ylazetidin-3-yl)oxy-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
126	N-[4-(2-methoxy-1-methyl-ethoxy)-6-methyl-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
127	N-(6-isopropoxy-4-methyl-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine
128	N-[4-methyl-6-(oxetan-3-yloxy)-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
129	N-[6-[(1S)-2-methoxy-1-methyl-ethoxy]-4-methyl-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
130	tert-butyl 3-[[4-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]-2-pyridyl]oxy]azetidine-1-carboxylate
131	N-[4-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
132	N-[4-(difluoromethyl)-6-(oxetan-3-yloxy)-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
133	N-(6-methoxypyrimidin-4-yl)-5-(2-pyridyl)thiazol-2-amine
134	N-(6-ethoxy-2-methyl-pyrimidin-4-yl)-5-(2-pyridyl)thiazol-2-amine
135	N-[4-methyl-6-(oxetan-3-ylmethoxy)-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine

Cmpd No.	Compound name
136	N-[6-(cyclopropylmethoxy)-4-methyl-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
137	2-methyl-4-[[4-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]-2-pyridyl]oxy]butan-2-ol
138	N-[4-(2-methoxy-2-methyl-propoxy)-6-methyl-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
139	N-(4-methyl-6-tetrahydropyran-3-yloxy-2-pyridyl)-5-(2-pyridyl)thiazol-2-amine
140	N-(6-methoxy-2-methyl-pyrimidin-4-yl)-5-(2-pyridyl)thiazol-2-amine
141	N-(2-chloro-6-tetrahydrofuran-3-yloxy-pyrimidin-4-yl)-5-(2-pyridyl)thiazol-2-amine
142	5-(2-fluorophenyl)-N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]thiazol-2-amine
143	N-[3-fluoro-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
144	5-fluoro-2-methyl-N6-(3-methyloxetan-3-yl)-N4-[5-(2-pyridyl)thiazol-2-yl]pyrimidine-4,6-diamine
145	N-[5-fluoro-2-methyl-6-[4-(3-methyloxetan-3-yl)piperazin-1-yl]pyrimidin-4-yl]-5-(2-pyridyl)thiazol-2-amine
146	N-[3-fluoro-6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
147	[2-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]-4-pyridyl]-morpholino-methanone
148	2-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]-N-(2,2,2-trifluoroethyl)pyridine-4-carboxamide
149	N-(2,2-difluoroethyl)-2-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]pyridine-4-carboxamide
150	(3,3-difluoroazetidin-1-yl)-[2-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]-4-pyridyl]methanone
151	N-[6-methyl-4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
152	N-[4-(4-methoxy-1-piperidyl)-6-methyl-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine

Cmpd No.	Compound name
153	N-[4-[4-(3-methoxypropyl)piperazin-1-yl]-6-methyl-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
154	N-[4-[4-(dimethylamino)-1-piperidyl]-6-methyl-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine
155	N,N,2-trimethyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]pyridine-4-carboxamide
156	N-(2-methoxyethyl)-2-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]pyridine-4-carboxamide
157	N-[6-methyl-4-(3-morpholinoazetidin-1-yl)-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine

Salts, Compositions, Uses, Formulation, Administration and Additional Agents

Pharmaceutically acceptable salts and compositions

- 5 **[00169]** As discussed herein, the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein are useful for the treatment of neurodegenerative or neurological diseases or disorders related to axonal damage, demyelinating diseases, central pontine myelinolysis, nerve injury diseases or disorders, metabolic diseases, mitochondrial diseases, metabolic axonal
- 10 degeneration, a leukoencephalopathy or a leukodystrophy. In one embodiment, said neurodegenerative or neurological diseases or disorders related to axonal damage, demyelinating diseases, central pontine myelinolysis, nerve injury diseases or disorders, metabolic diseases, mitochondrial diseases, metabolic axonal degeneration, a leukoencephalopathy or a leukodystrophy include, but are not limited to spinal cord
- 15 injury, stroke, multiple sclerosis, progressive multifocal leukoencephalopathy, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelolysis, hypoxic demyelination, ischemic demyelination, neuromyelitis optica, adrenoleukodystrophy, Alexander's disease, Niemann-Pick disease, Pelizaeus Merzbacher disease, periventricular leukomalacia,
- 20 globoid cell leukodystrophy (Krabbe's disease), Wallerian degeneration, optic neuritis, transverse myelitis, amyotrophic lateral sclerosis (Lou Gehrig's disease), Huntington's disease, Alzheimer's disease, Parkinson's disease, Tay-Sacks disease, Gaucher's disease, Hurler Syndrome, traumatic brain injury, post radiation injury, neurologic complications of chemotherapy, neuropathy, acute ischemic optic neuropathy,

neuromyelitis optica, vitamin B12 deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, Leber's hereditary optic atrophy/Leber congenital amaurosis, Marchiafava-Bignami syndrome, metachromatic leukodystrophy, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, schizophrenia, cerebral ischemia, multiple system atrophy, traumatic glaucoma, tropical spastic paraparesis/human T-lymphotropic virus 1 (HTLV-1) associated myelopathy, essential tremor or osmotic hyponatremia.

[00170] In another embodiment, the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein are useful for treating, preventing or ameliorating one or more symptoms of multiple sclerosis or another neurodegenerative disease selected from auditory impairment, optic neuritis, decreased visual acuity, diplopia, nystagmus, ocular dysmetria, internuclear ophthalmoplegia, movement and sound phosphenes, afferent pupillary defect, paresis, monoparesis, paraparesis, hemiparesis, quadraparesis, plegia, paraplegia, hemiplegia, tetraplegia, quadraplegia, spasticity, dysarthria, motor dysfunction, walking impairment, muscle atrophy, spasms, cramps, hypotonia, clonus, myoclonus, myokymia, restless leg syndrome, gait disturbances, footdrop, dysfunctional reflexes, paraesthesia, anaesthesia, neuralgia, neuropathic and neurogenic pain, L'hermitte's, proprioceptive dysfunction, trigeminal neuralgia, ataxia, intention tremor, dysmetria, vestibular ataxia, vertigo, speech ataxia, dystonia, disability progression, dysdiadochokinesia, frequent micturation, bladder spasticity, flaccid bladder, detrusor- sphincter dyssynergia, erectile dysfunction or anorgasmy.

[00171] Accordingly, in another aspect of the invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents. In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers or vehicles.

[00172] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity,

irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A “pharmaceutically acceptable salt” means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term “inhibitorily active metabolite or residue thereof” means that a metabolite or residue thereof is also useful for treating or lessening the severity of, in a subject, a disease or disorder selected from neurodegenerative or neurological diseases or disorders related to axonal damage, demyelinating diseases, central pontine myelinolysis, nerve injury diseases or disorders, metabolic diseases, mitochondrial diseases, metabolic axonal degeneration, a leukoencephalopathy or a leukodystrophy.

[00173] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, **1977**, 66, 1-19, incorporated herein by reference.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or

oil-soluble or dispersable products may be obtained by such quaternization.

Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations
5 formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[00174] As described herein, the pharmaceutically acceptable compositions of the invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid
10 vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable
15 compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the
20 scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or
25 electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives
30 such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene

glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00175] In another aspect, the invention features a pharmaceutical composition comprising the compound of the invention and a pharmaceutically acceptable carrier.

10 [00176] In another aspect, the invention features a pharmaceutical composition comprising a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof of the compounds of formula (I) or (IV) and one or more pharmaceutically acceptable carriers or vehicles.

15 *Uses of Compounds and Pharmaceutically Acceptable Salts and Compositions*

[00177] In one embodiment, the methods described herein also provide a method of promoting oligodendrocyte proliferation, differentiation or survival comprising contacting oligodendrocytes with a compound of formula (I) or (IV) or a composition thereof.

20 [00178] In another embodiment, a method of the present invention comprises promoting oligodendrocyte proliferation, differentiation or survival. In another embodiment, a method of the present invention comprises promoting oligodendrocyte proliferation, differentiation or survival with a compound of formula (I) or (IV) or a composition thereof. In another embodiment, a method of the present invention is useful for treating or lessening the severity of a disease or disorder selected from a disease or disorder associated with a lack of oligodendrocyte proliferation, differentiation or survival comprising administering a therapeutically effective amount of the compounds of formula (I) or (IV) or compositions thereof to a subject

25

30 in need thereof.

[00179] In another embodiment, a method of the present invention comprises promoting myelination by contacting neuronal cells, oligodendrocyte cells or oligodendrocyte precursor cells. In one embodiment, a method of the present invention comprises promoting myelination by contacting neuronal cells,

oligodendrocyte cells or oligodendrocyte precursor cells with a compound of formula (I) or (IV) or a composition thereof.

[00180] In another embodiment, a method of the present invention comprises promoting survival of cells of the nervous system. In another embodiment, a method of the present invention comprises promoting survival of cells of the nervous system comprising contacting the cells with a compound or composition of formula (I) or (IV). In one embodiment, the cells of the nervous system comprise brain cells, cortical neurons, oligodendrocytes or oligodendrocyte precursor cells.

[00181] In another embodiment, a method of the present invention is useful for treating or lessening the severity of a disease or disorder selected from a disease or condition associated with demyelination comprising administering a therapeutically effective amount of the compounds of formula (I) or (IV) or compositions thereof to a subject in need thereof. In one embodiment, the disease or condition associated with demyelination is a CNS disorder or a CNS demyelinating disease as described herein. In one embodiment, the disease is multiple sclerosis.

[00182] In another embodiment, the subject has, or is at risk of having, multiple sclerosis. The subject with multiple sclerosis can be at any stage of treatment or disease. In one embodiment, the subject with multiple sclerosis has one or more of: benign multiple sclerosis, relapsing remitting multiple sclerosis, quiescent relapsing remitting multiple sclerosis, active relapsing remitting multiple sclerosis, primary progressive multiple sclerosis, or secondary progressive multiple sclerosis, clinically isolated syndrome, or clinically defined multiple sclerosis. In one embodiment, the type of multiple sclerosis is primary progressive multiple sclerosis. In another embodiment, the type of multiple sclerosis is relapsing-remitting multiple sclerosis. In yet another embodiment, the type of multiple sclerosis is secondary progressive multiple sclerosis. In still a further embodiment, the type of multiple sclerosis is progressive relapsing multiple sclerosis. In another embodiment, the subject is asymptomatic. In another embodiment, the subject has one or more multiple sclerosis-like symptoms, such as those having clinically isolated syndrome or clinically defined multiple sclerosis. In yet other embodiments, the subject has one or more multiple sclerosis relapses.

[00183] In another embodiment, the subject has a relapsing form of multiple sclerosis such as relapsing remitting multiple sclerosis or relapsing secondary

progressive multiple sclerosis. In one embodiment, the subject has relapsing remitting multiple sclerosis and has one or more ongoing clinical exacerbations. In another embodiment, the subject has relapsing remitting multiple sclerosis and one or more subclinical activities. In one embodiment, the clinical exacerbation or subclinical activity is shown by gadolinium enhancement of white matter lesions using T1/T2 magnetic resonance imaging. In another embodiment, the clinical exacerbation or subclinical activity is shown by development of new or enlarged white matter lesions on magnetic resonance imaging of the brain or spinal cord. In one embodiment, the development of new or enlarged white matter lesions is monitored by T1/T2 magnetic resonance imaging. In another embodiment, the development of new or enlarged white matter lesions is monitored by Proton Density magnetic resonance imaging. In yet another embodiment, the development of new or enlarged white matter lesions is monitored by MTR magnetic resonance imaging. See also, Gaitán, M. I. and Reich, D. S. (2014) MRI in Diagnosis and Disease Monitoring, in Multiple Sclerosis and CNS Inflammatory Disorders (eds L. M. Samkoff and A. D. Goodman), John Wiley & Sons, Ltd., Chichester, UK.

doi: 10.1002/9781118298633.ch4 which is incorporated herein in its entirety by reference.

[00184] In another embodiment, the clinical exacerbations or subclinical activities are monitored by a functional readout such as ambulatory changes (gait changes, sway changes, etc.), T25W changes and/or EDSS changes. In another embodiment, the clinical exacerbations or subclinical activities are monitored by a visual evoked potential assay, a visual acuity assay or a measurement of optic nerve thickness. In another embodiment, the clinical exacerbations or subclinical activities are monitored by a myelin labelling assay.

[00185] In another embodiment, the subject with multiple sclerosis can be at any stage of treatment or disease and treatment with compounds of formula (I) or (IV) of the present invention result in improvement of the disease or symptoms. In one embodiment, improvement in the disease or symptoms is evidenced by a reduction or disappearance of one or more white matter lesions in the brain. In another embodiment, improvement in the disease or symptoms is evidenced by improved function such as improved ambulation, improved gait, reduced sway, improved T25W scores or improved EDSS scores. In another embodiment, improvement in the

disease or symptoms is evidenced by improvements in a visual acuity assay or a visual evoked potential assay. In another embodiment, improvement in the disease or symptoms is evidenced by enhanced optic nerve thickness. In another embodiment, improvement in the disease or symptoms is evidenced by increased myelination in a myelin labelling assay.

[00186] In another embodiment, the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein are useful for promoting myelin regeneration in progressive demyelinating diseases. In one embodiment, the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein are useful for promoting myelin regeneration in primary progressive multiple sclerosis. In another embodiment, the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein are useful for promoting myelin regeneration in secondary progressive multiple sclerosis. In another embodiment, the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein are useful for promoting myelin regeneration in relapsing-remitting multiple sclerosis. In another embodiment, the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein are useful for promoting myelin regeneration in progressive relapsing multiple sclerosis.

[00187] In yet another embodiment, the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein are useful for promoting remyelination at the cellular level wherein oligodendrocyte cells are stimulated to regenerate or differentiate. In another embodiment, the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein are useful for promoting remyelination at the cellular level wherein oligodendrocyte cells are stimulated to remyelinate axons.

[00188] In another embodiment, the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein are useful for promoting remyelination at the cellular level whereby oligodendrocyte cells are stimulated to regenerate or differentiate thereby treating demyelinating diseases or disorders. In yet another embodiment, the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein are useful

for promoting remyelination at the cellular level whereby axons are remyelinated by oligodendrocyte cells thereby treating demyelinating diseases or disorders.

[00189] In another embodiment, the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein are useful for
5 inducing endogenous oligodendrocytes or oligodendrocyte precursor cells to contact an axon and produce myelin.

[00190] In another aspect, the present invention provides a method of treating or lessening the severity of, in a subject, a disease or disorder selected from a demyelinating disease, central pontine myelinolysis, a nerve injury disease or
10 disorder, a leukoencephalopathy or a leukodystrophy comprising administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula (I) or (IV).

[00191] In one aspect, the present invention provides a method of treating or lessening the severity of, in a subject, a disease or disorder selected from spinal cord
15 injury, stroke, multiple sclerosis, progressive multifocal leukoencephalopathy, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelinolysis, hypoxic demyelination, ischemic demyelination, neuromyelitis optica, adrenoleukodystrophy, Alexander's disease, Niemann-Pick disease, Pelizaeus Merzbacher disease, periventricular leukomalacia,
20 globoid cell leukodystrophy (Krabbe's disease), Wallerian degeneration, optic neuritis, transverse myelitis, amyotrophic lateral sclerosis (Lou Gehrig's disease), Huntington's disease, Alzheimer's disease, Parkinson's disease, Tay-Sacks disease, Gaucher's disease, Hurler Syndrome, traumatic brain injury, post radiation injury, neurologic complications of chemotherapy, neuropathy, acute ischemic optic neuropathy,
25 neuromyelitis optica, vitamin B12 deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, Leber's hereditary optic atrophy/Leber congenital amaurosis, Marchiafava-Bignami syndrome, metachromatic leukodystrophy, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, schizophrenia, cerebral ischemia, multiple system atrophy, traumatic glaucoma,
30 tropical spastic paraparesis/human T-lymphotropic virus 1 (HTLV-1) associated myelopathy, essential tremor or osmotic hyponatremia comprising administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula (I) or (IV).

[00192] In another aspect, the present invention provides a method of treating, preventing or ameliorating one or more symptoms of multiple sclerosis or another neurodegenerative disease selected from auditory impairment, optic neuritis, decreased visual acuity, diplopia, nystagmus, ocular dysmetria, internuclear ophthalmoplegia, movement and sound phosphenes, afferent pupillary defect, paresis, monoparesis, paraparesis, hemiparesis, quadraparesis, plegia, paraplegia, hemiplegia, tetraplegia, quadraplegia, spasticity, dysarthria, motor dysfunction, walking impairment, muscle atrophy, spasms, cramps, hypotonia, clonus, myoclonus, myokymia, restless leg syndrome, gait disturbances, footdrop, dysfunctional reflexes, paraesthesia, anaesthesia, neuralgia, neuropathic and neurogenic pain, L'hermitte's, proprioceptive dysfunction, trigeminal neuralgia, ataxia, intention tremor, dysmetria, vestibular ataxia, vertigo, speech ataxia, dystonia, disability progression, dysdiadochokinesia, frequent micturation, bladder spasticity, flaccid bladder, detrusor- sphincter dyssynergia, erectile dysfunction or anorgasmy comprising administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula (I) or (IV).

[00193] In yet another aspect, the present invention provides a method of treating or lessening the severity of, in a subject, a disease or disorder selected from a demyelinating disease, central pontine myelinolysis, a nerve injury disease or disorder, a leukoencephalopathy or a leukodystrophy comprising administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula (I) or (IV) with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition.

[00194] In another aspect, the present invention provides a method of treating or lessening the severity of, in a subject, a disease or disorder selected from spinal cord injury, stroke, multiple sclerosis, progressive multifocal leukoencephalopathy, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelolysis, hypoxic demyelination, ischemic demyelination, neuromyelitis optica, adrenoleukodystrophy, Alexander's disease, Niemann-Pick disease, Pelizaeus Merzbacher disease, periventricular leukomalacia, globoid cell leukodystrophy (Krabbe's disease), Wallerian degeneration, optic neuritis, transverse myelitis, amyotrophic lateral sclerosis (Lou Gehrig's disease), Huntington's

- disease, Alzheimer's disease, Parkinson's disease, Tay-Sacks disease, Gaucher's disease, Hurler Syndrome, traumatic brain injury, post radiation injury, neurologic complications of chemotherapy, neuropathy, acute ischemic optic neuropathy, neuromyelitis optica, vitamin B12 deficiency, isolated vitamin E deficiency
- 5 syndrome, Bassen-Kornzweig syndrome, Leber's hereditary optic atrophy/Leber congenital amaurosis, Marchiafava-Bignami syndrome, metachromatic leukodystrophy, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, schizophrenia, cerebral ischemia, multiple system atrophy, traumatic glaucoma, tropical spastic paraparesis/human T-lymphotropic virus 1 (HTLV-1) associated
- 10 myelopathy, essential tremor or osmotic hyponatremia comprising administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula (I) or (IV) with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition.
- 15 **[00195]** In another aspect, the present invention provides a method of treating or lessening the severity of, in a subject, a type of multiple sclerosis selected from primary progressive multiple sclerosis, relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis or progressive relapsing multiple sclerosis. In one aspect, the type of multiple sclerosis is primary progressive multiple sclerosis.
- 20 In another aspect, the type of multiple sclerosis is relapsing-remitting multiple sclerosis. In yet another aspect, the type of multiple sclerosis is secondary progressive multiple sclerosis. In still a further aspect, the type of multiple sclerosis is progressive relapsing multiple sclerosis.
- [00196]** In another aspect, the present invention provides a method for treating,
- 25 preventing or ameliorating one or more symptoms of multiple sclerosis or another neurodegenerative disease selected from auditory impairment, optic neuritis, decreased visual acuity, diplopia, nystagmus, ocular dysmetria, internuclear ophthalmoplegia, movement and sound phosphenes, afferent pupillary defect, paresis, monoparesis, paraparesis, hemiparesis, quadraparesis, plegia, paraplegia, hemiplegia,
- 30 tetraplegia, quadraplegia, spasticity, dysarthria, motor dysfunction, walking impairment, muscle atrophy, spasms, cramps, hypotonia, clonus, myoclonus, myokymia, restless leg syndrome, gait disturbances, footdrop, dysfunctional reflexes, paraesthesia, anaesthesia, neuralgia, neuropathic and neurogenic pain, L'hermitte's,

proprioceptive dysfunction, trigeminal neuralgia, ataxia, intention tremor, dysmetria, vestibular ataxia, vertigo, speech ataxia, dystonia, disability progression, dysdiadochokinesia, frequent micturation, bladder spasticity, flaccid bladder, detrusor- sphincter dyssynergia, erectile dysfunction or anorgasmy comprising

5 administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula (I) or (IV) with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition.

10 *Manufacture of Medicaments*

[00197] In one aspect, the present invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity of, in a subject, a disease or disorder selected from a demyelinating disease, central pontine myelinolysis, a nerve injury disease or

15 disorder or a leukoencephalopathy.

[00198] In another aspect, the present invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity of, in a subject, a disease or disorder selected from spinal cord injury, stroke, multiple sclerosis, progressive multifocal

20 leukoencephalopathy, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelolysis, hypoxic demyelination, ischemic demyelination, neuromyelitis optica, adrenoleukodystrophy, Alexander's disease, Niemann-Pick disease, Pelizaeus Merzbacher disease, periventricular leukomalacia, globoid cell leucodystrophy (Krabbe's disease), Wallerian degeneration,

25 optic neuritis, transverse myelitis, amyotrophic lateral sclerosis (Lou Gehrig's disease), Huntington's disease, Alzheimer's disease, Parkinson's disease, Tay-Sacks disease, Gaucher's disease, Hurler Syndrome, traumatic brain injury, post radiation injury, neurologic complications of chemotherapy, neuropathy, acute ischemic optic neuropathy, neuromyelitis optica, vitamin B12 deficiency, isolated vitamin E

30 deficiency syndrome, Bassen-Kornzweig syndrome, Leber's hereditary optic atrophy/Leber congenital amaurosis, Marchiafava-Bignami syndrome, metachromatic leukodystrophy, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, schizophrenia, cerebral ischemia, multiple system atrophy, traumatic glaucoma,

tropical spastic paraparesis/human T-lymphotropic virus 1 (HTLV-1) associated myelopathy, essential tremor or osmotic hyponatremia.

[00199] In another aspect, the present invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating, preventing or ameliorating one or more symptoms of multiple sclerosis or another neurodegenerative disease selected from auditory impairment, optic neuritis, decreased visual acuity, diplopia, nystagmus, ocular dysmetria, internuclear ophthalmoplegia, movement and sound phosphenes, afferent pupillary defect, paresis, monoparesis, paraparesis, hemiparesis, quadraparesis, plegia, paraplegia, hemiplegia, tetraplegia, quadraplegia, spasticity, dysarthria, motor dysfunction, walking impairment, muscle atrophy, spasms, cramps, hypotonia, clonus, myoclonus, myokymia, restless leg syndrome, gait disturbances, footdrop, dysfunctional reflexes, paraesthesia, anaesthesia, neuralgia, neuropathic and neurogenic pain, L'hermitte's, proprioceptive dysfunction, trigeminal neuralgia, ataxia, intention tremor, dysmetria, vestibular ataxia, vertigo, speech ataxia, dystonia, disability progression, dysdiadochokinesia, frequent micturation, bladder spasticity, flaccid bladder, detrusor- sphincter dyssynergia, erectile dysfunction or anorgasmy.

[00200] In yet another aspect, the present invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament in combination with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition.

[00201] In one aspect, the present invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity of, in a subject, a disease or disorder selected from a demyelinating disease, central pontine myelinolysis, a nerve injury disease or disorder or a leukoencephalopathy with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition.

[00202] In another aspect, the present invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity of, in a subject, a disease or disorder selected from spinal cord injury, stroke, multiple sclerosis, progressive multifocal

leukoencephalopathy, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelolysis, hypoxic demyelination, ischemic demyelination, neuromyelitis optica, adrenoleukodystrophy, Alexander's disease, Niemann-Pick disease, Pelizaeus Merzbacher disease, periventricular leukomalacia, globoid cell leucodystrophy (Krabbe's disease), Wallerian degeneration, optic neuritis, transverse myelitis, amyotrophic lateral sclerosis (Lou Gehrig's disease), Huntington's disease, Alzheimer's disease, Parkinson's disease, Tay-Sachs disease, Gaucher's disease, Hurler Syndrome, traumatic brain injury, post radiation injury, neurologic complications of chemotherapy, neuropathy, acute ischemic optic neuropathy, neuromyelitis optica, vitamin B12 deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, Leber's hereditary optic atrophy/Leber congenital amaurosis, Marchiafava-Bignami syndrome, metachromatic leukodystrophy, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, schizophrenia, cerebral ischemia, multiple system atrophy, traumatic glaucoma, tropical spastic paraparesis/human T-lymphotropic virus 1 (HTLV-1) associated myelopathy, essential tremor or osmotic hyponatremia in combination with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition.

[00203] In another aspect, the present invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity of, in a subject, a type of multiple sclerosis selected from primary progressive multiple sclerosis, relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis or progressive relapsing multiple sclerosis. In one aspect, the type of multiple sclerosis is primary progressive multiple sclerosis. In another aspect, the type of multiple sclerosis is relapsing-remitting multiple sclerosis. In yet another aspect, the type of multiple sclerosis is secondary progressive multiple sclerosis. In still a further aspect, the type of multiple sclerosis is progressive relapsing multiple sclerosis.

[00204] In yet another aspect, the present the present invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating, preventing or ameliorating one or more symptoms of multiple sclerosis or another neurodegenerative disease selected from auditory impairment, optic neuritis, decreased visual acuity, diplopia, nystagmus, ocular

dysmetria, internuclear ophthalmoplegia, movement and sound phosphenes, afferent pupillary defect, paresis, monoparesis, paraparesis, hemiparesis, quadraparesis, plegia, paraplegia, hemiplegia, tetraplegia, quadraplegia, spasticity, dysarthria, motor dysfunction, walking impairment, muscle atrophy, spasms, cramps, hypotonia, clonus, myoclonus, myokymia, restless leg syndrome, gait disturbances, footdrop, dysfunctional reflexes, paraesthesia, anaesthesia, neuralgia, neuropathic and neurogenic pain, L'hermitte's, proprioceptive dysfunction, trigeminal neuralgia, ataxia, intention tremor, dysmetria, vestibular ataxia, vertigo, speech ataxia, dystonia, disability progression, dysdiadochokinesia, frequent micturation, bladder spasticity, flaccid bladder, detrusor- sphincter dyssynergia, erectile dysfunction or anorgasmy in combination with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition.

15 *Administration of Pharmaceutically acceptable salts and Compositions*

[00205] In certain embodiments of the invention an "effective amount" of the compound, a pharmaceutically acceptable salt thereof or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of, in a subject, a disease or disorder selected from one or more of a demyelinating disease, central pontine myelinolysis, a nerve injury disease or disorder or a leukoencephalopathy.

[00206] The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of

the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal,
5 preferably a mammal, and most preferably a human

[00207] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of
10 the disease being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00208] Liquid dosage forms for oral administration include, but are not limited to,
15 pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn,
20 germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00209] Injectable preparations, for example, sterile injectable aqueous or
25 oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are
30 water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or

diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00210] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00211] In order to prolong the effect of a compound of the invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00212] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00213] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar,

calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00214] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00215] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00216] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are prepared by dissolving or dispensing the compound in the proper medium.

10 Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Additional Therapeutic Agents

15 [00217] It will also be appreciated that the the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with

20 another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated.” Additional appropriate therapeutic agents or approaches are described generally in The Merck

25 Manual, Nineteenth Edition, Ed. Robert S. Porter and Justin L. Kaplan, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., 2011, and the Food and Drug Administration website, www.fda.gov, the entire contents of which are hereby incorporated by reference.

30

[00218] In one embodiment, the additional therapeutic agents is an immunomodulatory agent, such as an IFN- β 1 molecule including but not limited to an interferon beta 1a (Avonex®, Rebif®) or an interferon beta 1b (Betaseron®, Betaferon®, Extavia®). Immunomodulatory agents also include other interferons and
5 fragments, analogues, homologues, derivatives, and natural variants thereof with substantially similar biological activity to interferon beta 1a molecules.

[00219] In another embodiment, the additional therapeutic agent is a polymer of glutamic acid, lysine, alanine and tyrosine such as glatiramer acetate (Copaxone®).

[00220] In another embodiment, the additional therapeutic agent is an antibody or
10 fragment thereof against α -4 integrin (e.g., natalizumab (Tysabri®)).

[00221] In another embodiment, the additional therapeutic agent is an anthracenedione molecule such as mitoxantrone (Novantrone®).

[00222] In another embodiment, the additional therapeutic agent is a sphingosine 1-phosphate receptor modulator such as fingolimod (Gilenya®) and those described in
15 WO 2012/109108 the entire contents of which is hereby incorporated by reference.

[00223] In another embodiment, the additional therapeutic agent is a dimethyl fumarate such as an oral dimethyl fumarate (Tecfidera®).

[00224] In another embodiment, the additional therapeutic agent is an antibody to the α subunit of the IL-2 receptor of T cells such as daclizumab (Zenapax®).

20 [00225] In another embodiment, the additional therapeutic agent is an antibody against CD52 such as alemtuzumab (Lemtrada®).

[00226] In another embodiment, the additional therapeutic agent is an inhibitor of a dihydroorotate dehydrogenase such as teriflunomide (Aubagio®).

[00227] In another embodiment, the additional therapeutic agent is an antibody to
25 CD20 such as ocrelizumab, rituximab or ofatumumab.

[00228] In another embodiment, the additional therapeutic agent is a corticosteroid such as, but not limited to methylprednisolone, Depo-Medrol®, Solu-Medrol®, Deltasone®, Delta-Cortef®, Medrol®, Decadron® or Acthar®.

[00229] In another embodiment, the additional therapeutic agent is an anti-VLA4
30 antibody, such as Natalizumab (Tysabri®) or a related VLA-4 antibodies such as those described in US 5,840,299, US 6,602,503, Sanchez-Madrid et al, (1986) Eur. J. Immunol 16: 1343-1349; Hemler et al, (1987) J Biol. Chem. 262: 11478-11485; Issekutz et al. (1991) J Immunol 147: 109 (TA-2 mab); Pulido et al. (1991) J Biol. Chem. 266:

10241-10245; and U.S. Pat. No. 5,888,507 the entire contents of each patent or publication hereby incorporated by reference in their entirety.

[00230] In another embodiment, the additional therapeutic agent is a LINGO-1 antagonist (e.g., an antibody against LINGO (e.g., LINGO-1, LINGO-2, LINGO-3, 5 LINGO-4) or a Nogo receptor-1 (NgR1) modulator and compositions thereof such as those disclosed in WO2004/085648, WO2006/002437, WO2007/008547, WO2007/025219, WO2007/064882, WO2007/056161, WO2007/133746, WO2007/098283, WO2008/086006, WO2009/061500, WO2010/005570, WO2010/062904, WO 2013/173364, WO2014/058875, each of which is hereby 10 incorporated by reference in its entirety.

[00231] In another embodiment, the additional therapeutic agent is a TAJ modulator, such as those disclosed in WO2006/017673, which is hereby incorporated by reference in its entirety.

[00232] In another embodiment, the additional therapeutic agent is a TrkA 15 antagonist such as those disclosed in WO2008/013782 or a TrkB antagonist such as those disclosed in WO2009/048605, each of which is hereby incorporated by reference in its entirety.

[00233] In another embodiment, the additional therapeutic agent is a sclerostin modulator such as those disclosed in WO2013/063095, which is hereby incorporated 20 by reference in its entirety.

[00234] In another embodiment, the additional therapeutic agent is an autotaxin (ATX) inhibitor or LPA receptor antagonist, such as those described in WO2015048301, WO2015042053, WO2015042052, WO2015008230, WO2015008229, WO2014202458, WO2014139882, WO2014133112, 25 WO2014097151, WO2014110000, WO2014/081756, WO2014/081752, WO2014/048865, WO2014168824, WO2014143583, WO2014139978, WO2013/186159, WO2012/024620, WO2012/166415, WO2012078593, WO2012078805, WO2012024620, WO2013070879, WO2013/061297, WO2013/054185, WO2014/018881, WO2014/018887, WO2014/018891, 30 WO2014/025708, WO2014/025709, WO2014/152725, WO2012028243, WO2012005227, WO2011/159635, WO2011/159550, WO2011116867, WO2011053948, WO2011041729, WO2011041694, WO2011041462, WO2011041461, WO2011017561, WO2011017350, WO2010115491,

WO2011006569, WO20110141761, WO2010112124, WO2010112116,
WO2010077883, WO2010077882, WO2010068775, WO2010063352,
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5 2010/141768, US2006/194850, US 2003/114505, US 2004/122236, US 2006/194850,
US 6964945, US2005/0256160, US 2006/148830, US 2008/0293764,
US2010/0249157, the disclosure of each patent application and patent hereby
incorporated by reference in its entirety.

[00235] In another embodiment, the additional therapeutic agent is a Nox4
10 modulator such as those described in WO2013/037499, which is hereby incorporated
by reference in its entirety.

[00236] In another embodiment, the additional therapeutic agent is a remyelinating
antibody such as rHIgM22.

[00237] In another embodiment, the additional therapeutic agent is dalfampridine
15 (Ampyra®)

[00238] In another embodiment, the additional therapeutic agent is a death receptor
6 (DR6) antagonist, a p75 antagonist or a combination thereof such as those disclosed
in US8894999 and WO2014106104 each of which is incorporated herein by reference
in its entirety.

20 [00239] In another embodiment, the additional therapeutic agent is Cethrin™.

[00240] In another embodiment, the additional therapeutic agent is an activin
receptor modulator such as those described in WO2015/001352, which is hereby
incorporated by reference in its entirety.

[00241] In another embodiment, the additional therapeutic agent is a GLP-1 like
25 peptide or a derivative of GLP-1 like peptides such as those disclosed in
WO2015/000942, WO2014/202727, WO2012/140117, WO2012/062803, WO
2012/062804, WO2011/080102 and WO2009/030771, each of which is incorporated
herein by reference in its entirety. In another embodiment, the GLP-1 derivative is
Liraglutide or Semaglutide.

30 [00242] In another embodiment, the additional therapeutic agent is a RXR
modulator such as those disclosed in US2015/0038585 and WO2013056232 each of
which is incorporated herein by reference in its entirety. In another embodiment, the
RXR modulator is HX630.

[00243] In another embodiment, the additional therapeutic agent is an activator of the NRF2/KEAP1/ARE pathway such as those disclosed in WO2014/197818 which is hereby incorporated by reference in its entirety.

5 [00244] In another embodiment, the additional therapeutic agent is a PPAR agonist such as those disclosed in WO2014/165827 which is hereby incorporated by reference in its entirety.

[00245] In another embodiment, the additional therapeutic agent is an inhibitor of HDAC4 such as those disclosed in WO2013/080120 which is hereby incorporated by reference in its entirety.

10 [00246] In another embodiment, the additional therapeutic agent is a gamma secretase inhibitor such as DAPT.

[00247] In another embodiment, the additional therapeutic agent is an antipsychotic medication such as quetiapine.

15 [00248] In another embodiment, the additional therapeutic agent is a thyroid hormone.

[00249] In another embodiment, the additional therapeutic agent is a thyroid translocator protein (TSPO) such as etifoxine.

[00250] In another embodiment, the additional therapeutic agent is insulin-like growth factor 1 (IGF-1).

20 [00251] In another embodiment, the additional therapeutic agent is an anticholinergic such as benztropine.

[00252] In another embodiment, the additional therapeutic agent is an antihistamine/anticholinergic such as clemastine or clemastine fumarate.

25 [00253] In another embodiment, the additional therapeutic agent is one that removes aquaporin by plasmapheresis.

[00254] In another embodiment, the additional therapeutic agent is a hyaluronan inhibitor or antagonist such as those described in WO2015023691, which is hereby incorporated by reference in its entirety.

30 [00255] In another embodiment, the additional therapeutic agent is a hyaluronidase inhibitor such as a PH20 inhibitor or those described in WO2013/102144, WO2011/133862, and WO2010/007729 each of which is hereby incorporated by reference in its entirety.

[00256] In another embodiment, the additional therapeutic agent is a Toll-Like Receptor-2 (TLR-2) inhibitor.

[00257] In another embodiment, the additional therapeutic agent is a Semaphorin 3A antagonist or antibody such as those disclosed in WO2014123186, which is
5 hereby incorporated by reference in its entirety.

[00258] In another embodiment, the additional therapeutic agent is a CXCR2 inhibitor or antagonist.

[00259] In another embodiment, the additional therapeutic agent is a Semaphorin 3F agonist.

10 [00260] In another embodiment, the additional therapeutic agent is a Wnt polypeptide or Wnt inhibitor such as those disclosed in WO 2013/040309 and WO 2012/097093, each of which is hereby incorporated by reference in its entirety.

[00261] In another embodiment, the additional therapeutic agent is a mitochondrial pore modulator such as Olesoxime.

15 [00262] In another embodiment, the additional therapeutic agent is a PSA NCAM antagonist, a CXCR2 inhibitor or antagonist, a MRF agonist, a GM-98 agonist, a Tcf4 inhibitor, a retinoid, a neuregulin 1-erbB signaling modulator, a zpf191 activator, an miR219 activator, an miR338 activator or an miR138 activator.

[00263] In certain embodiments, the additional agent is an immunomodulatory
20 agent such as an IFN- β 1 molecule which is administered intravenously, subcutaneously or intramuscularly. In one embodiment, the IFN- β 1 molecule is administered at 20-45 microgram once a week by intramuscular injection. In another embodiment, the IFN- β 1 molecule is administered at 20-30 microgram three times a week by intramuscular injection. In another embodiment, the IFN- β 1 molecule is
25 administered at 40-50 micrograms once a week, by subcutaneous injection.

[00264] In another embodiment, the IFN- β 1 molecule is administered in an amount of between 10 and 50 μ g intramuscularly three times a week.

[00265] In another embodiment, the IFN- β 1 molecule is administered in an amount of between 10 and 50 μ g intramuscularly every five to ten days.

30 [00266] In another embodiment, the IFN- β 1 molecule is administered in an amount between 200 and 600 μ g every other day by subcutaneous injection. In one embodiment, the IFN- β 1 molecule is an interferon β -1b (Betaseron®, Betaferon®, or Extavia®).

[00267] These combinations are useful for treating or lessening the severity of, in a subject, the diseases described herein including neurodegenerative diseases such as multiple sclerosis. These combinations are also useful in the kits described herein.

[00268] It will also be appreciated that the the compounds of formula (I) or (IV) of the present invention and the methods, compositions and kits disclosed herein can be employed in combination therapies to not only treat or lessen the severity of, in a subject, the diseases described herein but may also be used in symptom management. Those additional agents include those useful for treating symptoms such as bladder problems (e.g., Botox®, DDAVP Nasal Spray®, Detrol®, Ditropan®, Ditropan XL®, Enablex®, Flomax®, Hytrin®, Minipress®, Oxytrol®, Pro-Banthine®, Sanctura®, Tofranil®, Vesicare®); infections (Bactrim®, Septra®, Cipro®, Macrodantin®, Hiprex®, Pyridium®); bowel dysfunction (Colace®, Dulcolax®, Enemeez®, Fleet enema, Mineral oil, Metamucil®, Milk of Magnesia®, glycerin suppositories); depression (Cymbalta®, Effexor®, Paxil®, Prozac®, Wellbutrin®, Zoloft®); dizziness and vertigo (Antivert®); emotional changes (Nuedexta®), Fatigue (Amantadine®, Provigil®, Prozac®), itching (Atarax®); pain (Dilantin®, Elavil®, Klonopin®, Neurontin®, Pamelor®, Aventyl®, Tegetrol®); sexual problems (Cialis®, Levitra®, Papaverine®, MUSE®, Prostin VR®, Viagra®); spasticity (Dantrium®, Gablofen®, Klonopin®, Lioresal®, Valium®, Zanaflex®); tremors (Laniazid®, Nydrasid®, Klonopin®, Rivotril®); and walking or gait difficulties (Ampyra®).

[00269] The amount of additional therapeutic agent present in or with the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00270] In another aspect, the present invention features a kit comprising a compound and/or pharmaceutical composition of formula (I) or (IV) of the present invention and instructions for use thereof.

[00271] In another embodiment, the kits of the present invention further comprise one or more additional therapeutic agent(s). In another embodiment, the additional

therapeutic agent is selected from an immunomodulatory agent, such as an IFN- β 1 molecule including but not limited to an interferon beta 1a (Avonex®, Rebif®) or an interferon beta 1b (Betaseron®, Betaferon®, Extavia®).

[00272] In another embodiment, the additional therapeutic agent is a polymer of
5 glutamic acid, lysine, alanine and tyrosine such as glatiramer acetate (Copaxone®).

[00273] In another embodiment, the additional therapeutic agent is an antibody or fragment thereof against alpha-4 integrin (e.g., natalizumab (Tysabri®)).

[00274] In another embodiment, the additional therapeutic agent is an anthracenedione molecule such as mitoxantrone (Novantrone®).

10 [00275] In another embodiment, the additional therapeutic agent is a sphingosine 1-phosphate receptor modulator such as fingolimod (Gilenya®) and those described in WO 2012/109108 the entire contents of which is hereby incorporated by reference.

[00276] In another embodiment, the additional therapeutic agent is a dimethyl fumarate such as an oral dimethyl fumarate (Tecfidera®).

15 [00277] In another embodiment, the additional therapeutic agent is an antibody to the alpha subunit of the IL-2 receptor of T cells such as daclizumab (Zenapax®).

[00278] In another embodiment, the additional therapeutic agent is an antibody against CD52 such as alemtuzumab (Lemtrada®).

[00279] In another embodiment, the additional therapeutic agent is an inhibitor of a
20 dihydroorotate dehydrogenase such as teriflunomide (Aubagio®).

[00280] In another embodiment, the additional therapeutic agent is an antibody to CD20 such as ocrelizumab, rituximab or ofatumumab.

[00281] In another embodiment, the additional therapeutic agent is a corticosteroid such as, but not limited to methylprednisolone, Depo-Medrol®, Solu-Medrol®,
25 Deltasone®, Delta-Cortef®, Medrol®, Decadron® or Acthar®.

[00282] In another embodiment, the additional therapeutic agent is one or more compounds useful for treating symptoms of the disease such as bladder problems (e.g., Botox®, DDAVP Nasal Spray®, Detrol®, Ditropan®, Ditropan XL®, Enablex®, Flomax®, Hytrin®, Minipress®, Oxytrol®, Pro-Banthine®, Sanctura®,
30 Tofranil®, Vesicare®); infections (Bactrim®, Septra®, Cipro®, Macrodantin®, Hiprex®, Pyridium®); bowel dysfunction (Colace®, Dulcolax®, Enemeez®, Fleet enema, Mineral oil, Metamucil®, Milk of Magnesia®, glycerin suppositories); depression (Cymbalta®, Effexor®, Paxil®, Prozac®, Wellbutrin®, Zoloft®);

dizziness and vertigo (Antivert®); emotional changes (Nuedexta®), Fatigue (Amantadine®, Provigil®, Prozac®), itching (Atarax®); pain (Dilantin®, Elavil®, Klonopin®, Neurontin®, Pamelor®, Aventyl®, Tegetrol®); sexual problems (Cialis®, Levitra®, Papaverine®, MUSE®, Prostin VR®, Viagra®); spasticity (Dantrium®, Gablofen®, Klonopin®, Lioresal®, Valium®, Zanaflex®); tremors (Laniazid®, Nydrasid®, Klonopin®, Rivotril®); or walking or gait difficulties (Ampyra®).

[00283] In another embodiment, the kits of the present invention are drawn to kits wherein the compounds or the pharmaceutical compositions of the present invention and the one or more additional therapeutic agent(s) are in separate containers.

[00284] In another embodiment, the kits of the present invention are drawn to kits wherein the compounds or the pharmaceutical compositions of the present invention and the one or more additional therapeutic agent(s) are in the same container.

[00285] In another embodiment, the container is a bottle, vial, or blister pack, or combination thereof.

SCHEMES AND EXAMPLES

The compounds of the invention may be readily prepared by known methods and by using the following methods, schemes and examples. Illustrated below in Scheme A through Scheme Q are general methods for preparing the compounds of the present invention. Compounds were named using either IUPAC nomenclature or the nomenclature used in ChemBioDraw Ultra (Version 12.0.2.1076, CambridgeSoft®).

EXAMPLES

General methods. ¹H NMR (obtained on a Bruker 400MHz Advance III QNP probe 1H/13C/19F or a Bruker 300MHz Advance I QNP probe 1H/13C/19F) spectra were obtained as solutions in an appropriate deuterated solvent such as dimethyl sulfoxide-*d*₆ (DMSO-D₆ or DMSO-*d*₆). Mass spectra (MS) were obtained using a Waters Acquity UPLC-MS system equipped with a Waters 3100 mass detector and one of the following HPLC (High Performance Liquid Chromatography) or UPLC (Ultra Performance Liquid Chromatography) methods:

UPLC method A: Mobile phase A: water (0.1 % trifluoroacetic acid). Mobile phase B: acetonitrile (0.1 % trifluoroacetic acid). Column: Waters Acquity CSH C18, 2.1 x

50 mm, 1.7 μ m particle size. Flow rate = 0.6 mL/min, injection volume = 2 μ L, and column temperature = 25 °C. Gradient 5%-95% Phase B 1.4 minutes.

UPLC method B: Mobile phase A: water (0.1 % trifluoroacetic acid). Mobile phase B: acetonitrile (0.1 % trifluoroacetic acid). Column: Waters Acquity CSH C18, 2.1 x 50 mm, 1.7 μ m particle size. Flow rate = 0.6 mL/min, injection volume = 2 μ L, and column temperature = 25 °C. Gradient 10-60% phase B over 1.4 minutes.

UPLC method C: Mobile phase A: water (0.1 % trifluoroacetic acid). Mobile phase B: acetonitrile (0.1 % trifluoroacetic acid). Column 4.6 x 100mm Sunfire C18 column. Flow rate = 1.5 mL/min. Gradient 2-98% phase B over 3.8 minutes.

UPLC method D: Mobile Phase A: 95% water [50 mM ammonium formate pH 9]: 5% acetonitrile. Mobile Phase B: acetonitrile. Column: Waters Acquity BEH C8, 2.1 x 50 mm, 1.7 μ m particle size. Flow rate=0.6ml/min ; Injection Volume: 2 μ L. Gradient 5-95% phase B over 1.4 minutes.

UPLC method E: Mobile Phase A: water (0.1 % trifluoroacetic acid). Mobile phase B: acetonitrile (0.1 % trifluoroacetic acid); Column: Waters Acquity CSH Fluoro-Phenyl, 2.1 x 50 mm, 1.7 μ m particle size; Flow rate=0.6ml/min ; Injection Volume: 2 μ L; Gradient 5-95% phase B over 1.4 minutes.

HPLC method F: Mobile phase A: water (0.1 % trifluoroacetic acid). Mobile phase B: acetonitrile (0.1 % trifluoroacetic acid). Column: Waters Xselect C18, 4.6 x 50 mm, 5 μ m particle size. Flow rate = 1.5 mL/min, injection volume = 10 μ L. Gradient 5-95% phase B over 3 minutes.

Normal phase silica gel flash chromatography was performed using pre-packed Isco RediSepRf regular or high performance (Isco Gold) columns as well as specialty capped silica gel columns such as Isco Gold Amine, Isco Gold Diol, Isco Gold Cyano as specified in the Examples. Reverse phase chromatography was performed using pre-packed Isco RediSepRf reverse phase columns such as Isco C18 and Isco Gold C18Aq. Pyridine, dichloromethane (CH₂Cl₂ or DCM), tetrahydrofuran (THF), dimethylformamide (DMF), acetonitrile (ACN), methanol (MeOH), and 1,4-dioxane were from Baker or Aldrich and in some cases the reagents were Aldrich Sure-Seal bottles kept under dry nitrogen. All reactions were stirred magnetically unless otherwise noted.

[00286] The following definitions describe terms and abbreviations used herein:

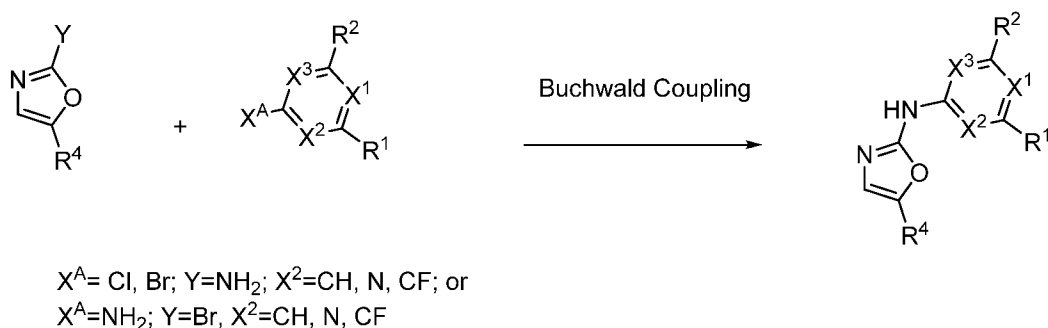
DCM dichloromethane

	DMA	diethylacetamide
	EtOAc/EA	ethyl acetate
	Hex	hexanes
	HEP	heptanes
5	HPLC	high-performance liquid chromatography
	LCMS	liquid chromatography-mass spectrometry
	ESI-MS	electrospray ionization mass spectrometry
	TLC	thin layer chromatography
	DMF	N,N-dimethylformamide
10	DMSO	dimethylsulfoxide
	THF	tetrahydrofuran
	Et ₃ N	triethylamine
	NMP	N-methylpyrrolidone
	HOAc	acetic acid
15	TFA	trifluoroacetic acid
	ACN	acetonitrile
	DCM	dichloromethane
	DCE	dichloroethane
	DMA	dimethylacetamide
20	N ₂	nitrogen
	R.T./RT/rt	room temperature
	AT	ambient temperature
	MeOH	methanol
	EtOH	ethanol
25	<i>t</i> -BuOH	<i>t</i> -butanol
	<i>t</i> -BuONa	sodium <i>t</i> -butoxide
	Pd/C	palladium on carbon
	SnAr	nucleophilic aromatic substitution mechanism
	<i>t</i> -BuXPhos Palladacycle	chloro(2-di- <i>t</i> -butylphosphino-2',4',6'-tri- <i>i</i> -propyl-1,1'-
30	biphenyl) [2-(2-aminoethyl)phenyl]palladium(II)	
	RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
	BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-
	biphenyl	

- BrettPhos Precatalyst Chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl] [2-(2-aminoethyl)phenyl]palladium(II) 1:1 molar mixture
- Pd₂(dba)₃ tris(dibenzylideneacetone)dipalladium
- 5 ISCO flash chromatography system
- SiO₂ silica gel
- MP-TMT macroporous polystyrene-bound trimecaptotriazine
- PL-HCO₃ MP SPE polymer supported bicarbonate resin
- RBF round-bottom flask
- 10 Cmpd Compound

Scheme A: General Route A to Compounds of Formula I or III

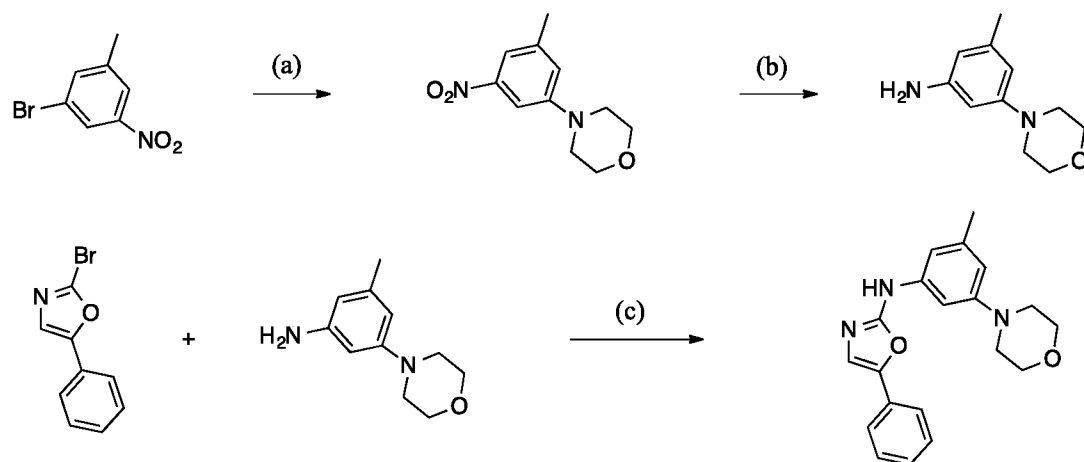
- Compounds of formula I or III of the present invention wherein R⁴ is oxygen (oxazole ring) may be prepared as generally outlined in Scheme A, which shows representative structures wherein R¹ is L¹-G¹-R⁶, X¹ is CR^{X1}, X³ is CR^{X3}, R⁴ is optionally substituted phenyl, and L¹, G¹, R⁶, X², R^{X1}, and R^{X3} are as defined herein.
- 15



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EXAMPLE 1

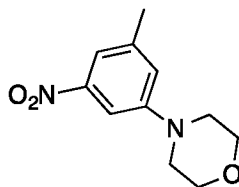
Preparation of N-(3-methyl-5-morpholino-phenyl)-5-phenyl-oxazol-2-amine
(Compound 10)



Reagents and conditions: (a) $\text{Pd}_2(\text{dba})_3$, RuPhos, Cs_2CO_3 , 90 °C, morpholine, 1,4-dioxane (b) 10% Pd/C (wet), EtOH, H_2 (c) *t*-BuXPhos Palladacycle, NaOtBu, 1,4-dioxane, 90 °C.

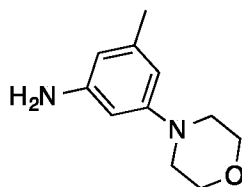
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Preparation of 4-(3-methyl-5-nitrophenyl)morpholine



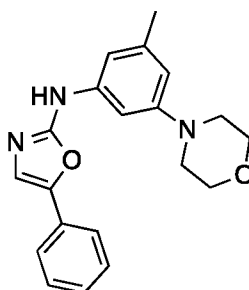
[00287] Cesium carbonate (4.2 g, 12.89 mmol) was added to a solution of 1-bromo-3-methyl-5-nitro-benzene (947 mg, 4.38 mmol), morpholine (458 μL , 5.25 mmol) and 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) (83 mg, 0.17 mmol) in dry 1,4-dioxane at room temperature and the mixture was purged with a stream of nitrogen for ten minutes. Tris(dibenzylideneacetone)dipalladium(0) (80 mg, 0.09 mmol) was added and nitrogen purge continued for 5 minutes, then the vial was sealed and heated at 90 °C for 18 hours. The mixture was cooled, diluted with water and extracted twice with ethyl acetate. The combined organic layers were washed with water and brine, filtered through a plug of Florisil, and concentrated. Flash chromatography on silica gel (40 g column) eluting with 0-20% ethyl acetate/heptane afforded 4-(3-methyl-5-nitrophenyl)morpholine (447 mg, 46%) as an off-white solid. ^1H NMR (300 MHz, CDCl_3) δ 7.54 (s, 2H), 7.01 (s, 1H), 3.94 - 3.84 (m, 4H), 3.29 - 3.18 (m, 4H), 2.43 (s, 3H) ppm. ESI-MS m/z calc. 222.1, found 223.1 ($\text{M}+1$) $^+$; Retention time: 0.86 minutes.

Preparation of 3-methyl-5-morpholino-aniline



[00288] A Parr bottle was purged with nitrogen and charged with 10% Pd/C (220 mg, wet), followed by the addition of nitrogen purged ethanol (75 mL) and 4-(3-methyl-5-nitro-phenyl)morpholine (440 mg, 1.98 mmol). The bottle was placed under vacuum and refilled with hydrogen gas two times. The mixture was shaken under 35 psi of hydrogen for 18 hours, purged with nitrogen, filtered and washed with ethanol. The filtrate was concentrated to dryness and the residue purified by flash chromatography on silica gel (12 g column) eluting with 0-40% ethyl acetate/dichloromethane to afford 3-methyl-5-morpholino-aniline (170 mg, 45%) as a tan solid. ¹H NMR (300 MHz, CDCl₃) δ 6.20 (t, J = 1.7 Hz, 1H), 6.09 (dt, J = 7.6, 2.1 Hz, 2H), 3.90 - 3.80 (m, 4H), 3.59 (s, 2H), 3.22 - 3.05 (m, 4H), 2.25 (s, 3H) ppm. ESI-MS m/z calc. 192.13, found 193.1 (M+1)⁺; Retention time: 0.53 minutes.

Preparation of N-(3-methyl-5-morpholinophenyl)-5-phenyl-oxazol-2-amine



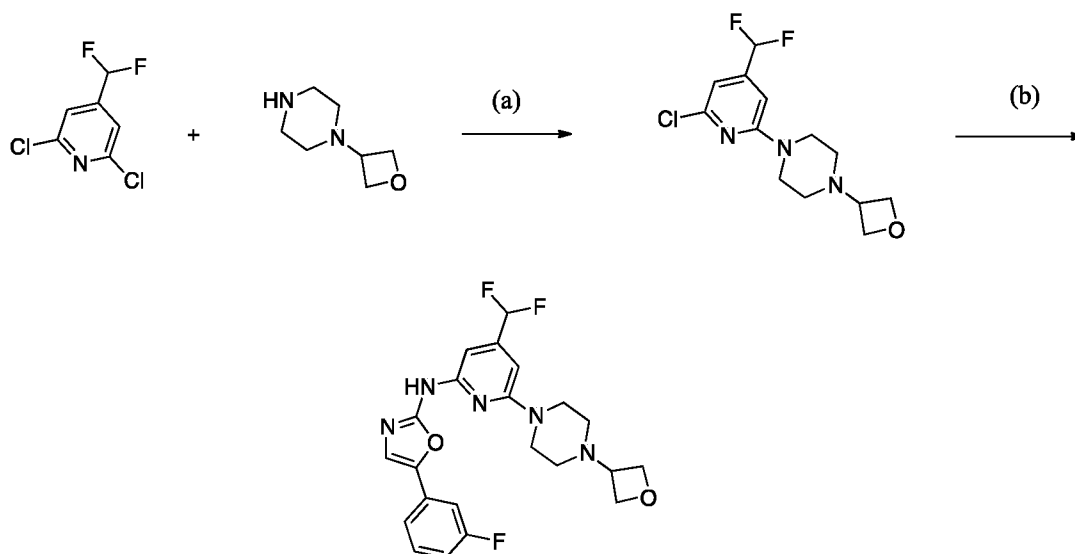
[00289] Sodium t-butoxide (101 mg, 1.05 mmol) was added to a solution of 2-bromo-5-phenyl-oxazole (72 mg, 0.32 mmol) and 3-methyl-5-morpholino-aniline (63 mg, 0.33mmol) in dry 1,4-dioxane (2 mL) at room temperature. The mixture was purged with nitrogen for 3 minutes. Chloro(2-di-t-butylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXPhos Palladacycle) (8 mg, 0.01 mmol) was added and after purging with nitrogen for two more minutes, the vial was sealed and heated at 60 °C for 20 hours. The reaction was cooled, diluted with pH7 buffer and water, then extracted with ethyl acetate. The organic layer was washed with brine, filtered through a plug of Florisil, dried over sodium sulfate,

filtered and concentrated. The residue was purified by flash chromatography on silica gel (12 g column; 10-60% ethyl acetate/dichloromethane) to afford the desired product. The above product was further triturated twice with ether to give N-(3-methyl-5-morpholinophenyl)-5-phenyl-oxazol-2-amine (11 mg, 10%) as a colorless solid. ¹H NMR (300 MHz, CDCl₃) δ 7.60-7.51 (m, 2H), 7.45 - 7.36 (m, 2H), 7.32-7.23 (m, 1H), 7.17 (s, 1H), 7.06 (d, J = 2.1 Hz, 2H), 6.78 (s, 1H), 6.46 (t, J = 1.7 Hz, 1H), 3.94 - 3.85 (m, 4H), 3.26 - 3.17 (m, 4H), 2.36 (s, 3H) ppm. ESI-MS m/z calc. 335.1, found 336.1 (M+1)⁺; Retention time: 0.75 minutes.

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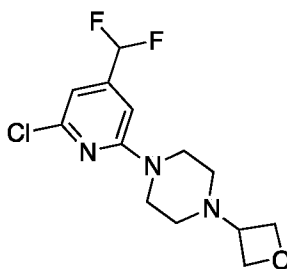
EXAMPLE 2

Preparation of N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3-fluorophenyl)oxazol-2-amine (Compound 1)



15 Reagents and conditions: (a) DIPEA, 1,4-dioxane, 160 °C (b) 5-(3-fluorophenyl)oxazol-2-amine, *t*-BuXPhos Palladacycle, NaOtBu, 1,4-dioxane, 125 °C.

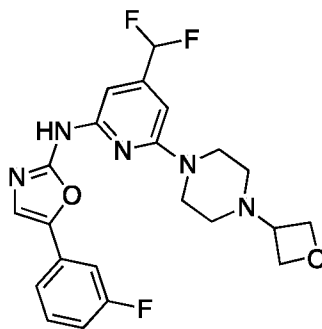
Preparation of 1-[6-chloro-4-(difluoromethyl)-2-pyridyl]-4-(oxetan-3-yl)piperazine



[00290] A mixture of 2,6-dichloro-4-(difluoromethyl)pyridine (400 mg, 2.02 mmol), 1-(oxetan-3-yl)piperazine (432.0 mg, 3.04 mmol), DIPEA (700 μ L, 4.02 mmol) and 1,4-dioxane (12.00 mL) in a sealed tube was heated at 160 °C for 20 min.

- 5 The reaction mixture was concentrated. The crude material was subjected to flash chromatography purification (12g silica; 0% to 5% to 10% of methanol in dichloromethane) to give 1-[6-chloro-4-(difluoromethyl)-2-pyridyl]-4-(oxetan-3-yl)piperazine (510 mg, 83%). ^1H NMR (300 MHz, CDCl_3) δ 6.71 (s, 1H), 6.69 (s, 1H), 6.58 (s, 1H), 6.41 (t, J = 55.8 Hz, 1H), 4.81 - 4.58 (m, 4H), 3.79 - 3.61 (m, 4H),
 10 3.60 - 3.47 (m, 1H), 2.59 - 2.30 (m, 4H) ppm. ESI-MS m/z calc. 303.10, found 304.46 ($M+1$) $^+$; Retention time: 0.61 minutes.

Preparation of N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3-fluorophenyl)oxazol-2-amine (Compound 1)



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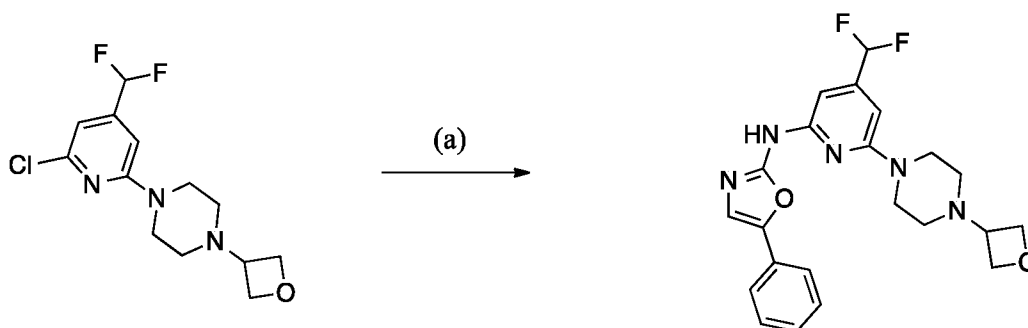
- [00291]** 1-[6-chloro-4-(difluoromethyl)-2-pyridyl]-4-(oxetan-3-yl)piperazine (100 mg, 0.33 mmol), 5-(3-fluorophenyl)oxazol-2-amine (64 mg, 0.36 mmol) and sodium *t*-butoxide (65 mg, 0.68 mmol) were suspended in 1,4-dioxane (4 mL) and purged with N_2 for several minutes before addition of chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXPhos Palladacycle) (17.4 mg, 0.025 mmol). The mixture was microwaved at 125 °C for 70
 20 minutes. The reaction was quenched with methanol (2 mL), diluted with dichloromethane (15 mL), washed with water (5 mL), brine (5 mL), dried over

sodium sulfate, filtered and concentrated. The crude material was subjected to flash chromatography purification (12g silica; 0% to 5% to 10% of methanol in dichloromethane) and CH₃CN trituration to give N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3-fluorophenyl)oxazol-2-amine (90 mg, 55%).
 5 ¹H NMR (300 MHz, CDCl₃) δ 7.49 (d, J = 9.6 Hz, 2H), 7.37 (qd, J = 7.9, 3.5 Hz, 2H), 7.27 - 7.19 (m, 2H), 7.03 - 6.94 (m, 1H), 6.78 - 6.41 (m, 2H), 4.73 (d, J = 6.2 Hz, 4H), 3.67 (s, 5H), 2.49 (s, 4H) ppm. ESI-MS m/z calc. 445.17, found 446.12 (M+1)⁺; Retention time: 0.68 minutes.

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EXAMPLE 3

Preparation of N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-phenyloxazol-2-amine (Compound 3)



15 Reagents and conditions: (a) 5-phenyloxazol-2-amine, *t*-BuXPhos Palladacycle, NaOtBu, 1,4-dioxane, 125°C.

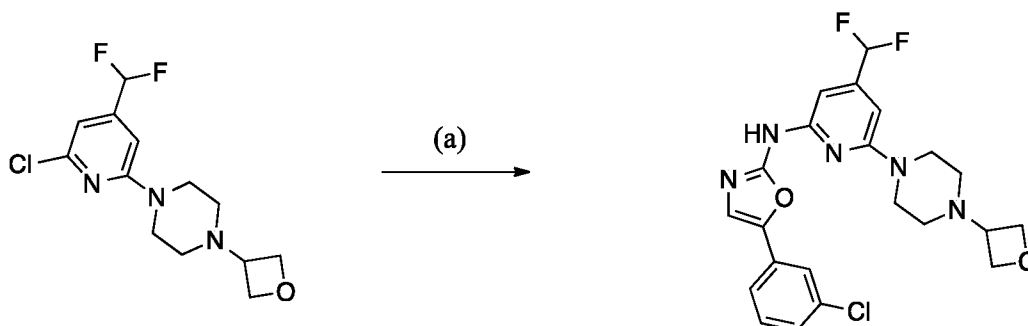
[00292] 1-[6-chloro-4-(difluoromethyl)-2-pyridyl]-4-(oxetan-3-yl)piperazine (50 mg, 0.16 mmol), 5-phenyloxazol-2-amine (53 mg, 0.33 mmol) and sodium *t*-butoxide (32 mg, 0.33 mmol) were suspended in 1,4-dioxane (3 mL) and purged with N₂ for several minutes before addition chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXPhos Palladacycle) (10 mg, 0.014 mmol). The mixture was microwaved at 125°C for 70 minutes. The reaction was quenched with methanol (2 mL), diluted with dichloromethane (15 mL), washed with water (5 mL), brine (5 mL), dried over sodium sulfate, filtered and concentrated.
 25 The crude material was subjected to flash chromatography purification (12g silica; 0% to 5% to 10% of ethanol in ethyl acetate) to provide N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-phenyloxazol-2-amine (50 mg, 68%). ¹H

NMR (300 MHz, CDCl_3) δ 7.55 (dd, $J = 14.0, 6.7$ Hz, 4H), 7.42 (t, $J = 7.6$ Hz, 2H), 7.35 - 7.25 (m, 2H), 6.68 (d, $J = 56.0$ Hz, 1H), 6.44 (s, 1H), 4.83 - 4.60 (m, 4H), 3.79 - 3.49 (m, 5H), 2.57 - 2.35 (m, 4H) ppm. ESI-MS m/z calc. 427.18, found 428.03 ($M+1$)⁺; Retention time: 0.67 minutes.

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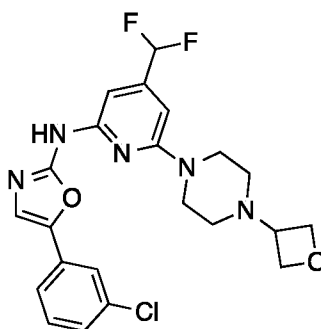
EXAMPLE 4

Preparation of N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3-chlorophenyl)oxazol-2-amine (Compound 5)



10 Reagents and conditions: (a) 5-(3-chlorophenyl)oxazol-2-amine, *t*-BuXPhos Palladacycle, NaOtBu, 1,4-dioxane, 125 °C.

Preparation of N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3-chlorophenyl)oxazol-2-amine (Compound 5)



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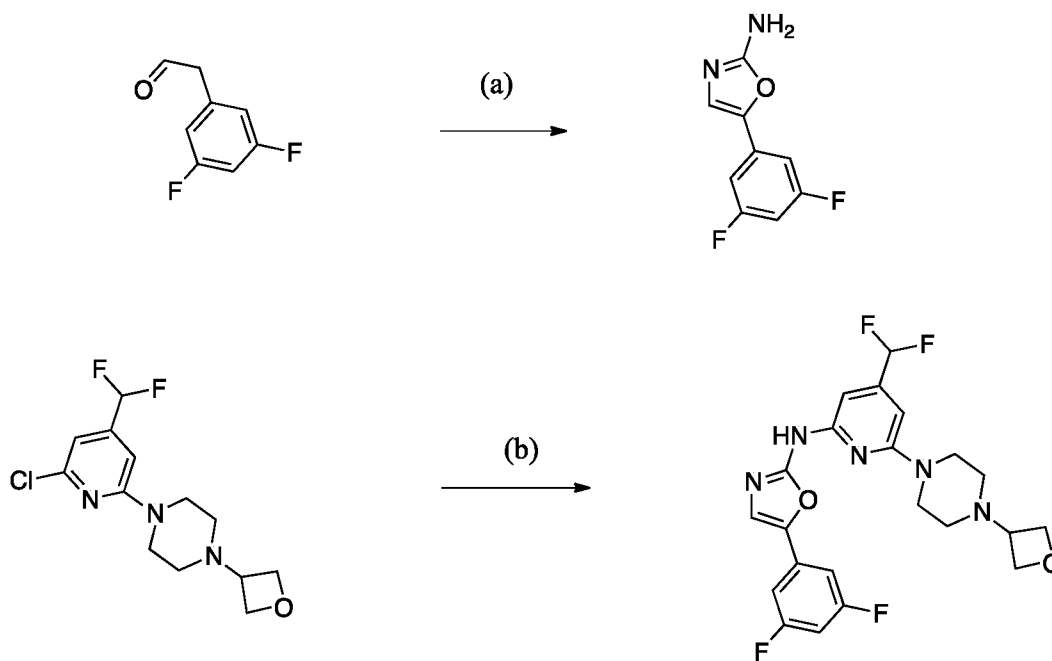
[00293] 1-[6-chloro-4-(difluoromethyl)-2-pyridyl]-4-(oxetan-3-yl)piperazine (100 mg, 0.33 mmol), 5-(3-chlorophenyl)oxazol-2-amine (103 mg, 0.53 mmol) and sodium *t*-butoxide (64 mg, 0.67 mmol) were suspended in 1,4-dioxane (4 mL) and purged with N_2 for several minutes before addition of chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXPhos Palladacycle) (18 mg, 0.026 mmol). The mixture was microwaved at 125 °C for 70

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minutes. The reaction was quenched with methanol (2 mL), diluted with dichloromethane (15 mL), washed with water (5 mL), brine (5 mL), dried over sodium sulfate, filtered and concentrated. The crude material was subjected to flash chromatography purification (12g silica; 0% to 5% to 10% of methanol in dichloromethane) to provide 5-(3-chlorophenyl)-N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]oxazol-2-amine (71 mg, 44%). ¹H NMR (300 MHz, CDCl₃) δ 7.55 (t, J = 1.7 Hz, 1H), 7.51 (s, 2H), 7.46 - 7.40 (m, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.28 - 7.24 (m, 1H), 7.23 (d, J = 3.8 Hz, 1H), 6.68 (d, J = 56.0 Hz, 1H), 6.46 (s, 1H), 4.74 (d, J = 6.5 Hz, 4H), 3.70 (s, 5H), 2.53 (s, 4H) ppm. ESI-MS *m/z* calc. 461.14, found 462.05 (M+1)⁺; Retention time: 0.71 minutes.

EXAMPLE 5

Preparation of N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3,5-difluorophenyl)oxazol-2-amine (Compound 2)

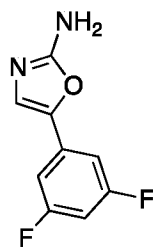


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Reagents and conditions: (a) i. Br₂, DCM, 0 °C; ii. urea, DMF, 90 °C (b) 5-(3,5-difluorophenyl)oxazol-2-amine, *t*-BuXPhos Palladacycle, NaOtBu, 1,4-dioxane, 125 °C.

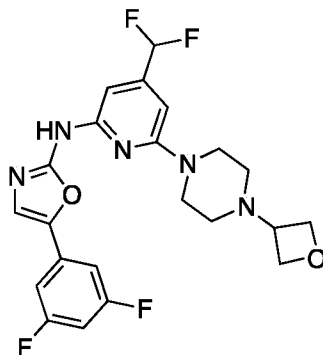
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Preparation of 5-(3,5-difluorophenyl)oxazol-2-amine



[00294] To a solution of 2-(3,5-difluorophenyl)acetaldehyde (2 g, 12.81 mmol) in 1,4-dioxane (3 mL) at 0 °C was slowly added Br₂ (727 µL, 14.11 mmol). The reaction mixture was stirred at 0 °C for 30 minutes, then warmed up to room temperature. Dichloromethane (5 mL) was added to the mixture and stirred for another 30 minutes. The above reaction mixture was slowly added to a preheated solution of urea (1.58 g, 26.32 mmol) in dimethylformamide (30.00 mL) at 90 °C and the resultant mixture was heated for 3 hours, then stirred at room temperature for 8 hours. The reaction mixture was concentrated. The residue was treated with saturated Na₂CO₃ (60 mL) and extracted with ethyl acetate (2 x100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. The crude material was subjected to flash chromatography purification (1st column: 40g silica; 0% to 10% to 20% of methanol in dichloromethane; 2nd column: 12g silica, 0 to 5% ethanol in ethyl acetate) to give 5-(3,5-difluorophenyl)oxazol-2-amine (60 mg, 2%). ¹H NMR (300 MHz, Methanol-*d*₄) δ 7.34-6.97 (m, 3H), 6.87-6.66 (m, 1H) ppm. ESI-MS *m/z* calc. 196.05, found 197.0 (M+1)⁺; Retention time: 0.61 minutes.

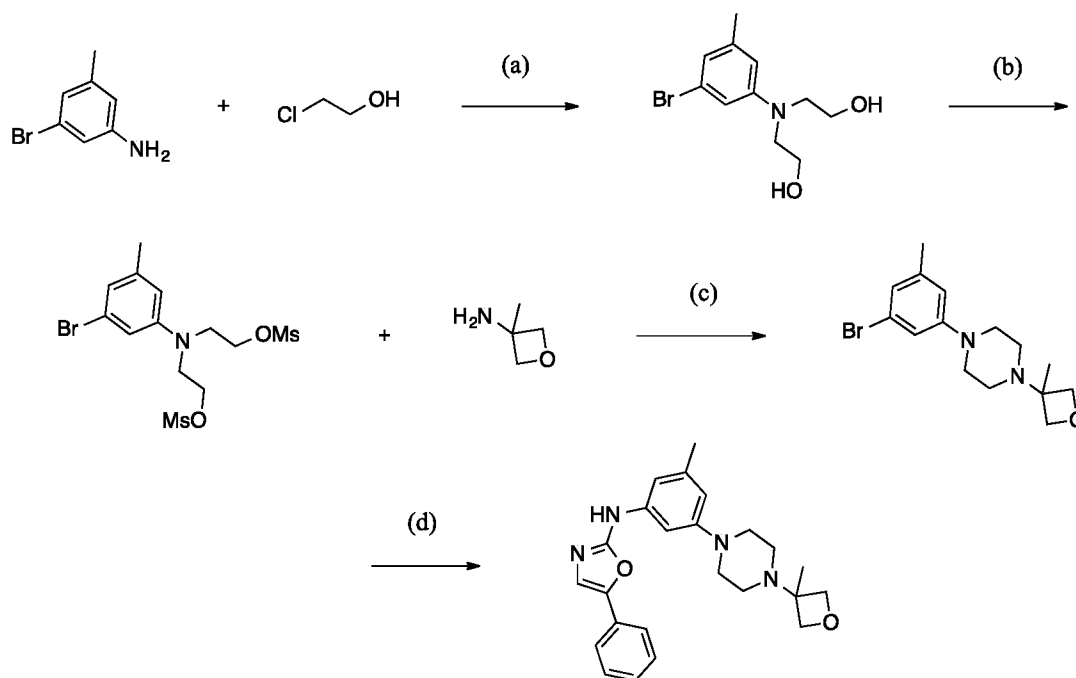
Preparation N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3,5-difluorophenyl)oxazol-2-amine (Compound 2)



[00295] 1-[6-chloro-4-(difluoromethyl)-2-pyridyl]-4-(oxetan-3-yl)piperazine (60 mg, 0.2 mmol), 5-(3,5-difluorophenyl)oxazol-2-amine (60 mg, 0.31 mmol) and sodium t-butoxide (40 mg, 0.42 mmol) were suspended in 1,4-dioxane (4 mL) and purged with N₂ for several minutes before addition of chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXPhos Palladacycle) (12.0 mg, 0.017 mmol). The mixture was microwaved at 125 °C for 90 minutes. The reaction was quenched with methanol (2 mL), diluted with dichloromethane (15 mL), washed with water (5 mL), brine (5 mL), dried over sodium sulfate, filtered and concentrated. The crude material was subjected to flash chromatography purification (12 g silica; 0% to 5% to 10% of ethanol in ethyl acetate) and CH₃CN trituration to give N-[4-(difluoromethyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(3,5-difluorophenyl)oxazol-2-amine (50 mg, 51%). ¹H NMR (300 MHz, CDCl₃) δ 7.50 (s, 2H), 7.25 (s, 1H), 7.06 (d, J = 6.2 Hz, 2H), 6.82 - 6.54 (m, 2H), 6.46 (s, 1H), 4.82-4.61 (m, 4H), 3.65 (d, J = 4.5 Hz, 4H), 3.60 - 3.44 (m, 1H), 2.46 (d, J = 4.6 Hz, 4H) ppm. ESI-MS m/z calc. 463.16, found 463.94 (M+1)⁺; Retention time: 0.7 minutes.

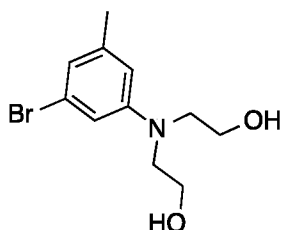
EXAMPLE 6

Preparation of N-[3-methyl-5-[4-(3-methyloxetan-3-yl)piperazin-1-yl]phenyl]-5-phenyl-oxazol-2-amine (Compound 6)



Reagents and conditions: (a) KI, CaCO₃, EtOH, water, 100-120 °C;
 (b) methanesulfonyl chloride, Et₃N, EtOAc; (c) K₂CO₃, 1,4-dioxane, 160 °C; (d) 5-phenyloxazol-2-amine, *t*-BuXPhos Palladacycle, NaOtBu, 1,4-dioxane, 125 °C.

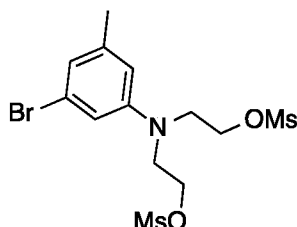
Preparation of 2-[3-bromo-N-(2-hydroxyethyl)-5-methyl-anilino]ethanol



[00296] A mixture of 3-bromo-5-methyl-aniline (1.86 g, 10 mmol), 2-chloroethanol (3.22 g, 40.00 mmol), KI (166 mg, 1.00 mmol) and CaCO₃ (2.00 g, 20.00 mmol) in water (6 mL) and ethanol (6 mL) was heated at 100 °C for 36 hours, then at 120 °C for 20 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with water, saturated NaCl and dried. The excess solvent was evaporated under reduced pressure. The crude material was subjected to flash chromatography purification (40g silica; 0 % to 5% to 10% of methanol in dichloromethane) to give 2-[3-bromo-N-(2-hydroxyethyl)-5-methyl-anilino]ethanol (1.4 g, 51%). ¹H NMR (300 MHz, CDCl₃) δ 6.71 (d, J = 22.0 Hz, 2H), 6.47 (s, 1H),

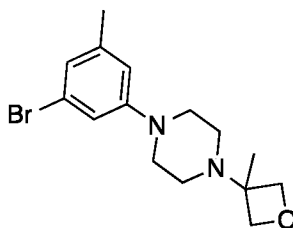
3.87 (t, J = 4.9 Hz, 4H), 3.61 - 3.53 (m, 4H), 3.41 (s, 2H), 2.29 (s, 3H) ppm. ESI-MS m/z calc. 273.04, found 274.31 (M+1)⁺; Retention time: 0.68 minutes.

Preparation of 2-[3-bromo-5-methyl-N-(2-methylsulfonyloxyethyl)anilino]ethyl methanesulfonate



[00297] A solution of 2-[3-bromo-N-(2-hydroxyethyl)-5-methyl-anilino]ethanol (720 mg, 2.63 mmol) in ethyl acetate (15 mL) was treated with methanesulfonyl chloride (902 mg, 7.88 mmol). Et₃N (930.0 mg, 9.19 mmol) was then added to above mixture. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with water, saturated NaHCO₃ and saturated NaCl, then dried over sodium sulfate, filtered and concentrated. The crude material was subjected to flash chromatography purification (40g silica; 10% to 50% to 100% of ethyl acetate in hexanes) to give 2-[3-bromo-5-methyl-N-(2-methylsulfonyloxyethyl)anilino]ethyl methanesulfonate (950 mg, 84%).
¹H NMR (300 MHz, CDCl₃) δ 6.79 (s, 1H), 6.67 (d, J = 1.8 Hz, 1H), 6.47 (s, 1H), 4.37 (t, J = 5.8 Hz, 4H), 3.76 (t, J = 5.8 Hz, 4H), 3.02 (s, 6H), 2.30 (s, 3H) ppm. ESI-MS m/z calc. 428.99, found 430.24 (M+1)⁺; Retention time: 0.85 minutes.

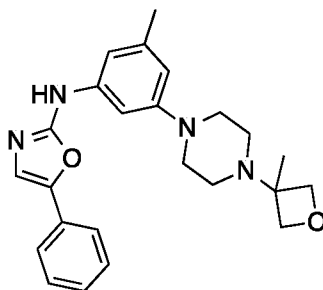
Preparation of 1-(3-bromo-5-methyl-phenyl)-4-(3-methyloxetan-3-yl)piperazine



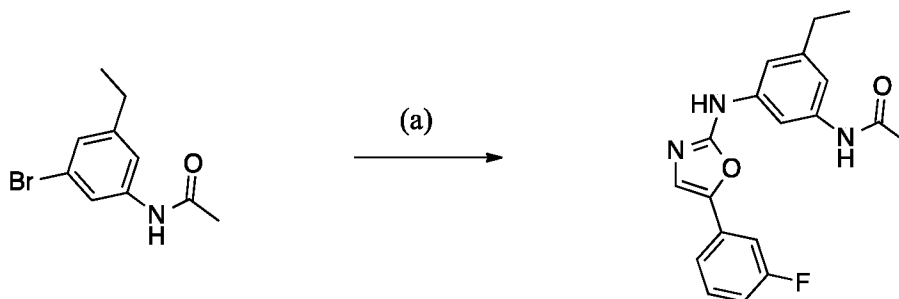
[00298] A mixture of 2-[3-bromo-5-methyl-N-(2-methylsulfonyloxyethyl)anilino]ethyl methanesulfonate (220 mg, 0.51 mmol), 3-methyloxetan-3-amine (54 mg, 0.62 mmol) and K₂CO₃ (212 mg, 1.53 mmol) in 1,4-dioxane (15 mL) was microwaved at 160 °C for 16 h. The reaction mixture was diluted with ethyl acetate, washed with water, saturated NaHCO₃, saturated NaCl and

dried. The excess solvent was evaporated under reduced pressure. The crude material was subjected to flash chromatography purification (12 g silica; 10% to 50% to 100% of ethyl acetate in hexanes) to give 1-(3-bromo-5-methyl-phenyl)-4-(3-methyloxetan-3-yl)piperazine (85 mg, 51%). ¹H NMR (300 MHz, CDCl₃) δ 6.86 (d, J = 1.8 Hz, 1H), 6.83 (s, 1H), 6.65 (s, 1H), 4.64 (d, J = 5.4 Hz, 2H), 4.29 (d, J = 5.8 Hz, 2H), 3.29 - 3.13 (m, 4H), 2.61 - 2.44 (m, 4H), 2.35 - 2.22 (m, 3H), 1.42 (s, 3H) ppm. ESI-MS m/z calc. 324.08, found 325.39 (M+1)⁺; Retention time: 0.64 minutes.

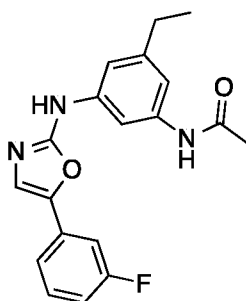
10 Preparation of N-[3-methyl-5-[4-(3-methyloxetan-3-yl)piperazin-1-yl]phenyl]-5-phenyl-oxazol-2-amine (Compound 6)



[00299] 5-phenyloxazol-2-amine (63 mg, 0.39 mmol), 1-(3-bromo-5-methyl-phenyl)-4-(3-methyloxetan-3-yl)piperazine (80 mg, 0.25mmol) and sodium t-butoxide (50 mg, 0.52 mmol) were suspended in 1,4-dioxane (4 mL) and purged with N₂ for several minutes before addition of chloro(2-di-t-butylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXPhos Palladacycle) (13 mg, 0.02 mmol). The mixture was microwaved at 125 °C for 60 minutes. The reaction was quenched with methanol (2 mL) and diluted with dichloromethane. After filtration (Florisil/10 g), the excess solvent was evaporated under reduced pressure. The crude material was subjected to flash chromatography purification (12g silica; 0% to 5% of ethanol in ethyl acetate) to give N-[3-methyl-5-[4-(3-methyloxetan-3-yl)piperazin-1-yl]phenyl]-5-phenyl-oxazol-2-amine (75 mg, 72%). ¹H NMR (300 MHz, CDCl₃) δ 7.61 - 7.49 (m, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.26 (d, J = 7.4Hz, 1H), 7.17 (s, 1H), 7.03 (s, 1H), 6.93 (s, 1H), 6.79 (s, 1H), 6.47 (s, 1H), 4.71 (d, J = 5.5 Hz, 2H), 4.30 (d, J = 5.8 Hz, 2H), 3.49 - 3.18 (m, 4H), 2.74 - 2.45 (m, 4H), 2.35 (s, 3H) ppm. ESI-MS m/z calc. 404.22, found 405.28 (M+1)⁺; Retention time: 0.64 minutes.

EXAMPLE 7Preparation of N-[3-ethyl-5-[[5-(3-fluorophenyl)oxazol-2-yl]amino]phenyl]acetamide (Compound 4)

- 5 Reagents and conditions: (a) 5-(3-fluorophenyl)oxazol-2-amine, *t*-BuXPhos Palladacycle, NaOtBu, 1,4-dioxane, 125 °C

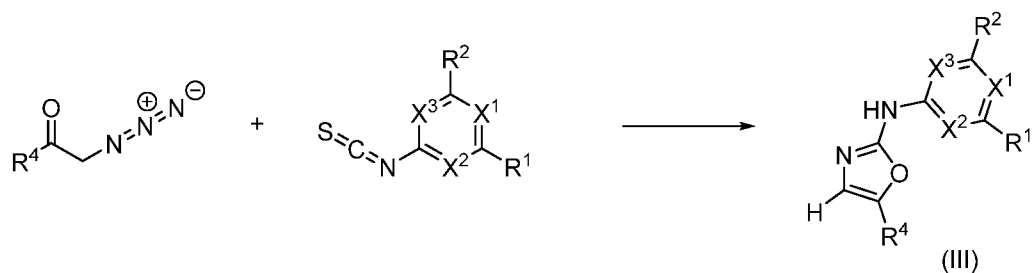
Preparation of N-[3-ethyl-5-[[5-(3-fluorophenyl)oxazol-2-yl]amino]phenyl]acetamide

- 10 **[00300]** 5-(3-fluorophenyl)oxazol-2-amine (77 mg, 0.43 mmol), N-(3-bromo-5-ethyl-phenyl)acetamide (100 mg, 0.39 mmol) and sodium *t*-butoxide (80 mg, 0.83 mmol) were suspended in 1,4-dioxane (4 mL) and purged with N₂ for several minutes before addition of chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXPhos Palladacycle) (20 mg, 0.03 mmol).
- 15 The mixture was microwaved at 125 °C for 75 minutes. The reaction was quenched with methanol (2 mL), diluted with dichloromethane (20 mL), washed with water (5 mL), dried over sodium sulfate, filtered and concentrated. The crude material was subjected to flash chromatography purification (12 g silica; 0% to 5% to 10% of methanol in dichloromethane) to provide N-[3-ethyl-5-[[5-(3-fluorophenyl)oxazol-2-
- 20 yl]amino]phenyl]acetamide (50 mg, 36%). ¹H NMR (300 MHz, Methanol-*d*₄+CDCl₃) δ 7.55 (d, *J* = 1.9 Hz, 1H), 7.36 (t, *J* = 5.4 Hz, 2H), 7.29 - 7.23 (m, 1H), 7.18 (s, 1H), 7.15 (s, 1H), 7.07 (s, 1H), 7.00 - 6.90 (m, 1H), 2.65 (q, *J* = 7.6 Hz, 2H),

2.16 (s, 3H), 1.26 (t, J = 7.6 Hz, 3H) ppm. ESI-MS m/z calc. 339.14, found 340.06 (M+1)⁺; Retention time: 0.81 minutes.

[00301] Using the general synthetic scheme outlined in Scheme A and experimental procedures analogous to those listed above in Examples 1-7, the following
5 compounds can be prepared: 12-17, 19, 7, 3-5, 8, 25, 22 and 23.

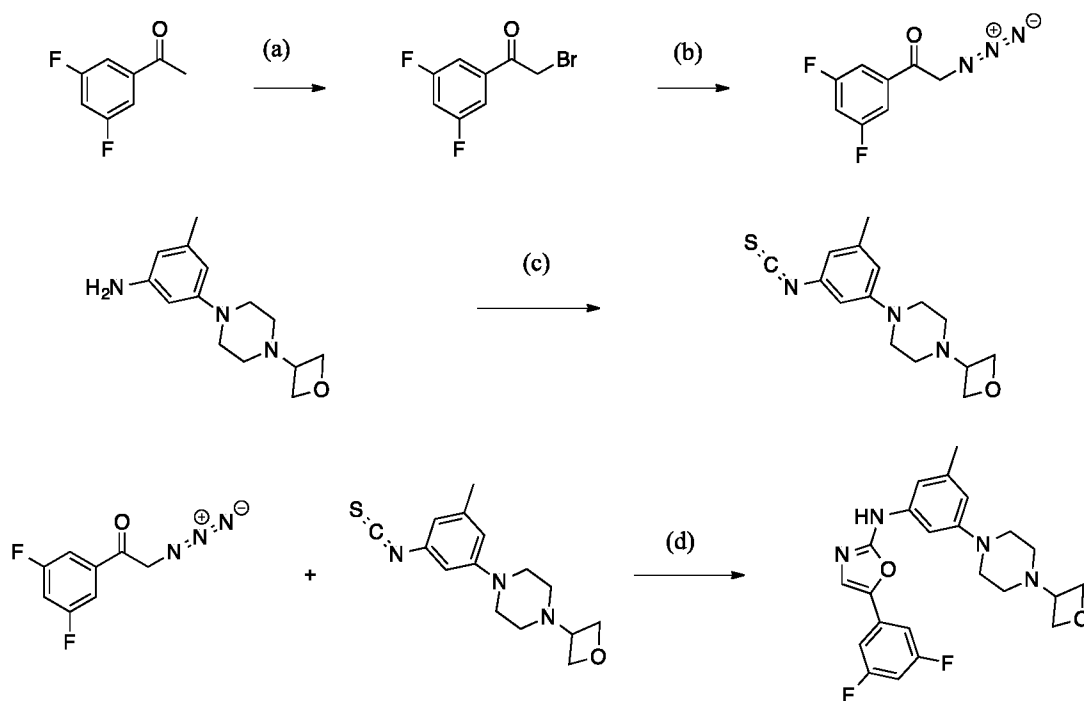
Scheme B: General Route B for Preparation of Compounds of Formula III



10 Compounds of the invention of Formula III may be prepared as generally outlined in Scheme B, where X¹, X², X³, R¹, R² and R⁴ are as described herein.

EXAMPLE 8

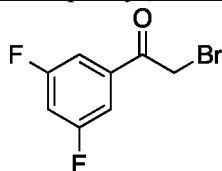
Preparation of 5-(3,5-difluorophenyl)-N-[3-methyl-5-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]oxazol-2-amine (Compound 21)
15



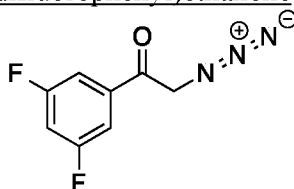
Reagents and conditions: (a) trimethylphenylammonium tribromide, THF, 0 °C (b) NaN₃, MeOH (c) thiocarbonyl dichloride, DCM, 0 °C (d) PPh₃, DCM.

5

Preparation of 2-bromo-1-(3,5-difluorophenyl)ethanone



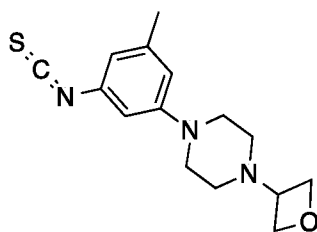
[00302] To a solution of 1-(3,5-difluorophenyl)ethanone (10 g, 64.05 mmol) in THF (70 mL) at 0 °C was added trimethylphenylammonium tribromide (26.5 g, 70.49 mmol) in 2 portions 10 minutes apart. The reaction mixture was stirred for 30 minutes, then warmed to room temperature and stirred for 3 hours. The reaction was quenched with water (100 mL) and the aqueous solution was extracted with diethyl ether (2 x 100 mL). The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was subjected to flash chromatography purification (330 g Gold Silica; 10-70% dichloromethane/hexanes) to give 2-bromo-1-(3,5-difluorophenyl)ethanone (9.8 g, 65%). ¹H NMR (300 MHz, CDCl₃) δ 7.61 - 7.40 (m, 2H), 7.16 - 6.93 (m, 1H), 4.41 (s, 2H) ppm. Does not ionize in LCMS.

Preparation of 2-azido-1-(3,5-difluorophenyl)ethanone

- 5 **[00303]** To a solution of 2-bromo-1-(3,5-difluorophenyl)ethanone (2.46 g, 10.47 mmol) in methanol (20 mL) was added NaN₃ (776 mg, 11.94 mmol) and the resulting mixture was stirred for 2 hours at room temperature. The solvent was removed under vacuum. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent
- 10 was removed under reduced pressure to give 2-azido-1-(3,5-difluorophenyl)ethanone (2 g, 97%). ¹H NMR (300 MHz, Methanol-*d*₄) δ 7.48 - 7.33 (m, 2H), 7.06 (tt, J = 8.4, 2.3 Hz, 1H), 4.48 (s, 2H) ppm.

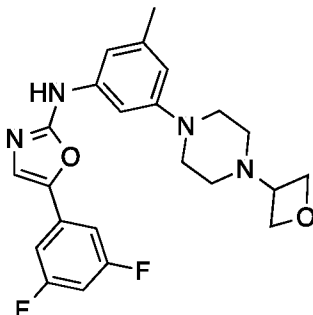
Preparation of 1-(3-isothiocyanato-5-methyl-phenyl)-4-(oxetan-3-yl)piperazine

15



- [00304]** To a solution of 3-methyl-5-[4-(oxetan-3-yl)piperazin-1-yl]aniline (1 g, 4.04 mmol) in dichloromethane (10 mL) at 0 °C was slowly added thiocarbonyl dichloride (502 mg, 333 μL, 4.37 mmol). The reaction was stirred for 2 hours at room
- 20 temperature, then saturated NaHCO₃ was added and the mixture was stirred for another 1 hour. The layers were separated and the aqueous layer was washed with dichloromethane (2 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give 1-(3-isothiocyanato-5-methyl-phenyl)-4-(oxetan-3-yl)piperazine (1.17 g; 100%).
- 25 ¹H NMR (300 MHz, Methanol-*d*₄) δ 6.60 (s, 1H), 6.56 - 6.45 (m, 2H), 4.65(dq, J = 12.6, 6.4 Hz, 3H), 3.58 - 3.43 (m, 1H), 3.31 - 3.08 (m, 4H), 2.52 - 2.41 (m, 3H), 2.25 (s, 3H) ppm. ESI-MS *m/z* calc. 289.12, found 290.21 (M+1)⁺; Retention time: 0.63 minutes.

Preparation 5-(3,5-difluorophenyl)-N-[3-methyl-5-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]oxazol-2-amine, trifluoroacetic acid salt (Compound 21)



5

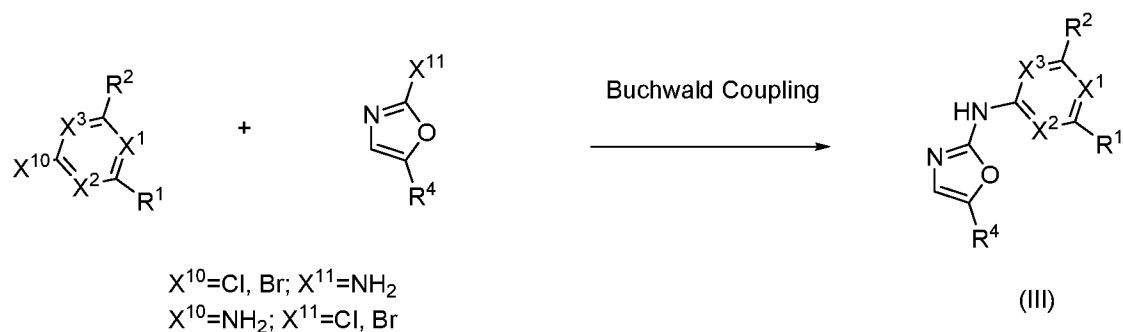
[00305] To a mixture of 1-(3-isothiocyanato-5-methyl-phenyl)-4-(oxetan-3-yl)piperazine (1.21 g, 4.18 mmol) and PPh₃ (1.11 g, 4.22 mmol) in dichloromethane (10 mL) was added a solution of 2-azido-1-(3,5-difluorophenyl)ethanone (824 mg, 4.18 mmol) in dichloromethane (3 mL) over 1 hour at room temperature. The resultant mixture was stirred for another 2 hours, quenched with 2N HCl (30 mL) and stirred for 1 hour. The resulting biphasic mixture was separated and the aqueous layer was washed with dichloromethane (20 mL). The pH of aqueous layer was adjusted to 12 with 6N NaOH and an extraction with dichloromethane (3 x 20 mL) was performed. The combined organic layers were washed with brine, dried, filtered and concentrated. The product was purified via reverse phase column chromatography (120g C18 silica; 10-95% ACN/water 0.1% TFA) to give 5-(3,5-difluorophenyl)-N-[3-methyl-5-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]oxazol-2-amine (trifluoroacetic acid salt(1)) (72.6 mg, 3%). ¹H NMR (300 MHz, Methanol-*d*₄) δ 7.42 (s, 1H), 7.31 - 7.12 (m, 3H), 6.90 - 6.74 (m, 2H), 6.57 (s, 1H), 5.48 (d, J = 2.5 Hz, 1H), 5.01 - 4.87 (m, 5H), 4.50 (dd, J = 12.3, 6.9 Hz, 1H), 3.52 (s, 4H), 3.38 (s, 3H), 2.32 (s, 3H), 1.41 - 1.12 (m, 3H), 0.97 - 0.83 (m, 1H) ppm. ESI-MS *m/z* calc. 426.19, found 427.34 (M+1)⁺; Retention time: 0.63 minutes.

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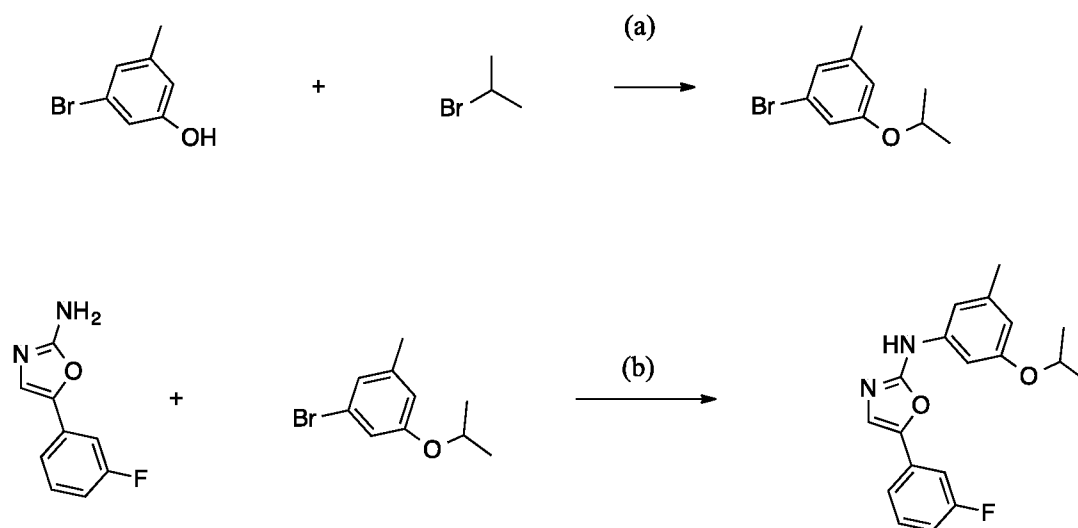
Scheme C: General Route C for Preparation of Compounds of Formula III



Compounds of the invention may be prepared as generally outlined in Scheme C, where R^1 is $-\text{OC}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{haloalkyl}$, $-\text{O}-\text{C}_{2-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl}$, $-\text{O}-\text{G}^1-\text{R}^6$, $-\text{O}-\text{G}^2$, or $-\text{O}-\text{G}^3$, and R^2 , R^4 , X^1 , X^2 , and X^3 are as described herein.

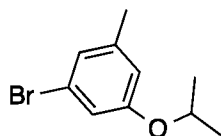
EXAMPLE 9

Preparation of 5-(3-fluorophenyl)-N-(3-isopropoxy-5-methyl-phenyl)oxazol-2-amine (Compound 9)



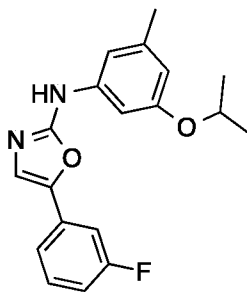
Reagents and conditions: (a) K_2CO_3 , 50 °C, DMF (b) *t*-BuXPhos Palladacycle, NaOtBu, 1,4-dioxane, 90 °C.

Preparation of 1-bromo-3-isopropoxy-5-methyl-benzene

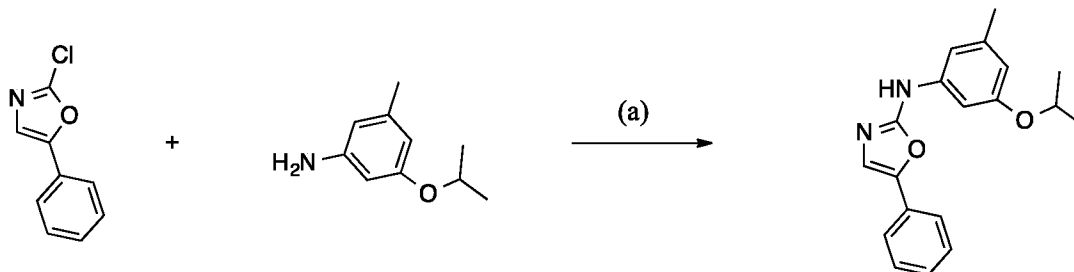


[00306] A mixture of 2-bromopropane (8.55 g, 6.53 mL, 69.50 mmol), 3-bromo-5-methyl-phenol (6.5 g, 34.75 mmol) and potassium carbonate (14.41 g, 104.3 mmol) in dimethylformamide (60 mL) was heated to 50 °C for 4 hours. The reaction was diluted with water (100 mL) and extracted with ethyl acetate (200 mL). The organic layer was washed with water (3 x 100 mL), saturated NaCl and dried with sodium sulfate. After filtration, the solvent was removed under vacuum to give 1-bromo-3-isopropoxy-5-methyl-benzene (6.95 g, 83%). ¹H NMR (300 MHz, CDCl₃) δ 6.91 (s, 1H), 6.87 (d, J = 1.9 Hz, 1H), 6.65 (d, J = 0.7 Hz, 1H), 4.60 - 4.44 (m, 1H), 2.30 (d, J = 0.5 Hz, 3H), 1.34 (d, J = 6.1 Hz, 6H) ppm. ESI-MS *m/z* calc. 228.01, found 229.22 (M+1)⁺; Retention time: 1.08 minutes.

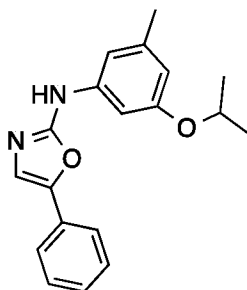
Preparation of 5-(3-fluorophenyl)-N-(3-isopropoxy-5-methyl-phenyl)oxazol-2-amine



[00307] 1-Bromo-3-isopropoxy-5-methyl-benzene (80 μL, 0.45 mmol), 5-(3fluorophenyl)oxazol-2-amine (89 mg, 0.50 mmol) and sodium t-butoxide (100 mg, 1.04 mmol) were suspended in 1,4-dioxane (4 mL) and purged with N₂ for several minutes before addition of chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXPhos Palladacycle) (24 mg, 0.035 mmol). The mixture was microwaved at 125 °C for 70 minutes. The reaction was quenched with methanol (2 mL), diluted with dichloromethane (15 mL), washed with water (5 mL), washed with brine (5 mL), dried over sodium sulfate, filtered and concentrated. The desired product was triturated with dichloromethane, then CH₃CN to give 5-(3-fluorophenyl)-N-(3-isopropoxy-5-methyl-phenyl)oxazol-2-amine (80 mg, 51%). ¹H NMR (300 MHz, CDCl₃) δ 7.45 - 7.29 (m, 3H), 7.26 - 7.18 (m, 2H), 7.03 - 6.93 (m, 2H), 6.84 (s, 1H), 6.47 (s, 1H), 4.59 (dt, J = 12.1, 6.0 Hz, 1H), 2.35 (s, 3H), 1.38 (d, J = 6.1 Hz, 6H) ppm. ESI-MS *m/z* calc. 326.14, found 327.33 (M+1)⁺; Retention time: 0.98 minutes.

EXAMPLE 10Preparation of N-(3-isopropoxy-5-methyl-phenyl)-5-phenyl-oxazol-2-amine
(Compound 24)

5 Reagents and conditions: (a) *t*-BuXPhos Palladacycle, NaOtBu, 1,4-dioxane, 90 °C.

Preparation of N-(3-isopropoxy-5-methyl-phenyl)-5-phenyl-oxazol-2-amine
(Compound 24)

10

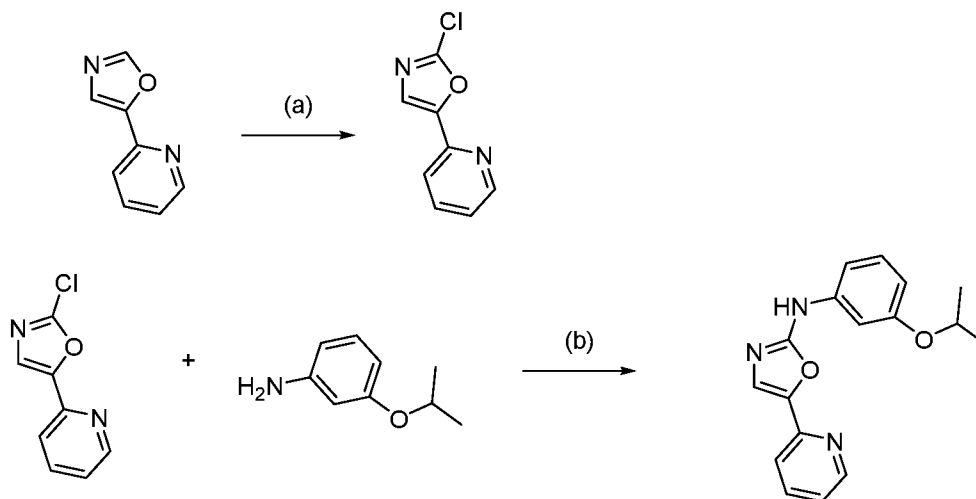
[00308] Sodium *t*-butoxide (122 mg, 1.27 mmol) was added to a solution of 2-chloro-5-phenyl-oxazole (68 mg, 0.38 mmol) and 3-isopropoxy-5-methyl-aniline (72 mg, 0.44 mmol) in anhydrous 1,4-dioxane (2 mL) and *t*-Butanol (0.5 mL) at room temperature. Nitrogen was bubbled through the mixture for 5 minutes, then chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (*t*-BuXPhos Palladacycle) (10 mg, 0.015 mmol) was added and nitrogen bubbled through for 5 more minutes. The vial was sealed and heated at 90 °C for 3 hours, cooled, diluted with pH 7 phosphate buffer and water, extracted twice with ethyl acetate. The combined organic extracts were washed with water and brine then

15

20 filtered through a plug of Florisil, and concentrated. The crude material was subjected to flash chromatography purification (12 g silica gel column; 0-30% ethyl acetate/hexanes to afford N-(3-isopropoxy-5-methyl-phenyl)-5-phenyl-oxazol-2-amine (20 mg, 16%) as a colorless solid. ¹H NMR (300 MHz, CDCl₃) δ 7.82 - 7.68

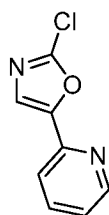
(m, 2H), 7.66 - 7.51 (m, 2H), 7.52 - 7.39 (m, 2H), 7.25 (s, 1H), 7.17 (t, $J = 2.3$ Hz, 1H), 7.03 (s, 1H), 6.62 (s, 1H), 4.77 (ddd, $J = 10.2, 8.1, 5.0$ Hz, 1H), 2.52 (s, 3H), 1.55 (d, $J = 6.1$ Hz, 6H) ppm. ESI-MS m/z calc. 308.15, found 309.15 ($M+1$)⁺; Retention time: 0.93 minutes.

5

EXAMPLE 11**Preparation of N-(3-isopropoxyphenyl)-5-(2-pyridyl)oxazol-2-amine (Compound 20)**

Reagents and conditions: (a) i. LiHMDS, THF, -78 °C; ii. C_2Cl_6 , RT (b) toluene, 170 °C.

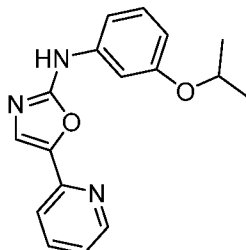
10

Preparation of 2-chloro-5-(2-pyridyl)oxazole

[00309] To a solution of 2-oxazol-5-ylpyridine (488 mg, 3.34 mmol) in THF (5 mL) at -78 °C was added a solution of LiHMDS in THF (3.7 mL of 1M, 3.7 mmol) over 30 minutes. 1,1,1,2,2,2-hexachloroethane (1.03 g, 4.34 mmol) was added and the reaction was stirred at room temperature overnight. The reaction mixture was poured onto an ice/saturated NH_4Cl mixture and extracted twice with ethyl acetate. The combined organics were dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (40 g column; 0-10% methanol in

dichloromethane) gave 2-chloro-5-(2-pyridyl)oxazole (500 mg, 83%). ESI-MS m/z calc. 180.01, found 180.95 ($M+1$)⁺; Retention time: 0.64 minutes.

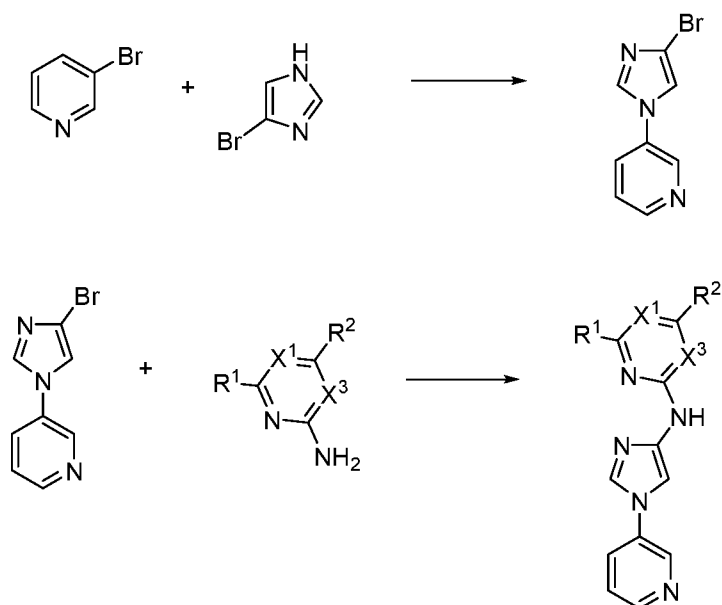
Preparation of N-(3-isopropoxyphenyl)-5-(2-pyridyl)oxazol-2-amine (Compound 20)



5
[00310] A mixture of 2-chloro-5-(2-pyridyl)oxazole (250 mg, 1.38 mmol), 3-isopropoxyaniline (408 μ L, 2.77 mmol) and toluene (1 mL) was microved at 170 °C for 15 minutes. The crude product was purified by preparatory HPLC (Waters) using a water/CH₃CN gradient with 0.1%. The pure fractions were combined, treated with
 10 1M aqueous NaOH and extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to yield the desired product. Addition of diethyl ether to the concentrated material caused precipitation and the precipitate was collected by filtration to afford N-(3-isopropoxyphenyl)-5-(2-pyridyl)oxazol-2-amine (22 mg, 5%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.44 (s, 1H), 8.55 (d, *J* = 4.1 Hz, 1H), 7.85 (td, *J* = 7.8, 1.7 Hz, 1H), 7.60 (s, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 2.1 Hz, 1H), 7.29 - 7.21 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 9.0 Hz, 1H), 6.59 - 6.49 (m, 1H), 4.57 (sept, *J* = 6.0 Hz, 1H), 1.28 (d, *J* = 6.0 Hz, 6H) ppm. ESI-MS m/z calc. 295.13, found 296.41 ($M+1$)⁺; Retention time: 0.63 minutes.

20
[00311] Using the general synthetic scheme outlined in Scheme C and experimental procedures analogous to those listed above in Examples 9-11, the following compounds can be prepared: 11 and 18.

25 **Scheme D: General Route AA for Preparation of Compounds of Formula IV**

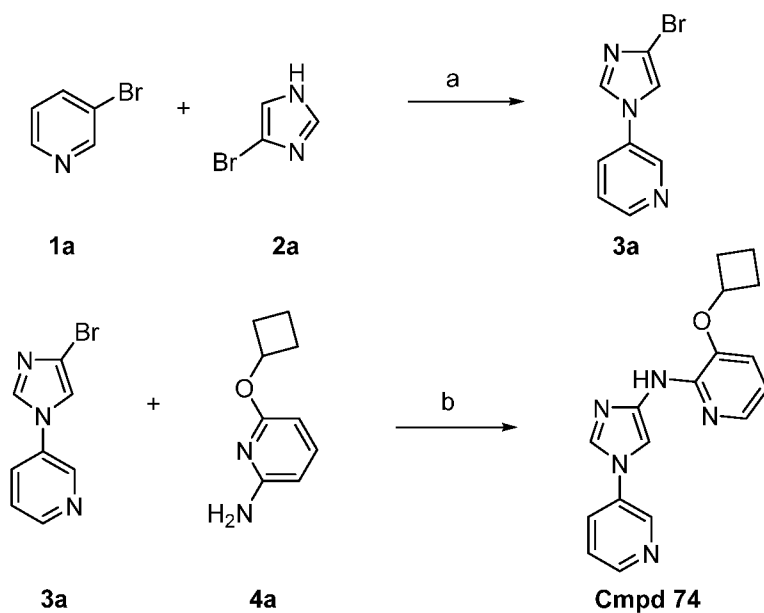


Compounds of Formula IV of the present invention may be prepared as generally outlined in Scheme D, where R^1 , R^2 , X^1 , and X^3 are as described herein.

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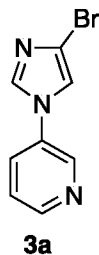
EXAMPLE 12

Preparation of 6-cyclobutoxy-*N*-(1-(pyridin-3-yl)-1*H*-imidazol-4-yl)pyridin-2-amine (Compound 74)



a) CuI, N,N,N',N' -tetramethylethane-1,2-diamine, Cs_2CO_3 , DMF; b) NaOtBu,

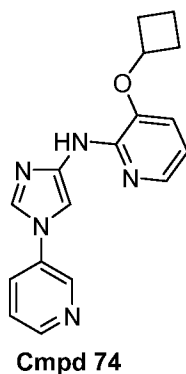
10 BrettPhos Precatalyst, 1,4 dioxane, Microwave 150 °C.

Preparation of 3-(4-bromoimidazol-1-yl)pyridine (3a)

[00312] To a 2L flask was added 3-bromopyridine (63.4 g, 401.3 mmol), 4-bromo-5H-imidazole (70.78 g, 481.6 mmol), N,N,N',N'-tetramethylethane-1,2-diamine (4.663 g, 6.056 mL, 40.13 mmol), cesium carbonate (130.8 g, 401.3 mmol), and dry dimethylformamide (50 mL). Nitrogen was bubbled in for ~10 min and iodocopper (3.820 g, 20.06 mmol) was added. The reaction was heated to 135 °C under nitrogen for 18 hours. The heat was removed and the reaction was stirred overnight. The dimethylformamide was evaporated under vacuum. The crude was dissolved in tetrahydrofuran (500 mL) and then the solution was filtered through a pad of Florisil. The filtrate was concentrated to obtain a thick reddish liquid which solidified. This material was triturated with acetonitrile to afford 64 g of desired product.

Preparation of 6-cyclobutoxy-N-(1-(pyridin-3-yl)-1H-imidazol-4-yl)pyridin-2-amine

15 (Compound 74)



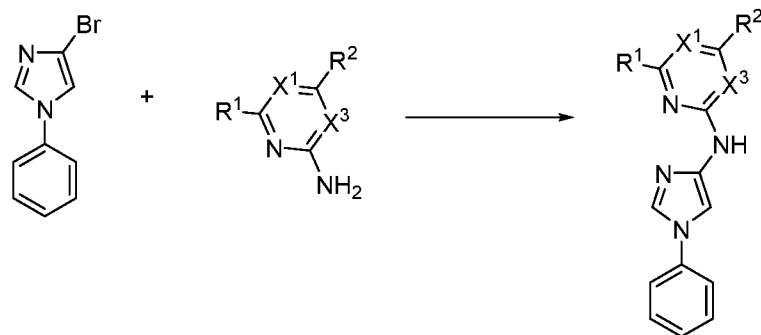
[00313] To a microwave tube was added 3-(4-bromoimidazol-1-yl)pyridine (170 mg, 0.7587 mmol), 6-(cyclobutoxy)pyridin-2-amine (186.9 mg, 1.138 mmol) and BrettPhos Precatalyst (18 mg, 0.02 mmol) into 1,4-dioxane (1.7 mL). The reaction was degassed with nitrogen for 20 minutes, then sodium *tert*-butoxide (182.3 mg, 1.9 mmol) was added. The solution was heated in a microwave reactor at 140 °C for 40 minutes. The solution was filtered through a plug of Celite and the solvent was

evaporated. The crude was purified on C18 reverse phase column to provide the purified product. The HCl salt was formed by adding HCl in 1,4-dioxane (4N) to a free base solution in dichloromethane. The solution was stirred for several minutes, then the solvent was evaporated and dried under vacuum to afford the desired

5 compound as the HCl salt. ESI-MS m/z calc. 307.1, found 308.3 (M+1)⁺; Retention time: 0.64 minutes (3 minutes run). ¹H NMR (300 MHz, Methanol-*d*₄) δ 9.36 (s, 1H), 8.98 - 8.89 (m, 2H), 8.82 (d, *J* = 8.3 Hz, 1H), 8.22 - 8.11 (m, 1H), 7.85 (dd, *J* = 9.3, 7.2 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 6.39 (d, *J* = 8.1 Hz, 1H), 5.08 (p, *J* = 7.1 Hz, 1H), 2.64 - 2.45 (m, 2H), 2.36 - 2.15 (m, 2H), 2.01 - 1.67 (m, 2H) ppm.

10 **[00314]** Using the general synthetic scheme outlined in Scheme AA and the experimental procedures listed above in Example 12, the following compounds can be prepared: 41,47,48,58,60, 64, 66, 68-70, 72, 73 and 75.

Scheme E: General Route BB for Preparation of Compounds of Formula IV

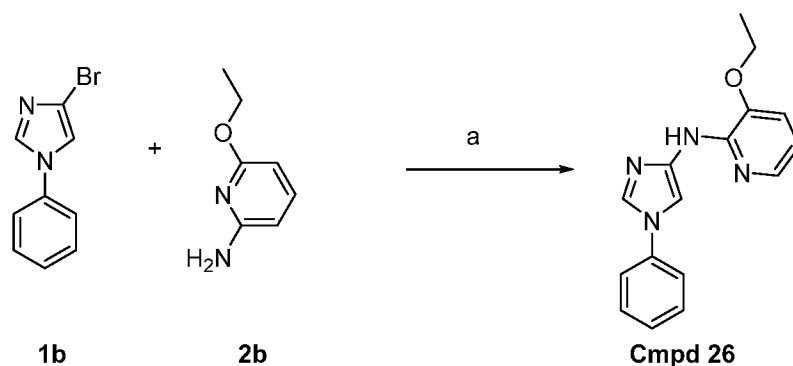


Compounds of Formula IV of the present invention may be prepared as generally outlined in Scheme E, where R¹, R², X¹, and X³ are as described herein.

20

EXAMPLE 13

Preparation of 6-ethoxy-N-(1-phenylimidazol-4-yl)pyridin-2-amine (Compound 26)



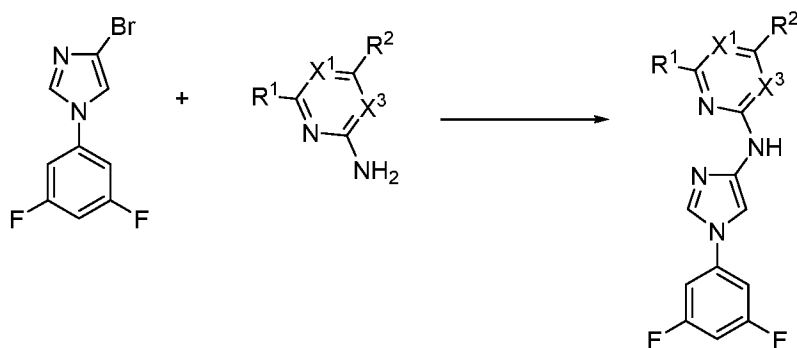
Reagents and conditions: (a) NaOtBu, BrettPhos Precatalyst, 1,4-dioxane, microwave 120 °C

5 **Preparation of 6-ethoxy-N-(1-phenylimidazol-4-yl)pyridin-2-amine (Compound 26)**

[00315] 4-bromo-1-phenyl-imidazole (281 mg, 1.260 mmol), sodium tert-butoxide (181.6 mg, 1.890 mmol), and 5 mol% BrettPhos Precatalyst were weighed into a microwave vial. The vial was flushed with nitrogen. 1,4-Dioxane (10.8 mL) was added and the reaction was degassed for 20 minutes. 6-Ethoxypyridin-2-amine (261 mg, 1.890 mmol) was added and this solution degassed for another 5 minutes. The vial was sealed and the reaction was heated at 120 °C in a microwave reactor for 30 minutes. The crude material was purified by silicagel chromatography (50 g amine Gold (ISCO) column; 0-50% (ethyl acetate:methanol (9:1))/heptane over 25 minutes). Desired fractions were combined and concentrated to yield 6-ethoxy-N-(1-phenylimidazol-4-yl)pyridin-2-amine (148.3 mg, 41%). ESI-MS *m/z* calc. 280.1, found 281.1 (M+1)⁺; Retention time: 2.32 minutes. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.39 (s, 1H), 8.09 (d, *J* = 1.6 Hz, 1H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.59 (dd, *J* = 8.6, 1.2 Hz, 2H), 7.56 - 7.48 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 6.46 (d, *J* = 7.5 Hz, 1H), 6.04 (d, *J* = 7.3 Hz, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 3H) ppm.

[00316] Using the general synthetic scheme outlined in Scheme E and the experimental procedures listed above in Example 13, the following compounds can be prepared: 28-34, 36, 38-40 and 50.

25 **Scheme F: General Route CC for Preparation of Compounds of Formula IV**

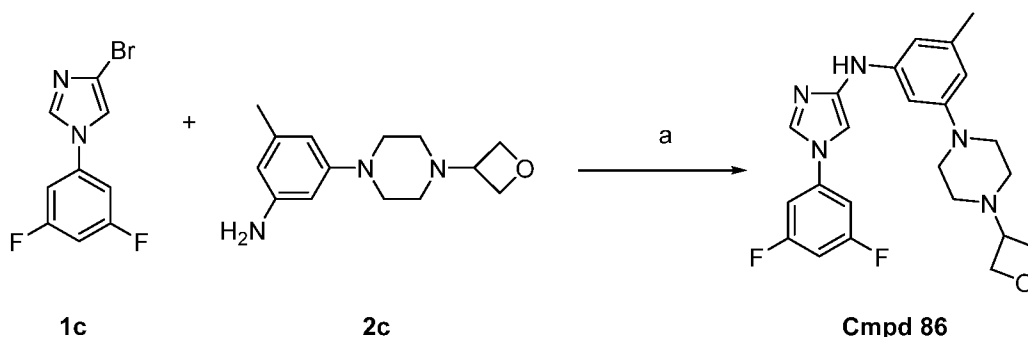


Compounds of Formula IV of the present invention may be prepared as generally outlined in Scheme F, where R^1 , R^2 , X^1 , and X^3 are as described herein.

5

EXAMPLE 14

Preparation of 1-(3,5-difluorophenyl)-N-[3-methyl-5-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]imidazol-4-amine (Compound 86)



10

(a) NaOtBu, *t*-BuXPhos Palladacycle, 1,4-dioxane, microwave 50 °C.

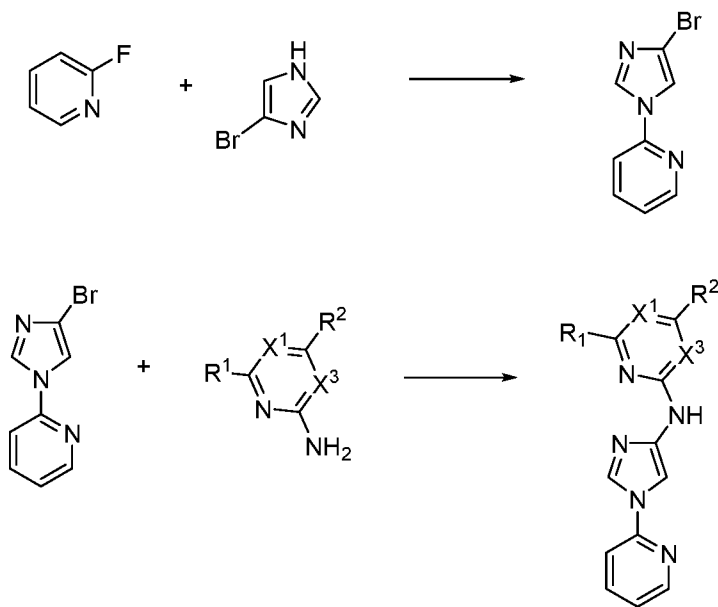
Preparation of 1-(3,5-difluorophenyl)-N-[3-methyl-5-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]imidazol-4-amine (Compound 86)

[00317] 4-bromo-1-(3,5-difluorophenyl)imidazole (100 mg, 0.39 mM) and 3-methyl-5-[4-(oxetan-3-yl)piperazin-1-yl]aniline; (145 mg, 0.58 mM) were dissolved in dry tert-butanol (5 mL); the solution was warmed and purged with nitrogen for several minutes. During the purge chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl) [2-(2-aminoethyl)phenyl]palladium(II) (*t*-Bu XPhos Palladacycle) (30 mg, 0.039 mM) and sodium tert-butoxide (60 mg, 0.58 mM) were added. The reaction was stirred in a microwave reactor at ~50 °C for 1.0 hour. The reaction was diluted with methanol and solvents were removed under reduced pressure. The

residue was partitioned between water and ethyl acetate; the organic layer was reduced to a solid under reduced pressure. The crude material was purified on a silica gel column eluting with dichloromethane:methanol (0-10%). The purified material was dissolved into dichloromethane and shaken with MP-TMT resin for 14 hours to remove residual palladium. The resin was filtered and the filtrate was concentrated to afford 46 mg of desired product in 25% yield. ESI-MS m/z calc. 425.5, found 426.5 ($M+1$)⁺; Retention time: 0.56 minutes; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.25 (s, 1H), 8.07 (s, 1H), 7.62 (d, *J* = 6.9 Hz, 2H), 7.39 (s, 1H), 7.19 (t, *J* = 9.3 Hz, 1H), 6.47 (s, 1H), 6.40 (s, 1H), 6.18 (s, 1H), 4.56 (t, *J* = 6.5 Hz, 2H), 4.47 (t, *J* = 6.0 Hz, 2H), 3.53 - 3.37 (m, 1H), 3.10 (s, 4H), 2.38 (s, 4H), 2.20 (s, 3H) ppm.

[00318] Using the general synthetic scheme outlined in Scheme F and the experimental procedures listed above in Example 14, the following compounds can be prepared: 42-46, 54 and 87.

15 Scheme G: General Route DD for Preparation of Compounds of Formula IV

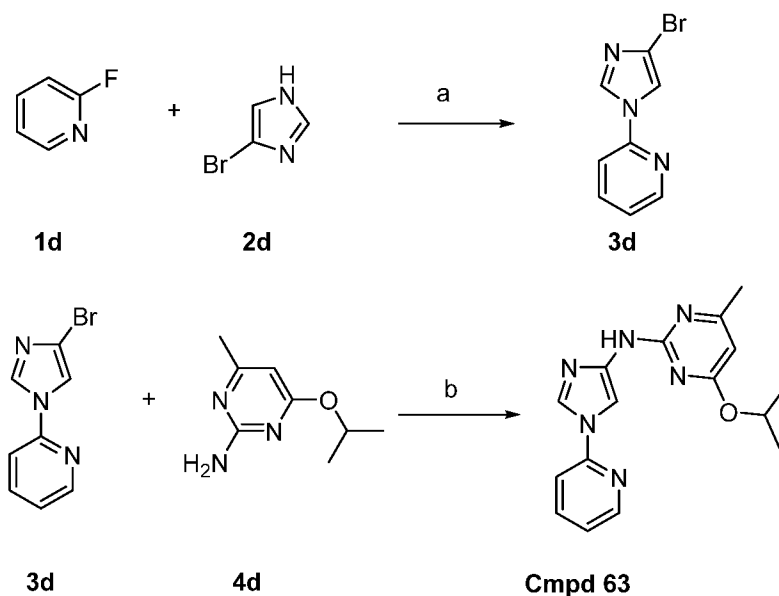


Compounds of Formula IV of the present invention may be prepared as generally outlined in Scheme G, where R¹, R², X¹, and X³ are as described herein.

20

EXAMPLE 15

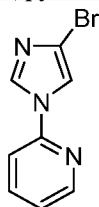
Preparation of 4-isopropoxy-6-methyl-N-[1-(2-pyridyl)imidazol-4-yl]pyrimidin-2-amine (Compound 63)



a) K_2CO_3 , DMF, 100 °C, 24hours; b) NaOtBu, BrettPhos Precatalyst, dioxane, microwave, 140 °C

5

Preparation of 2-(4-bromoimidazol-1-yl)pyridine (3d)



[00319] In a microwave flask containing 4-bromo-5H-imidazole (10 g, 68.04 mmol) in dimethylformamide (70.00 mL) was added 2-fluoropyridine (7.9 g, 7.0 mL, 82 mmol) and potassium carbonate (14.1 g, 102 mmol). The reaction was heated in a microwave reactor at 100 °C for 24 hours. LCMS showed that the product was formed. The reaction was added to water and a precipitate formed which was then filtered and dried under vacuum to afford the product in 92% yield. ESI-MS m/z calc. 223.0, found 234.1 ($M+1$)⁺; Retention time: 0.71 minutes.

Preparation of 4-isopropoxy-6-methyl-N-[1-(2-pyridyl)imidazol-4-yl]pyrimidin-2-amine (Compound 63)

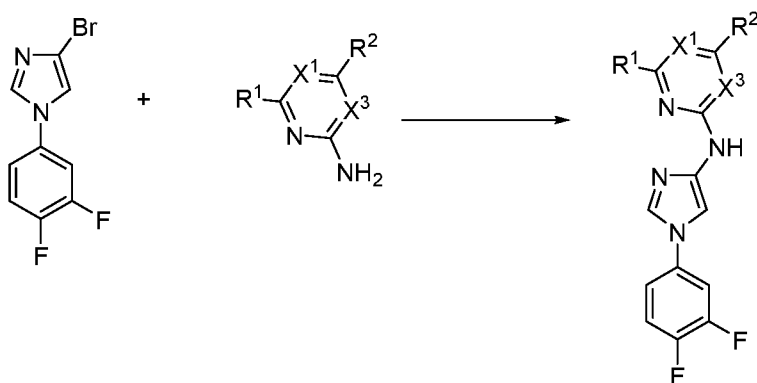
[00320] 2-(4-bromoimidazol-1-yl)pyridine (3d) (149 mg, 0.6131 mmol) was added into 1,4-dioxane (4 mL) in a microwave flask. The solution was degassed with

nitrogen for 20 minutes, then sodium tert-butoxide (176 mg, 1.84 mmol) and BrettPhos Precatalyst (24.5 mg, 0.031 mmol) were added into the solution. The reaction was heated in a microwave reactor at 140 °C for 50 minutes. The reaction mixture was filtered over Celite and the solvent was evaporated. The crude was
 5 purified by reverse phase chromatography (C18 100 g column (ISCO); 10-90% water/acetonitrile with a trifluoroacetic acid modifier) to afford purified product. Dichloromethane was added into the combined fractions and the fractions were then neutralized with A21 resin. After stirring for several minutes, methanol was added and the solution was filtered. The filtrate was then evaporated and dried under
 10 vacuum to afford 16.0 mg of desired product. ESI-MS m/z calc. 310.2, found 311.3 (M+1)⁺; Retention time: 0.61 minutes; ¹H NMR (300 MHz, Methanol-*d*₄) δ 8.49 (dd, J = 4.9, 1.1 Hz, 1H), 8.40 (d, J = 1.1 Hz, 1H), 8.03 - 7.93 (m, 2H), 7.65 (d, J = 8.2 Hz, 1H), 7.36 (dd, J = 6.9, 4.9 Hz, 1H), 6.15 (d, J = 6.1 Hz, 1H), 5.44 (dq, J = 12.4, 6.1 Hz, 1H), 2.36 (d, J = 5.0 Hz, 3H), 1.40 (t, J = 6.5 Hz, 6H) ppm.

15

[00321] Using the general synthetic scheme outlined in Scheme G and the experimental procedures listed above in Example 15, the following compounds can be prepared: 37, 59, 61, 65, 71, 80 and 82.

20 Scheme H: General Route EE for Preparation of Compounds of Formula IV

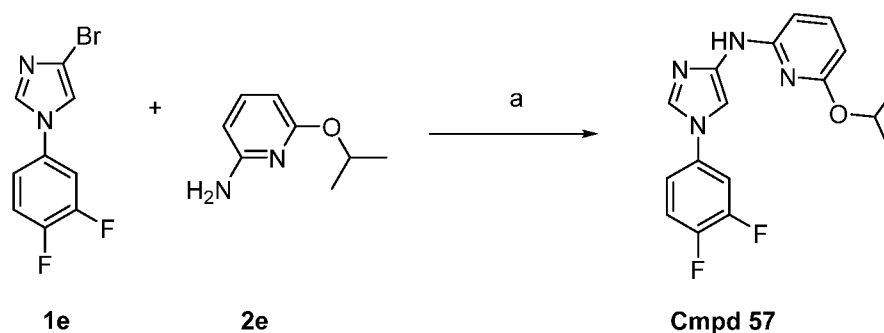


Compounds of Formula IV of the present invention may be prepared as generally outlined in Scheme H, where R¹, R², X¹, and X³ are as described herein.

25

EXAMPLE 16

Preparation of N-[1-(3,4-difluorophenyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine (Compound 57)



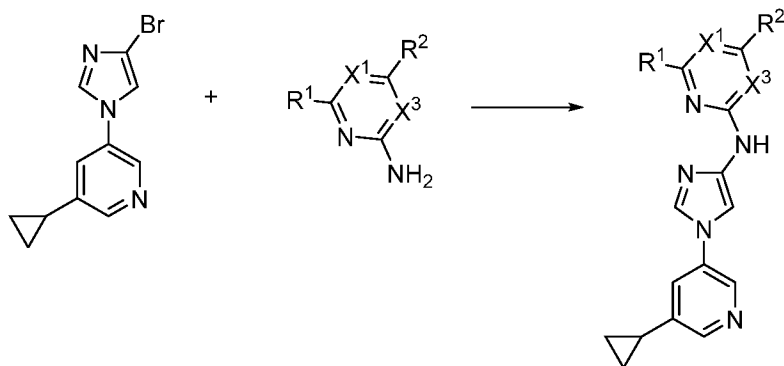
a) NaOtBu, BrettPhos Precatalyst, 1,4-dioxane, microwave, 140 °C

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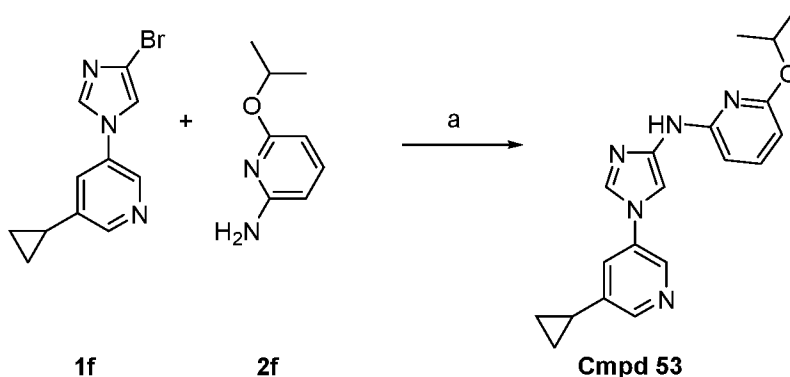
Preparation of N-[1-(3,4-difluorophenyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine (Compound 57)

[00322] To a microwave tube was added 4-bromo-1-(3,4-difluorophenyl)imidazole (157 mg, 0.6061 mmol), 6-isopropoxypyridin-2-amine (138 mg, 0.91 mmol) in 1,4-dioxane (4 mL). The mixture was degassed with nitrogen for 20 minutes, then sodium tert-butoxide (174.7 mg, 1.82 mmol) and BrettPhos Precatalyst (approximately 24 mg, 0.03 mmol) were added. The reaction was heated in a microwave reactor at 140 °C for 40 minutes. The reaction mixture was filtered over celite and the solvent evaporated. The crude was purified by reverse phase chromatography (C18 100 g column (ISCO); 10-90% water/acetonitrile with a trifluoroacetic acid modifier) to afford purified product. Dichloromethane was added into the combined fractions and the fractions were then neutralized with A21 resin. After stirring for several minutes, methanol was added and the solution was filtered. The solvent was then evaporated and dried under vacuum to afford 60.6 mg of desired product in 29% yield. ESI-MS m/z calc. 330.1, found 331.5 ($M+1$)⁺; Retention time: 0.71 minutes; ¹H NMR (300 MHz, Methanol-*d*₄) δ 8.40 - 8.32 (m, 1H), 7.78 - 7.63 (m, 2H), 7.58 - 7.41 (m, 3H), 6.42 (dd, *J* = 8.0, 0.7 Hz, 1H), 6.18 (dd, *J* = 7.9, 0.7 Hz, 1H), 5.19 (hept, *J* = 6.2 Hz, 1H), 1.37 (d, *J* = 6.2 Hz, 6H) ppm.

[00323] Using the general synthetic scheme outlined in Scheme H and the experimental procedures listed above in Example 16, the following compound can be prepared: 56.

Scheme I: General Route FF for Preparation of Compounds of Formula IV

Compounds of Formula IV of the present invention may be prepared as generally
 5 outlined in Scheme I, where R^1 , R^2 , X^1 , and X^3 are as described herein.

EXAMPLE 17**Preparation of N-[1-(5-cyclopropyl-3-pyridyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine (Compound 53)**

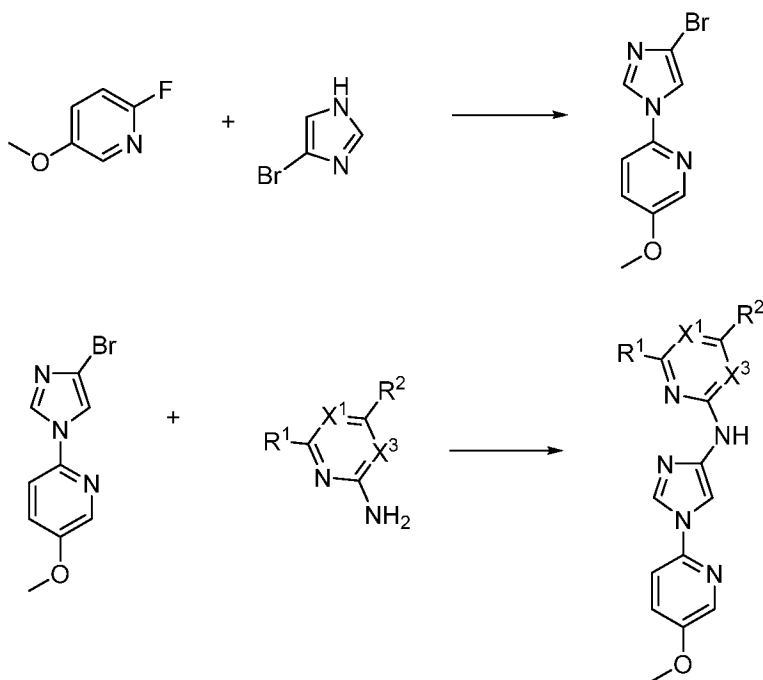
a) NaOtBu, BrettPhos Precatalyst, 1,4-dioxane, microwave 140 °C.

Preparation of N-[1-(5-cyclopropyl-3-pyridyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine (Compound 53)

- 15 **[00324]** To a microwave tube was added 3-(4-bromoimidazol-1-yl)-5-cyclopropylpyridine (108 mg, 0.41 mmol) and 6-isopropoxy-pyridin-2-amine (93 mg, 0.61 mmol) in 1,4-dioxane (3 mL). The reaction was degassed with nitrogen for 20 minutes, then sodium tert-butoxide (118 mg, 1.2 mmol) and BrettPhos Precatalyst (16 mg, 0.02 mmol) were added. The reaction was heated in a microwave at 140°C for 40 minutes.
- 20 The reaction mixture was filtered over celite and the solvent evaporated. The crude

was purified by reverse phase chromatography (C18 100 g column (ISCO); 10-90% water/acetonitrile with a trifluoroacetic acid modifier) to afford purified product. Dichloromethane was added into the combined fractions and the fractions were then neutralized with A21 resin. After stirring for several minutes, methanol was added and the solution was filtered. The solvent was then evaporated and dried under vacuum to afford 11.9 mg of desired product. ESI-MS m/z calc. 335.2, found 336.2 ($M+1$)⁺; Retention time: 0.80 minutes; ¹H NMR (300 MHz, Methanol-*d*₄) δ 8.71 - 8.61 (m, 2H), 8.51 (d, J = 1.9 Hz, 1H), 7.77 (q, J = 2.7, 2.2 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 6.45 (dd, J = 8.0, 0.6 Hz, 1H), 6.24 (dd, J = 8.0, 0.7 Hz, 1H), 5.20 (h, J = 6.2 Hz, 1H), 2.13 (tt, J = 8.4, 5.0 Hz, 1H), 1.39 (d, J = 6.2 Hz, 6H), 1.23 - 1.11 (m, 2H), 0.96 - 0.85 (m, 2H) ppm.

Scheme J: General Route GG for Preparation of Compounds of Formula IV

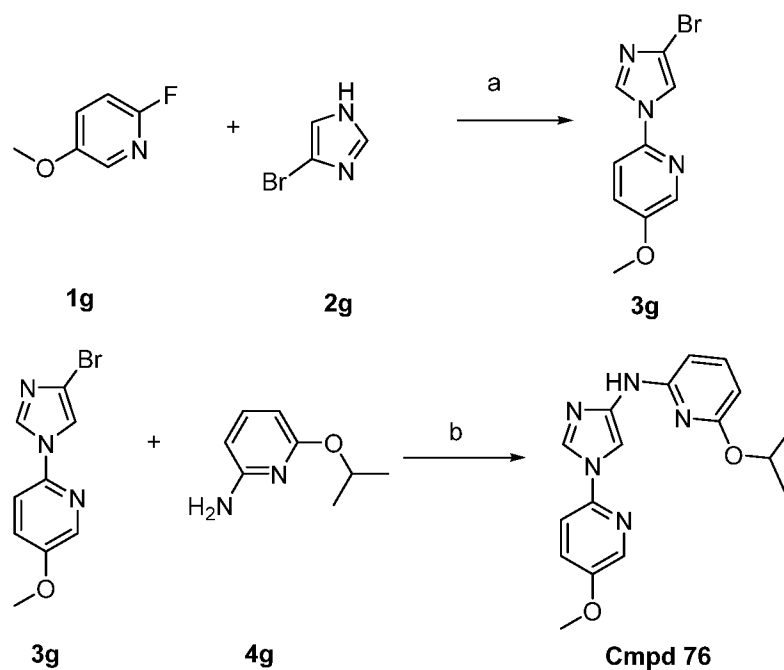


15

Compounds of Formula IV of the present invention may be prepared as generally outlined in Scheme J, where R¹, R², X¹, and X³ are as described herein.

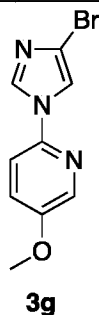
EXAMPLE 18

Preparation of 6-isopropoxy-N-[1-(5-methoxy-2-pyridyl)imidazol-4-yl]pyridin-2-amine (Compound 76)



- 5 a) Cs_2CO_3 , NMP, 140 °C; b) NaOtBu, BrettPhos Precatalyst, dioxane, microwave, 140 °C.

Preparation of 2-(4-bromoimidazol-1-yl)-5-methoxy-pyridine (**3g**)



10

[00325] 4-bromo-1H-imidazole (867 mg, 5.9 mmol), Cs_2CO_3 (1.28 g, 3.9 mmol), and 2-fluoro-5-methoxy-pyridine (500 mg, 3.9 mmol) were combined in NMP (5 mL) in a microwave vial. The reaction was heated in a microwave at 140°C for 60 minutes. The reaction was poured into water and the precipitate was filtered to afford

15

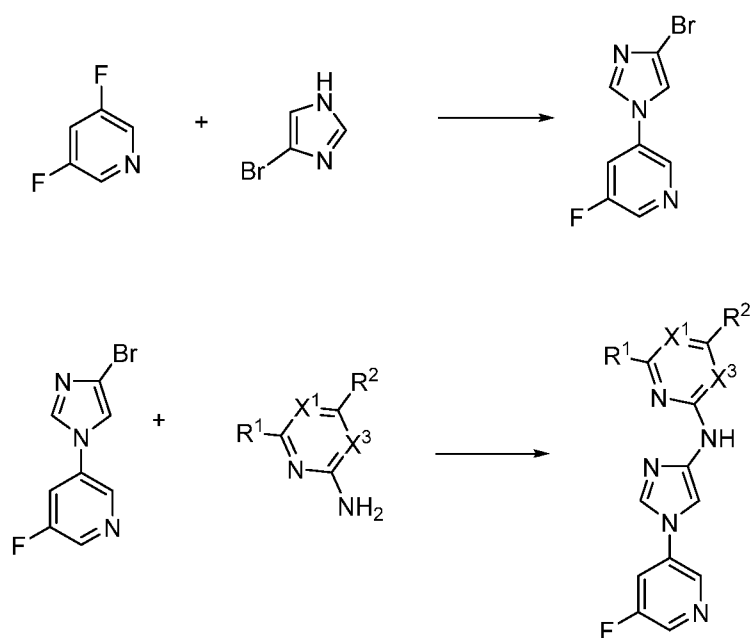
296 mg of desired product.

Preparation of 6-isopropoxy-N-[1-(5-methoxy-2-pyridyl)imidazol-4-yl]pyridin-2-amine (Compound 76)

[00326] To a microwave tube were added 2-(4-bromoimidazol-1-yl)-5-methoxy-pyridine (167 mg, 0.67 mmol) and 6-isopropoxypyridin-2-amine (150mg, 0.99 mmol) in 1,4-dioxane (1.5 mL). The reaction was degassed with nitrogen for 20 minutes, then sodium tert-butoxide (118 mg, 1.2 mmol) and BrettPhos Precatalyst (16 mg, 0.02 mmol) were added. The reaction was heated in a microwave at 140°C for 40 minutes. The reaction mixture was filtered over Celite and the solvent evaporated. The crude was purified by reverse phase chromatography (C18 100 g column (ISCO); 10-90% water/acetonitrile with a trifluoroacetic acid modifier) to afford purified product. Dichloromethane was added into the combined fractions and the fractions were then neutralized with A21 resin. The HCl salt was formed by adding HCl (4N)/dioxane to a dichloromethane solution at room temp. The solution was stirred for several minutes, then the solvent was evaporated and dried under vacuum to afford 88.6 mg of desired product as the HCl salt in 21% yield. ESI-MS *m/z* calc. 325.2, found 326.3 (M+1)⁺; Retention time: 0.85 minutes; ¹H NMR (300 MHz, Methanol-*d*₄) δ 8.22 (t, J = 8.6 Hz, 1H), 7.79 - 7.71 (m, 1H), 7.66 - 7.46 (m, 2H), 6.51 - 6.38 (m, 1H), 6.29 (dd, J = 11.4, 5.9 Hz, 1H), 5.25 - 5.11 (m, 1H), 3.99 - 3.91 (m, 3H), 1.49 - 1.32 (m, 7H) ppm.

[00327] Using the general synthetic scheme outlined in Scheme J and the experimental procedures listed above in Example 18, the following compound can be prepared: 78.

Scheme K: General Route HH for Preparation of Compounds of Formula IV

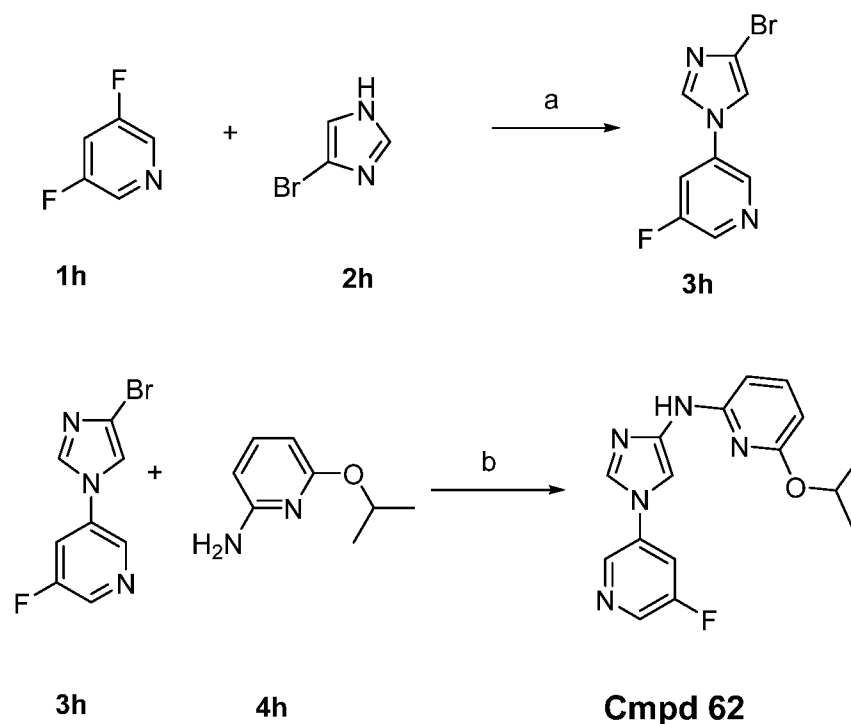


Compounds of Formula IV of the present invention may be prepared as generally outlined in Scheme K, where R¹, R², X¹, and X³ are as described herein.

5

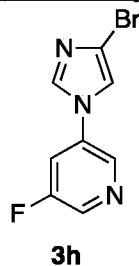
EXAMPLE 19

Preparation of N-[1-(5-fluoro-3-pyridyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine
(Compound 62)



a) K_2CO_3 , NMP, 140 °C; b) NaOtBu, BrettPhos Precatalyst/, 1,4-dioxane, microwave, 140 °C

5 Preparation 3-(4-bromoimidazol-1-yl)-5-fluoro-pyridine (3h)

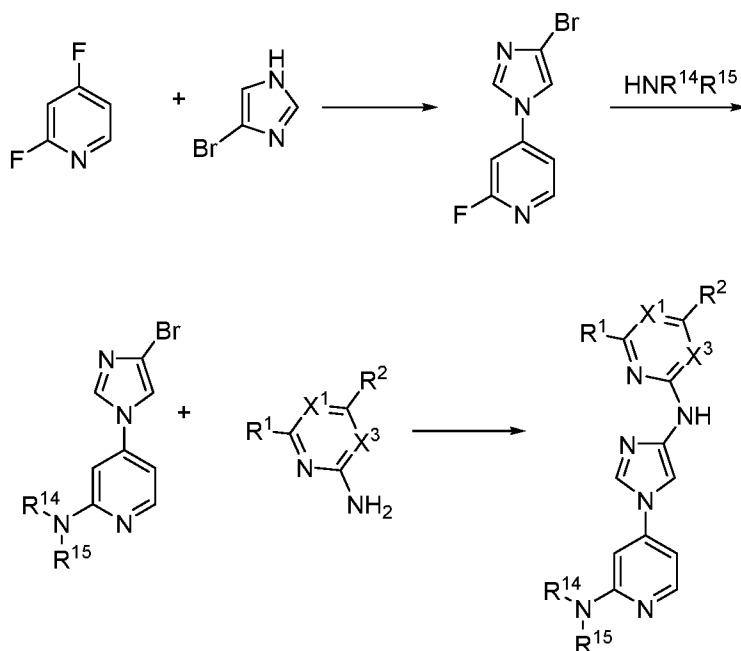


[00328] To a flask was added 4-bromo-5H-imidazole (approximately 455 mg, 3.1 mmol) in N-methylpyrrolidine (6 mL) and 3,5-difluoropyridine (366 mg, 3.1 mmol) and potassium carbonate (429 mg, 3.1 mmol). The reaction was heated at 100 °C for 12 hours. LCMS showed the formation of the product. The reaction was filtered and the crude product was purified by reverse phase chromatography (C18 100 g column (ISCO); 10-90% water/acetonitrile with a trifluoroacetic acid modifier) to afford purified product. The fraction were combined and neutralized with an SPE- CO_3H cartridge to afford the desired product.

Preparation of N-[1-(5-fluoro-3-pyridyl)imidazol-4-yl]-6-isopropoxy-pyridin-2-amine
(Compound **62**)

[00329] To a microwave tube were added 3-(4-bromoimidazol-1-yl)-5-fluoro-pyridine (109 mg, 0.42 mmol) and 6-isopropoxy-pyridin-2-amine (approximately 96 mg, 0.63 mmol) in 1,4-dioxane (1 mL). The mixture was degassed with nitrogen for 20 min, then sodium tert-butoxide (121 mg, 1.26 mmol) and BrettPhos Precatalyst (16 mg, 0.02 mmol) were added. The reaction was heated in a microwave at 140 °C for 40 minutes. The reaction mixture was filtered over Celite and the solvent evaporated. The crude was purified by reverse phase chromatography (C18 100 g column (ISCO); 10-90% water/acetonitrile with a trifluoroacetic acid modifier) to afford purified product. The combined fractions were then neutralized with an SPE-CO₃H cartridge to afford 9.8 mg of desired compound **62** as a freebase. ESI-MS *m/z* calc. 313.1, found 314.2 (M+1)⁺; Retention time: 0.68 minutes; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.45 (s, 1H), 8.78 (s, 1H), 8.58 (s, 1H), 8.26 (s, 1H), 8.13 (d, J = 9.8 Hz, 1H), 7.71 (s, 1H), 7.42 (s, 1H), 6.46 (d, J = 8.2 Hz, 1H), 6.02 (d, J = 6.8 Hz, 1H), 5.31 (s, 1H), 1.33 (t, J = 10.3 Hz, 6H) ppm.

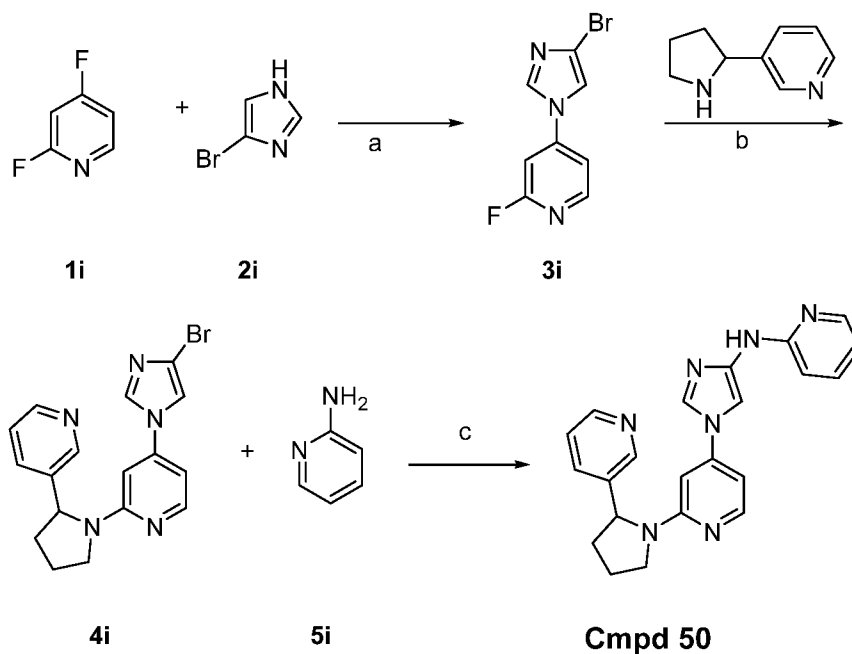
Scheme L: General Route II for Preparation of Compounds of Formula IV



Compounds of Formula IV of the present invention may be prepared as generally outlined in Scheme L, where R^1 , R^2 , X^1 , and X^3 are as described herein and $NR^{14}R^{15}$ represent an optionally substituted heterocyclic ring.

EXAMPLE 20

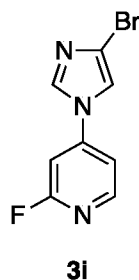
5 Preparation of N-[1-[2-[2-(3-pyridyl)pyrrolidin-1-yl]-4-pyridyl]imidazol-4-yl]pyridin-2-amine (Compound 50)



a) K_2CO_3 , DMF, 50 °C; b) K_2CO_3 , MeCN, 90 °C c) NaOtBu, BrettPhos Precatalyst, 1,4-dioxane, microwave 140 °C

10

Preparation of 4-(4-bromoimidazol-1-yl)-2-fluoro-pyridine (3i)

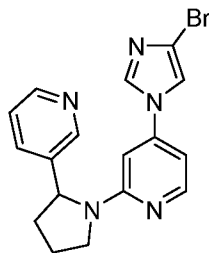


[00330] To a flask was added 2,4-difluoropyridine (**1i**, 5.48g, 47.60 mmol) in dimethylformamide (133.5 mL), 4-bromo-5H-imidazole (**2i**, 5.83g, 39.67 mmol) and potassium carbonate (5.4 g, 39.7 mmol). The reaction was heated at 50 °C for 12 hours. The reaction mixture was poured into water, the precipitate was filtered,

15

washed with water and dried under vacuum to afford desired product, **3i**. ESI-MS m/z calc. 241.0, found 242.0 ($M+1$)⁺; Retention time: 0.79 minutes.

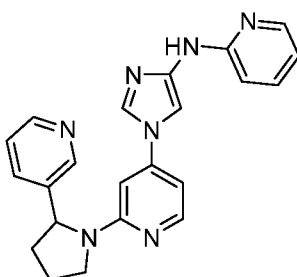
5 Preparation of N-[2-fluoro-5-methyl-3-(6-oxa-2-azaspiro[4.5]decan-2-yl)phenyl]-1-phenyl-1,2,4-triazol-3-amine (**4i**)



4i

[00331] To a flask was added 4-(4-bromoimidazol-1-yl)-2-fluoro-pyridine (500 mg, 1.55 mmol), 3-pyrrolidin-2-ylpyridine (344mg, 2.3 mmol) and potassium carbonate (321 mg, 2.3 mmol) in acetonitrile (2 mL). The reaction was heated at 90°C for 10
10 hours. The reaction mixture was filtered and solvent was evaporated. Purification by reverse phase chromatography (150 g C18 Aq Gold column (ISCO); 10-90% water-acetonitrile with a trifluoroacetic acid modifier) afforded desired product, **4i**. ESI-MS m/z calc. 369.1, found 370.0 ($M+1$)⁺; Retention time: 0.51 minutes.

15 Preparation of N-[1-[2-[2-(3-pyridyl)pyrrolidin-1-yl]-4-pyridyl]imidazol-4-yl]pyridin-2-amine (Compound **50**)

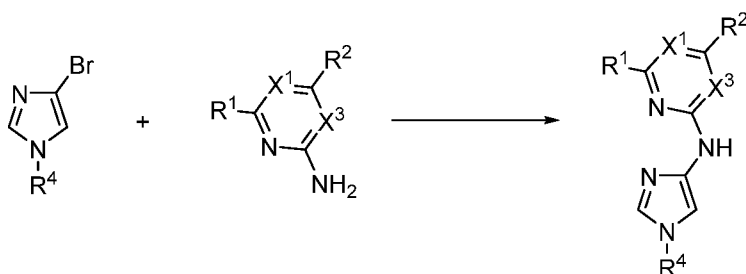


[00332] A microwave flask containing pyridin-2-amine (approximately 26.82 mg, 0.2850 mmol) in 1,4-dioxane (3mL) was degassed with nitrogen for 20 minutes, then
20 sodium tert-butoxide (54 mg, 0.5700 mmol) and BrettPhos Precatalyst (8 mg, 0.01mmol) were added. The reaction was heated in microwave at 140°C for 40 minutes. The reaction mixture was filtered over Celite and the solvent was

evaporated. Purification by reverse phase chromatography (150 g C18 Aq Gold column (ISCO); 10-90% water-acetonitrile with a trifluoroacetic acid modifier) afforded desired product. The desired fractions were neutralized with A21 resin in dichloromethane/ methanol and solvent was removed to afford 36.3 mg of desired product, compound **50**. ESI-MS m/z calc. 383.2, found 384.2 (M+1)⁺; Retention time: 0.45 minutes; ¹H NMR (300 MHz, Methanol-*d*₄) δ 8.83 - 8.74 (m, 1H), 8.73 - 8.61 (m, 1H), 8.50 - 8.38 (m, 2H), 8.17 - 8.03 (m, 3H), 8.02 - 7.88 (m, 1H), 7.63 (d, J = 1.6 Hz, 1H), 7.29 (dd, J = 9.0, 1.1 Hz, 1H), 7.11 (td, J = 5.9, 1.5 Hz, 2H), 7.01 - 6.92 (m, 1H), 5.59 - 5.48 (m, 1H), 4.04 (td, J = 8.2, 7.4, 4.8 Hz, 1H), 3.73 (td, J = 9.2, 6.8 Hz, 1H), 2.67 - 2.56 (m, 1H), 2.18 (ddt, J = 23.5, 19.2, 7.8 Hz, 4H) ppm.

[00333] Using the general synthetic scheme outlined in Scheme L and the experimental procedures listed above in Example 20, the following compounds can be prepared: 35 and 50.

15 **Scheme M: General Route JJ for Preparation of Compounds of Formula IV**

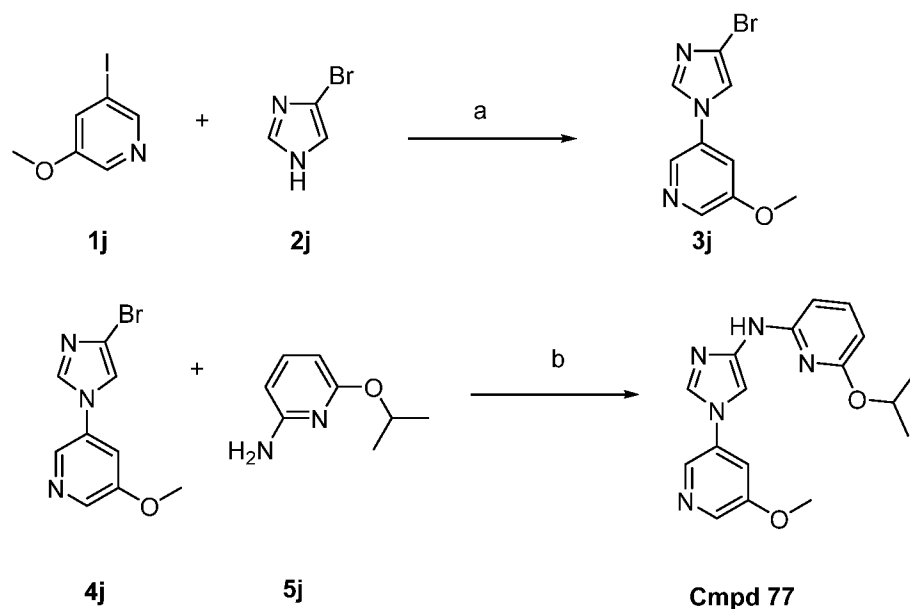


Compounds of Formula IV of the present invention may be prepared as generally outlined in Scheme M, where R¹, R², R⁴, X¹, and X³ are as described herein.

20

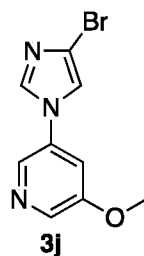
EXAMPLE 21

Preparation of 6-isopropoxy-N-[1-(5-methoxy-3-pyridyl)imidazol-4-yl]pyridin-2-amine (Compound 77)



a) Cs_2CO_3 , CuI, TMEDA, DMF, 90 °C; b) NaOtBu, BrettPhos Precatalyst, 1,4-dioxane, 140 °C

5 Preparation of 3-(4-bromoimidazol-1-yl)-5-methoxy-pyridine (3j)



[00334] In a flask containing 4-bromo-5H-imidazole (293 mg, 2.0 mmol) in dimethylformamide (7 mL) was added 3-iodo-5-methoxy-pyridine (293 mg, 1.2 mmol), copper iodide (12 mg, 0.06 mmol) and TMEDA (15 mg, 19 μL , 0.12 mmol).

- 10 The resulting mixture was stirred at 90 °C under an argon atmosphere for 48 hours. The reaction was cooled to room temperature. The reaction mixture was poured into water and a precipitate formed. After a few minutes of stirring, the precipitate was filtered and dried under vacuum to afford 114 mg of desired product, **3j**, in 34% yield. ESI-MS m/z calc. 253.0, found 254.1 ($\text{M}+1$)⁺; Retention time: 0.61 minutes.

15

Preparation of 6-isopropoxy-N-[1-(5-methoxy-3-pyridyl)imidazol-4-yl]pyridin-2-amine (Compound 77)

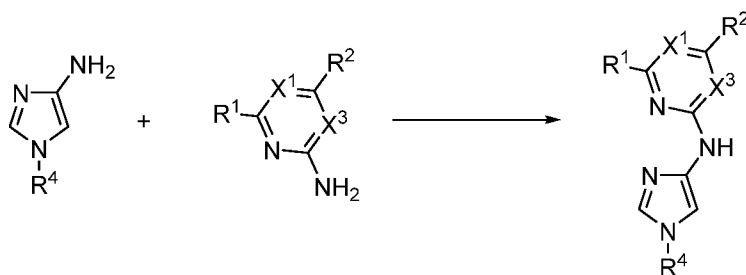
[00335] A microwave flask containing 3-(4-bromoimidazol-1-yl)-5-methoxy-pyridine (114 mg, 0.43 mmol), 6-isopropoxypyridin-2-amine (98 mg, 0.64 mmol) and BrettPhos Precatalyst (10 mg, 0.01 mmol) in 1,4-dioxane (1 mL) was degassed with nitrogen for 20 minutes, then sodium tert-butoxide (103 mg, 1.1 mmol) was added.

- 5 The reaction was heated in a microwave at 140 °C for 40 minutes. The reaction was filtered over Celite and the solvent was evaporated. The crude was purified by reverse phase chromatography (150 g C18 Aq Gold column (ISCO); 10-90% water-acetonitrile with a trifluoroacetic acid modifier). The desired fractions were combined and neutralized. The HCl salt was formed by adding HCl (4N)/Dioxane to
- 10 a dichloromethane solution at room temperature. The solution was stirred for several minutes, then the solvent was evaporated and dried under vacuum to afford 22.6 mg of desired product as the HCl salt. ESI-MS m/z calc. 325.2, found 254.1 (M+1)⁺; Retention time: 0.61 minutes; ¹H NMR (300 MHz, Methanol-*d*₄) δ 9.00 (s, 1H), 8.57 (s, 1H), 8.47 (s, 1H), 7.87 (t, J = 2.3 Hz, 1H), 7.69 (t, J = 8.1 Hz, 1H), 6.55 (d, J = 7.9
- 15 Hz, 1H), 6.35 (dd, J = 10.3, 8.1 Hz, 1H), 5.11 (dq, J = 11.8, 5.9 Hz, 1H), 3.31 (dt, J = 3.2, 1.6 Hz, 3H), 1.47 - 1.33 (m, 6H) ppm.

[00336] Using the general synthetic scheme outlined in Scheme M and the experimental procedures listed above in Example 21, the following compounds can be prepared: 67, 79 and 83-85.

20

Scheme N: General Route KK for Preparation of Compounds of Formula IV

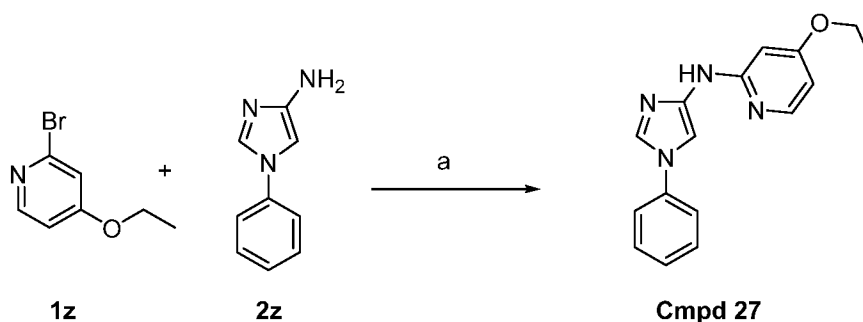


Compounds of Formula IV of the present invention may be prepared as generally outlined in Scheme N, where R¹, R², R⁴, X¹, and X³ are as described herein.

25

EXAMPLE 22

Preparation of 4-ethoxy-N-(1-phenylimidazol-4-yl)pyridin-2-amine (Compound 27)



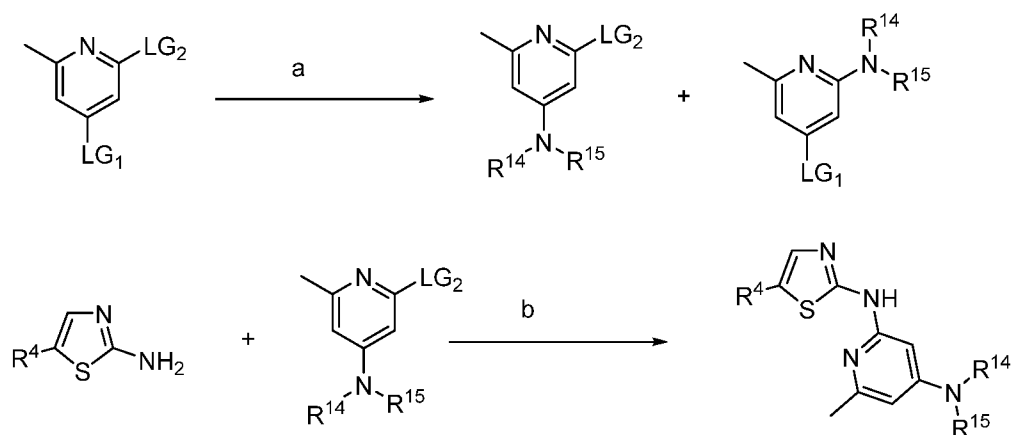
a) NaOtBu, t-BuXPhos Palladacycle, 1,4-dioxane, microwave 120 °C

Preparation of 4-ethoxy-N-(1-phenylimidazol-4-yl)pyridin-2-amine (Compound 27)

- 5 **[00337]** Sodium tert-butoxide (210 mg, 2.2 mmol), 1-phenylimidazol-4-amine (Hydrochloride salt) (245 mg, 1.3 mmol), and 2-bromo-4-ethoxy-pyridine (126 mg, 0.6 mmol) were weighed into a microwave vial. The mixture was diluted with 1,4-dioxane (5 mL) and degassed with nitrogen for 10 minutes. 0.1 Equivalents of
- 10 chloro(2-di-t-butylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl) [2-(2-aminoethyl)phenyl]palladium(II) (t-BuXPhos Palladacycle) was added and degassed with nitrogen for another 10 minutes. The vial was sealed and the reaction was heated at 120 °C for 30 minutes in a microwave. LC/MS showed the desired product. The crude was purified with double stacked 50 g amine silica columns eluting with 0-100%(Ethyl Acetate (10%Methanol)) in hexane over 30 minutes. The pure fractions
- 15 were combined and concentrated to dryness to afford 15.9 mg of desired product. ESI-MS m/z calc. 280.13242, found 281.07 (M+1)+; Retention time: 2.1 minutes; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.21 (s, 1H), 8.07 (d, J = 1.7 Hz, 1H), 7.99 (d, J = 5.9 Hz, 1H), 7.74 (d, J = 1.7 Hz, 1H), 7.62 (dt, J = 8.6, 1.1 Hz, 2H), 7.51 (tt, J = 10.7, 5.2 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 6.46 (d, J = 2.1 Hz, 1H), 6.31 (dd, J = 5.9, 2.2 Hz,
- 20 1H), 4.02 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H) ppm.

[00338] Using the general synthetic scheme outlined in Scheme N and the experimental procedures listed above in Example 22, the following compounds can be prepared: 55 and 81.

25 **Scheme M: General Route LL for Preparation of Compounds of Formula II**



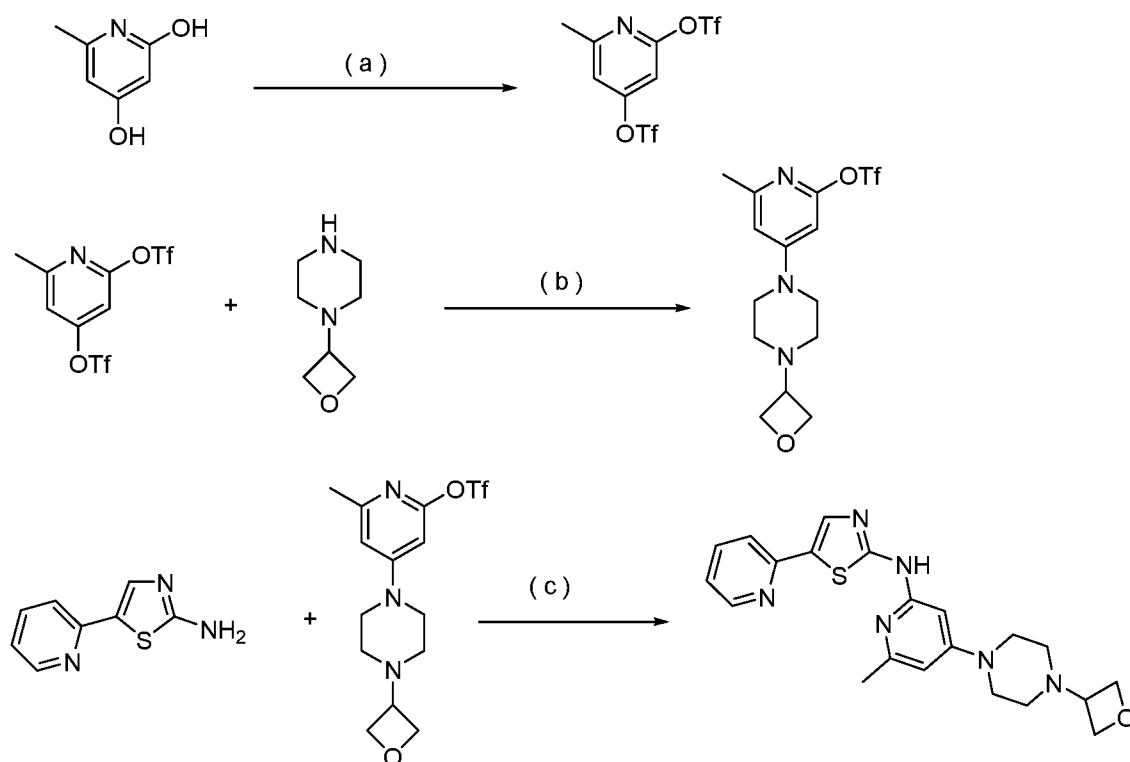
a: $NHR^{14}R^{15}$, K_2CO_3 , CH_3CN ; b: $NaOtBu$, *t*-BuXPhos Palladacycle, 1,4-dioxane

Compounds of Formula II of the present invention may be prepared as generally outlined in Scheme M, where R^4 is as described herein, LG_1 and LG_2 are leaving

5 groups, and $NR^{14}R^{15}$ represent an optionally substituted heterocyclic ring (e.g., G^1 , G^2).

EXAMPLE 23

Preparation of N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(2-
 10 pyridyl)thiazol-2-amine (Compound 91)



a) Comins' reagent, TEA, pyridine, THF; b). K_2CO_3 , CH_3CN ; c) $NaOtBu$, $t\text{-BuXPhos}$ Palladacycle, 1,4-dioxane, microwave, $120^\circ C$

5

Preparation of [2-methyl-6-(trifluoromethylsulfonyloxy)-4-pyridyl] trifluoromethanesulfonate

[00339] A 2 L flask was charged with 6-methylpyridine-2,4-diol (17 g, 135.9 mmol) and triethylamine (46 mL, 330 mmol) in tetrahydrofuran (500 mL) and pyridine (50 mL). The mixture was cooled in an ice bath and N-(5-chloro-2-pyridyl)-1,1,1-trifluoro-N-(trifluoromethyl-sulfonyl)methane-sulfonamide (Comins' reagent) (117.4 g, 299 mmol) was added, all at once. The reaction was allowed to warm to room temperature overnight. Water (400 mL) was added and the layers separated. The organic layer was washed with water and dried over sodium sulfate. After filtration, the solvent was removed under vacuum, affording [2-methyl-6-(trifluoromethylsulfonyloxy)-4-pyridyl] trifluoromethanesulfonate as a brown oil. The crude was chromatographed on a silica gel column eluting with 20% ethyl acetate/heptane to afford 48g of a pale yellow liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.14 (m, 1H), 6.96 (dd, $J = 1.8, 0.8$ Hz, 1H), 2.65 (d, $J = 0.7$ Hz, 3H) ppm.

Preparation of [6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl] trifluoromethane-sulfonate

[00340] To a mixture of 1-(oxetan-3-yl)piperazine (1.5 g, 10.5 mmol) and
5 potassium carbonate (3 g, 21.7 mmol) in acetonitrile (100 mL) at 0 °C was added [2-methyl-6-(trifluoromethyl-sulfonyloxy)-4-pyridyl] trifluoro-methanesulfonate (4 g, 10.3 mmol). The mixture was warmed to room temperature overnight. The solvent was evaporated under vacuum. The mixture was diluted with ethyl acetate (100 mL) and filtered to remove inorganic salt. The filtrate was concentrated under vacuum.
10 The crude was diluted with dichloromethane (50 mL), and stirred until the product solidified, filtered to collect [6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl] trifluoromethane-sulfonate (3.3 g, 82%). ¹H NMR (300 MHz, CDCl₃) δ 6.52 – 6.40 (m, 1H), 6.19 (d, J = 2.0 Hz, 1H), 4.70 – 4.46 (m, 6H), 3.59 – 3.41 (m, 3H), 3.40 – 3.25 (m, 4H), 2.45 – 2.28 (m, 9H) ppm.

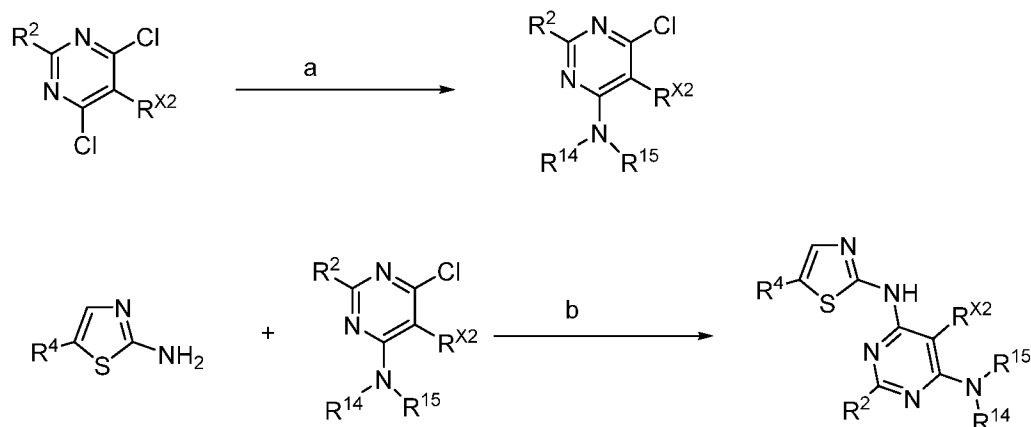
15

Preparation of N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine (Compound 91)

[00341] A mixture of [6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl] trifluoromethane-sulfonate (100 mg, 0.26 mmol), thiazol-2-amine (45 mg, 0.25 mmol)
20 and chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXPhos Palladacycle) (20 mg, 0.025 mmol) in 1,4-dioxane (2 mL) was bubbled with nitrogen for 5 minutes. To the mixture was added sodium *tert*-butoxide (0.3 mL of 2 M, 0.6 mmol) and the mixture was stirred overnight at 100 °C. The mixture was diluted with dichloromethane, filtered through a
25 layer of Celite, and concentrated under vacuum. The crude was purified on a 4 g silica gel cartridge eluting with 0-8% methanol /dichloromethane. Recovered N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine (13.5 mg, 12%). ¹H NMR (400 MHz, CDCl₃) δ 8.74 (dd, J = 2.3, 0.9 Hz, 1H), 8.43 (dd, J = 4.8, 1.6 Hz, 1H), 7.72 (dt, J = 8.0, 1.9 Hz, 1H), 7.52 (s, 1H), 7.24 (ddd, J =
30 7.9, 4.8, 0.9 Hz, 1H), 6.21 (d, J = 2.0 Hz, 2H), 4.60 (dt, J = 25.2, 6.4 Hz, 4H), 3.54 - 3.32 (m, 4H), 2.48 - 2.24 (m, 6H) ppm.

[00342] Using the general synthetic scheme outlined in Scheme M and the experimental procedures listed above in Example 23, the following compounds can be prepared: 93-95, 119, 120, 131, 151-154 and 157.

5 Scheme N: General Route MM for Preparation of Compounds of Formula II



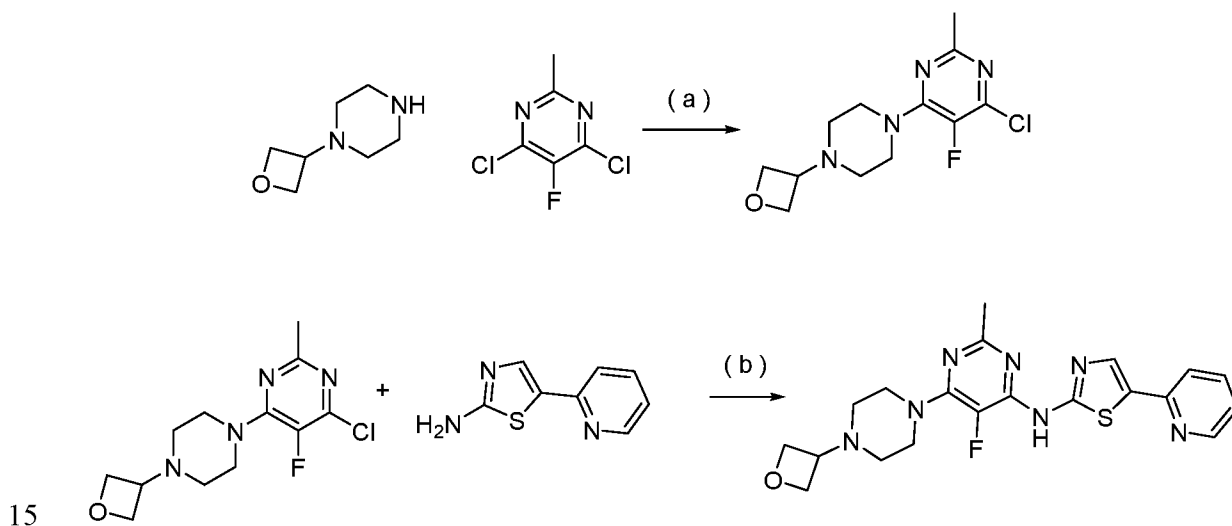
a: $NHR^{14}R^{15}$, DIPEA, DCM; b: NaOtBu, *t*-BuXPhos Palladacycle, 1,4-dioxane

Compounds of Formula II of the present invention may be prepared as generally outlined in Scheme N, where R^2 , R^4 , and R^{X2} are as described herein, and $NR^{14}R^{15}$

10 represent an optionally substituted heterocyclic ring (e.g., G^1 , G^2).

EXAMPLE 24

Preparation of 4-chloro-5-fluoro-2-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrimidine



a) DIPEA, DCM; b) *t*-BuXPhos Palladacycle, KOtBu, 1,4-dioxane, 70 °C

Preparation of 4-chloro-5-fluoro-2-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrimidine

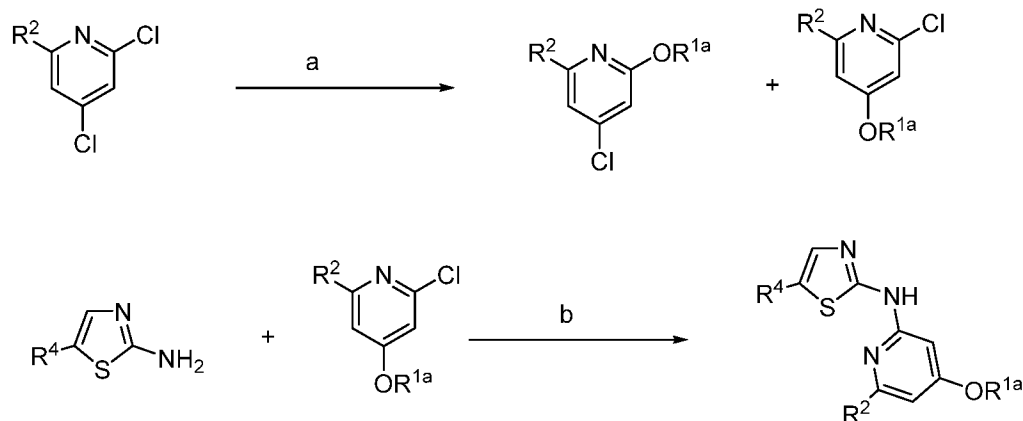
[00343] To a mixture of 4,6-dichloro-5-fluoro-2-methyl-pyrimidine (390 mg, 2.15 mmol) and diisopropylethylamine (900 μ L, 5.17 mmol) in dichloromethane (3.9 mL) was added 1-(oxetan-3-yl)piperazine (335 mg, 2.4 mmol). The mixture was stirred for 10 minutes. The resulting mixture was concentrated in vacuo then purified on a 40 g silica gel cartridge eluting with 0-80% ethyl acetate/heptane to provide 4-chloro-5-fluoro-2-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrimidine (550 mg, 89%). ¹H NMR (400 MHz, CDCl₃) δ 5.35 (s, 1H), 4.92 - 4.70 (m, 2H), 4.65 - 4.41 (m, 2H), 4.68 - 4.12 (m, 2H), 2.46 (d, *J* = 1.1 Hz, 3H), 1.79 (d, *J* = 0.7 Hz, 3H) ppm. ESI-MS *m/z* calc. 231.05746, found 232.0 (M+1)⁺; Retention time: 0.65 minutes.

Preparation of N-[5-fluoro-2-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrimidin-4-yl]-5-(2-pyridyl)thiazol-2-amine (Compound 108)

[00344] A mixture of 5-(2-pyridyl)thiazol-2-amine (45 mg, 0.25 mmol), 4-chloro-5-fluoro-2-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrimidine (90 mg, 0.31 mmol), chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXPhos Palladacycle) (20 mg, 0.029 mmol) and potassium *tert*-butoxide (65 mg, 0.58 mmol) in 1,4-dioxane (5 mL) was bubbled with nitrogen for 5 minutes. The mixture was stirred for 3 hours at 70 °C. The mixture was loaded onto a 4 g silica gel cartridge eluting with 0-10% methanol /DCM to provide N-[5-fluoro-2-methyl-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrimidin-4-yl]-5-(2-pyridyl)thiazol-2-amine (25.6 mg, 22.4%). ¹H NMR (400 MHz, CDCl₃) δ 9.08 (s, 1H), 8.78 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.45 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.76 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.58 (s, 1H), 7.25 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 4.71 - 4.50 (m, 4H), 3.82 - 3.71 (m, 4H), 3.46 (p, *J* = 6.4 Hz, 1H), 2.44 (d, *J* = 0.8 Hz, 3H), 2.39 - 2.29 (m, 4H) ppm. ESI-MS *m/z* calc. 427.15906, found 428.2 (M+1)⁺; Retention time: 0.65 minutes.

[00345] Using the general synthetic scheme outlined in Scheme N and the experimental procedures listed above in Example 24, the following compounds can be prepared: 92, 99, 108, 144 and 145.

5 Scheme O: General Route NN for Preparation of Compounds of Formula II

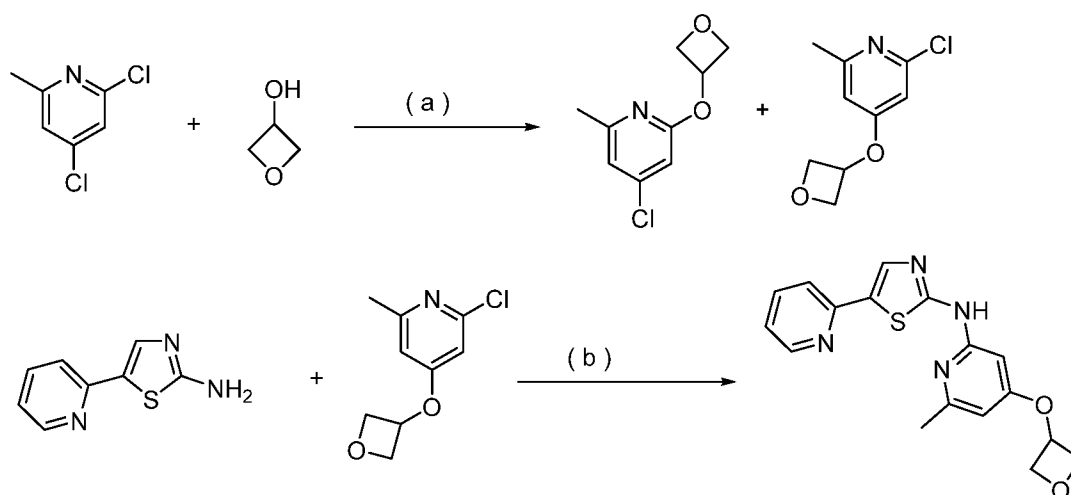


a) KOtBu, THF; b) NaOtBu, *t*-BuXPhos Palladacycle, 1,4-dioxane

Compounds of Formula II of the present invention may be prepared as generally outlined in Scheme O, where R² and R⁴ are as described herein and OR^{1a} is an R¹ moiety bonded to the parent molecule through an oxygen atom (e.g., OC₁₋₄alkyl, –OG², etc).

EXAMPLE 25

Preparation of N-[6-methyl-4-(oxetan-3-yloxy)-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine (Compound 113)



b) KOtBu, THF; b) NaOtBu, *t*-BuXPhos Palladacycle, 1,4-dioxane

Preparation of 4-chloro-2-methyl-6-(oxetan-3-yloxy)pyridine

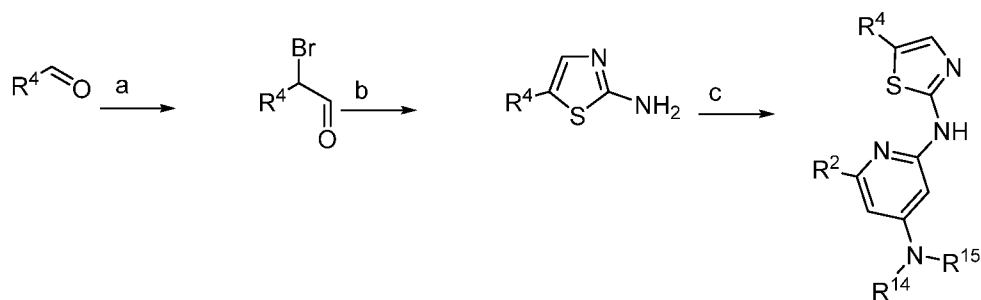
[00346] A mixture of 2,4-dichloro-6-methyl-pyridine (500 mg, 3.1 mmol), oxetan-3-ol (250 mg, 3.4 mmol) and potassium *tert*-butoxide (450 mg, 4.0 mmol) in dimethylsulfoxide (7 mL) was stirred for 15 minutes at room temperature. The mixture was diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, concentrated. The crude product was purified by silica gel chromatography (12g column; 0-30% ethyl acetate/heptane) to afford 4-chloro-2-methyl-6-(oxetan-3-yloxy)pyridine (120 mg, 19%) (less polar). ¹H NMR (400 MHz, CDCl₃) δ 6.77 (d, J = 1.6 Hz, 1H), 6.62 (d, J = 1.6 Hz, 1H), 5.69 - 5.46 (m, 1H), 4.97 (ddd, J = 7.4, 6.3, 1.0 Hz, 2H), 4.72 (ddt, J = 7.0, 5.4, 2.1 Hz, 2H), 2.37 (s, 3H), and 2-chloro-6-methyl-4-(oxetan-3-yloxy)pyridine (380 mg, 62%) (more polar). ¹H NMR (400 MHz, CDCl₃) δ 6.46 (t, J = 0.8 Hz, 2H), 5.25 (tt, J = 6.0, 5.0 Hz, 1H), 5.00 (ddd, J = 7.1, 6.0, 1.0 Hz, 2H), 4.75 (ddd, J = 7.5, 5.0, 1.0 Hz, 2H), 2.49 (d, J = 0.6 Hz, 3H) ppm.

Preparation N-[6-methyl-4-(oxetan-3-yloxy)-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine (Compound 113)

[00347] A mixture of 5-(2-pyridyl)thiazol-2-amine (40 mg, 0.23 mmol), 2-chloro-6-methyl-4-(oxetan-3-yloxy)pyridine (50 mg, 0.26 mmol), and chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (*t*-BuXPhos Palladacycle) (12 mg, 0.1 mmol) in 1,4-dioxane (1 mL) was bubbled with nitrogen for 5 minutes. To the mixture was added potassium *tert*-butoxide (0.2 mL, 2M, 0.4 mmol) and the mixture was stirred overnight at 70-80 °C. The reaction mixture was diluted with dichloromethane, filtered through a layer of Celite, and concentrated. The crude was purified by silica gel chromatography (4 g column; 0-8% methanol/dichloromethane). The product was repurified by reserve phase HPLC eluting with 10-90% acetonitrile/water to afford N-[6-methyl-4-(oxetan-3-yloxy)-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine (11 mg, 12%), ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.78 - 8.58 (m, 1H), 8.31 (m, 2H), 8.12 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 6.6 Hz, 1H), 6.99 (d, J = 2.3 Hz, 2H), 4.97 (s, 1H), 4.02 - 3.78 (m, 4H), 2.67 (s, 3H) ppm.

[00348] Using the general synthetic scheme outlined in Scheme O and the experimental procedures listed above in Example 25, the following compounds can be prepared: 88, 96-98, 100-107, 109-118, 121-130 and 132-141.

5 Scheme P: General Route OO for Preparation of Compounds of Formula II



a) i. $\text{PPh}_3\text{CH}_2\text{OCH}_3\text{Cl}$, KOtBu , THF; ii. Br_2 , CH_3CN ; b) Thiourea, EtOH; c) $\text{Pd}_2(\text{dba})_3$, XantPhos, Na_2CO_3 , toluene.

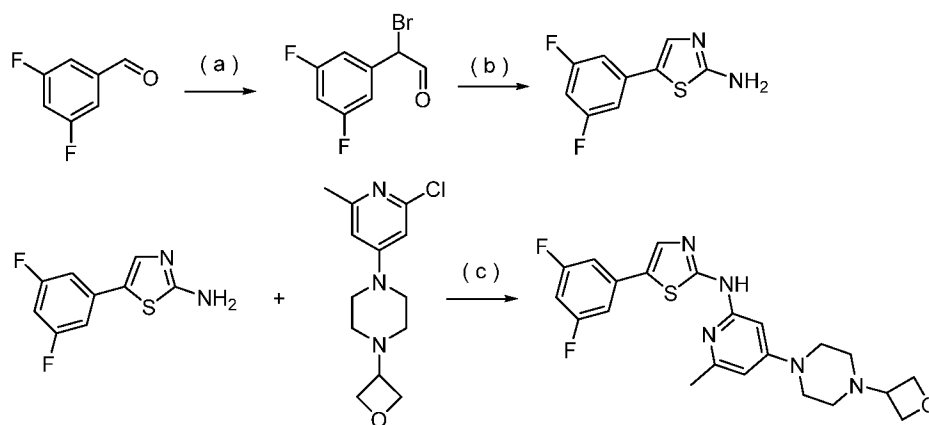
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Compounds of Formula II of the present invention may be prepared as generally outlined in Scheme P, where R^2 and R^4 are as described herein, and $\text{NR}^{14}\text{R}^{15}$ represents an optionally substituted heterocyclic ring (e.g., G^1 , G^2).

15

EXAMPLE 26

Preparation of 5-(3,5-difluorophenyl)-N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]thiazol-2-amine (Compound 90)



a) i. $\text{PPh}_3\text{CH}_2\text{OCH}_3\text{Cl}$, KOtBu , THF, 0°C -RT; ii. Br_2 , CH_3CN ; b) Thiourea, EtOH; c) $\text{Pd}_2(\text{dba})_3$, XantPhos, Na_2CO_3 , toluene.

20

Preparation of 1,3-difluoro-5-(2-methoxyvinyl)benzene

To a suspension of methoxymethyl-triphenyl-phosphonium chloride (64.75 g, 188.9 mmol) and 3,5-difluorobenzaldehyde (22.37 g, 157.4 mmol) in tetrahydrofuran (300 mL) at 0 °C was added potassium *tert*-butoxide (157.4 mL of 1 M, 157.4 mmol) dropwise over 15 minutes. The reaction mixture was stirred at 0 °C for 30 minutes following completion of addition, then for a further 30 minutes at room temperature. The reaction was quenched via addition of water (300 mL). The biphasic mixture was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was separated, washed with brine (500 mL) dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was treated with diethyl ether (100 mL) then heptane (100 mL) and agitated to give a slurry of yellow solid (triphenylphosphine oxide). The mixture was filtered, then washed with 1:1 diethyl ether: heptane (100 mL). The combined filtrate was concentrated and the residue was purified on a 220g silica gel cartridge eluting with 0-35% ethyl acetate/heptane. This afforded 1,3-difluoro-5-(2-methoxyvinyl)benzene (13.9 g, 52%) as a pale yellow oil. ¹H NMR showed a 1:1 mixture of *cis* and *trans* isomers. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.12-7.06 (m, 1H), 6.75-6.60 (m, 1H), 6.58-6.50 (m, 1H), 6.21, 5.74 (d, 1H), 5.17 (d, 1H), 3.84, 3.71 (s, 3H) ppm. NOTE: the resonances are listed for the mixture; 1H corresponds to a proton where the resonance for the individual components overlapped and integrated together as one proton; where the resonances are listed separated by comma rather than as a range, the two stereoisomers gave distinct peaks, and the sum of the two peaks integrated as the number of protons described in parantheses.

Preparation of 2-bromo-2-(3,5-difluorophenyl)acetaldehyde (E31446-97)

[00349] To a solution of 1,3-difluoro-5-(2-methoxyvinyl)benzene (7.6 g, 44.7 mmol) in diethyl ether (400 mL) at 0 °C was added a solution of bromine (7.1 g, 2.3 mL, 44.7 mmol) in dichloromethane (40 mL) dropwise via addition funnel over 15 minutes. The reaction mixture was stirred at 0 °C for 1 hour then treated with saturated aqueous sodium bicarbonate (400 mL). The resulting biphasic mixture was stirred at room temperature for 1.5 hours, the organics were separated, washed with brine (400 mL), dried over magnesium sulfate, then filtered and concentrated under vacuum. This provided 2-bromo-2-(3,5-difluorophenyl)acetaldehyde (10.5 g, 44.68

mmol). ^1H NMR (300 MHz, DMSO- d_6) δ 9.53 (s, 1H), 7.01-6.98 (m, 2H), 6.89-6.82 (m, 1H), 3.5 (d, 1H) ppm.

Preparation of 5-(3,5-difluorophenyl)thiazol-2-amine (E31446-98)

- 5 **[00350]** To a solution of 2-bromo-2-(3,5-difluorophenyl)acetaldehyde (10.5 g, 44.68 mmol) in ethanol (150 mL) at room temperature was added thiourea (6.80 g, 89.36 mmol). The mixture was stirred at room temperature for 30 minutes then warmed to 80 °C. After 18 hours, LC-MS shows desired product as the major UV-active component. Heating was ceased and the reaction mixture was stirred for 4 days to
10 give a suspension. The solid was isolated via filtration, then washed with ethanol (10 mL) to give 5-(3,5-difluorophenyl)thiazol-2-amine (5.68 g, 59%) as a white crystalline solid. ^1H NMR (300 MHz, DMSO- d_6) δ 9.36 (s, 2H), 7.98 (s, 1H), 7.52 - 7.34 (m, 2H), 7.25 (tt, J = 9.3, 2.2 Hz, 1H) ppm. ESI-MS m/z calc. 212.02197, found 213.2 (M+1) $^+$; Retention time: 0.6 minutes.

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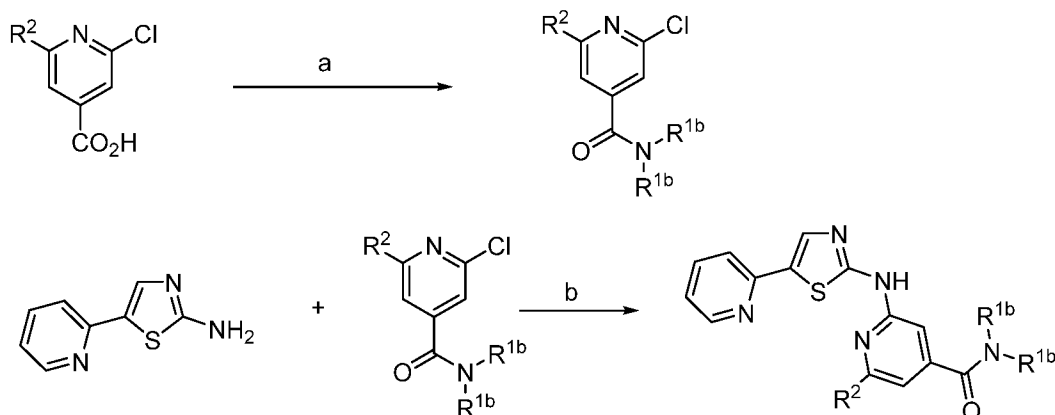
Preparation of 5-(3,5-difluorophenyl)-N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]thiazol-2-amine (Compound 90)

- [00351]** To a mixture of 5-(3,5-difluorophenyl)thiazol-2-amine (74 mg, 0.35 mmol), 1-(2-chloro-6-methyl-4-pyridyl)-4-(oxetan-3-yl)piperazine (77 mg, 0.28 mmol),
20 tris(dibenzylideneacetone)dipalladium(0) (8 mg, 0.0087 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos) (15 mg, 0.026 mmol) and sodium carbonate (43 mg, 0.40 mmol) in toluene (3 mL) was added water (6 μL , 0.3 mmol) under nitrogen. The mixture was stirred at 110 °C for 20 hours. LCMS showed a trace of desired product with both starting materials as major peaks. New
25 portions of tris(dibenzylideneacetone)dipalladium(0) (8 mg, 0.0087 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos) (15 mg, 0.026 mmol), sodium carbonate (43 mg, 0.40 mmol) and tetrahydrofuran (3 mL) were added and the mixture was heated in a microwave at 160 °C for 2 hours. LCMS showed desired product as the major peak. Water (30 mL) was added and the mixture was extracted
30 with ethyl acetate (3 X 30 mL). The organic layer was evaporated then the crude solid purified by silica gel chromatography (0-10% methanol/dichloromethane) to provide the first batch of product. The aqueous phase was extracted with dichloromethane (4 X 20 mL), evaporated under vacuum, then purified by silica gel

chromatography (0-10% methanol/dichloromethane) to provide a second batch of product. Obtained 5-(3,5-difluorophenyl)-N-[6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]thiazol-2-amine (69 mg, 52%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.01 (s, 1H), 7.91 (s, 1H), 7.29 (d, J = 7.1 Hz, 2H), 7.06 (t, J = 9.3 Hz, 1H), 6.46 (s, 1H), 6.27 (s, 1H), 4.57 (t, J = 6.5 Hz, 2H), 4.48 (t, J = 5.9 Hz, 2H), 3.50 - 3.40 (m, 1H), 3.30 (m, 8H), 2.39 - 2.36 (m, 3H) ppm. ESI-MS *m/z* calc. 443.15915, found 444.31 (M+1)⁺; Retention time: 0.68 minute.

[00352] Using the general synthetic scheme outlined in Scheme P and the experimental procedures listed above in Example 26, the following compounds can be prepared: 89 and 142

Scheme Q: General Route PP for Preparation of Compounds of Formula II

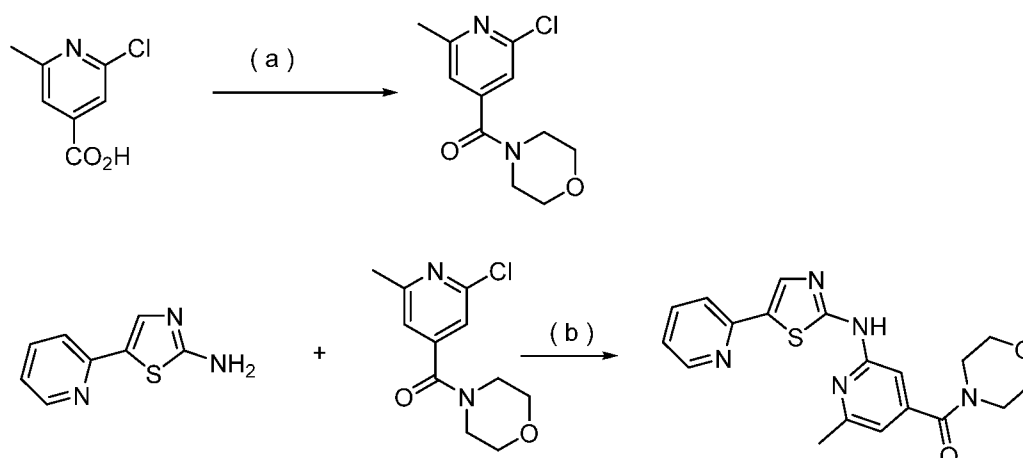


a) i. SOCl₂, DMF; ii. TEA, morpholine, DCM; b) NaOtBu, *t*-BuXPhos Palladacycle, 1,4-dioxane

Compounds of Formula II of the present invention may be prepared as generally outlined in Scheme Q, where R² is as described herein, and C(O)NR^{1b}R^{1b} is a nitrogen-containing R¹ moiety bonded to the parent molecule through a carbonyl moiety (e.g., -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)G²).

EXAMPLE 27

Preparation of [2-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]-4-pyridyl]-morpholinomethanone (Compound 147)



a) i. SOCl_2 , DMF; ii. TEA, morpholine, DCM; b) NaOtBu, *t*-BuXPhos Palladacycle, 1,4-dioxane

5 Preparation of 2-chloro-6-methyl-pyridine-4-carbonyl chloride

[00353] A mixture of 2-chloro-6-methyl-pyridine-4-carboxylic acid (1.29 g, 7.5 mmol) and thionyl chloride (5 mL, 68.55 mmol) in dichloromethane (10 mL) was stirred at 70 °C overnight. Concentrated under vacuum to provide 2-chloro-6-methyl-pyridine-4-carbonyl chloride which was carried to next step as is.

10

Preparation of (2-chloro-6-methyl-4-pyridyl)-morpholino-methanone

[00354] To a mixture of morpholine (100 μL , 1.15 mmol) and triethylamine (300 μL , 2.15 mmol) in dichloromethane (5 mL) was added 2-chloro-6-methyl-pyridine-4-carbonyl chloride (200 mg, 1.05 mmol) and the mixture stirred for 10 minutes. The reaction mixture was concentrated and purified by silica gel chromatography (12g column; 0-40% ethyl acetate/heptane) to provide (2-chloro-6-methyl-4-pyridyl)-morpholino-methanone (100 mg, 39%). ^1H NMR (300 MHz, CDCl_3) δ 7.18 - 7.12 (m, 1H), 7.08 (dd, J = 1.2, 0.6 Hz, 1H), 3.72 (d, J = 40.4 Hz, 6H), 3.39 (s, 2H), 2.59 (t, J = 0.6 Hz, 3H) ppm.

20

Preparation of [2-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]-4-pyridyl]-morpholino-methanone (Compound 147)

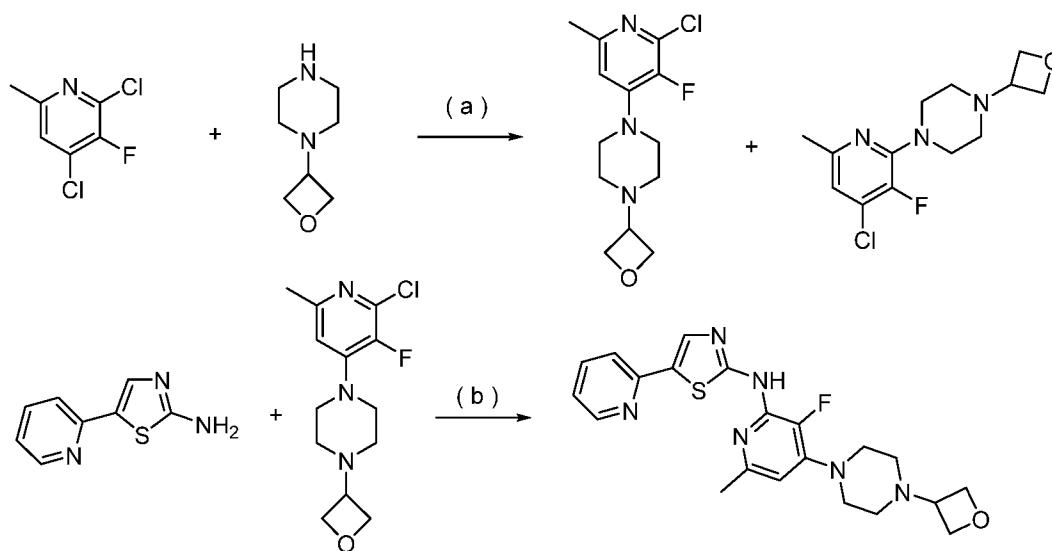
[00355] To a mixture of 5-(2-pyridyl)thiazol-2-amine (50 mg, 0.28 mmol), 2-chloropyridine (75 mg, 0.31 mmol) and chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXPhos

25

- Palladacycle) (25 mg, 0.03mmol) in 1,4-dioxane (1 mL) was added sodium *tert*-butoxide (0.3 mL of 2 M, 0.6mmol) and the mixture was stirred for 30 minutes at room temperature. The reaction was purified on a 4 g silica gel cartridge eluting with 0-8% methanol/dichloromethane which provided [2-methyl-6-[[5-(2-pyridyl)thiazol-2-yl]amino]-4-pyridyl]-morpholino-methanone (18.7 mg, 16.5%). ¹H NMR (400 MHz, CDCl₃) δ 10.81 (s, 1H), 8.78 (dd, J = 2.4, 0.9 Hz, 1H), 8.45 (dd, J = 4.8, 1.6 Hz, 1H), 7.78 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.62 (s, 1H), 7.34 - 7.25 (m, 1H), 6.76 - 6.57 (m, 2H), 3.63 (d, J = 63.6 Hz, 6H), 3.35 (s, 3H) ppm. ESI-MS *m/z* calc. 381.13, found 382.2 (M+1)⁺; Retention time: 0.62 minute.
- 10 **[00356]** Using the general synthetic scheme outlined in Scheme Q and the experimental procedures listed above in Example 27, the following compounds can be prepared: 147-150, 155 and 156.

EXAMPLE 28

- 15 Preparation of N-[3-fluoro-6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine (Compound 146)



a) TEA, DMSO, 80 °C; b) NaOtBu, *t*-BuXPhos Palladacycle, 1,4-dioxane 80 °C

20

Preparation of 1-(4-chloro-3-fluoro-6-methyl-2-pyridyl)-4-(oxetan-3-yl)piperazine

[00357] To a mixture of 2,4-dichloro-3-fluoro-6-methylpyridine (200 mg, 0.67 mmol) and 1-(oxetan-3-yl)piperazine (120 mg, 0.84 mmol) in dimethylsulfoxide (5

mL) was added triethylamine (180 μ L, 1.29 mmol) and the reaction was stirred overnight at 80 °C. LC-MS showed two products and small amount of SM. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate, and concentrated under vacuum. Crude product was purified on a 40 g silica gel cartridge eluting with 0-40% ethyl acetate in heptane to provide desired 1-(2-chloro-3-fluoro-6-methyl-4-pyridyl)-4-(oxetan-3-yl)piperazine (110 mg, 58%) (more polar; carried forward in the next step). ^1H NMR (400 MHz, CDCl_3) δ 6.55 (d, J = 5.8 Hz, 1H), 4.78 - 4.58 (m, 4H), 3.58 (tt, J = 6.8, 6.0 Hz, 1H), 3.47 - 3.20 (m, 4H), 2.62 - 2.24 (m, 7H). ESI-MS m/z calc. 285.10443, found 286.2 ($\text{M}+1$)⁺; Retention time: 0.62 minutes. Silica gel purification also provided the undesired regioisomer 1-(4-chloro-3-fluoro-6-methyl-2-pyridyl)-4-(oxetan-3-yl)piperazine (60 mg, 32%) (less polar). ^1H NMR (400 MHz, CDCl_3) δ 6.65 (dd, J = 4.0, 0.6 Hz, 1H), 4.74 - 4.64 (m, 4H), 3.65-3.49(m, 5H), 2.53 - 2.43 (m, 4H), 2.36 (dd, J = 1.2, 0.5 Hz, 3H). ESI-MS m/z calc. 285.10443, found 286.0 ($\text{M}+1$)⁺; Retention time: 0.74 minutes.

Preparation of N-[3-fluoro-6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine (Compound 146)

[00358] A mixture of 1-(2-chloro-3-fluoro-6-methyl-4-pyridyl)-4-(oxetan-3-yl)piperazine (50 mg, 0.17 mmol), 5-(2-pyridyl)thiazol-2-amine (40 mg, 0.23 mmol) and chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXPhos Palladacycle) (17 mg, 0.021 mmol) in 1,4-dioxane (1 mL) was bubbled with nitrogen for 2 minutes. To the mixture was added sodium *tert*-butoxide (220 μ L of 2 M, 0.44 mmol) and the mixture was stirred overnight at 80 °C. LC/MS showed desired product. The crude mixture was purified on a 4 g silica gel cartridge eluting with 0-8% methanol/dichloromethane which provided a minor amount of desired product, N-[3-fluoro-6-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]-5-(2-pyridyl)thiazol-2-amine (2.1 mg, 3%). ^1H NMR (400 MHz, CDCl_3) δ 8.95 - 8.77 (m, 1H), 8.52 (dd, J = 4.9, 1.6 Hz, 1H), 8.33 (s, 1H), 7.86 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.66 (s, 1H), 7.33 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 6.33 (d, J = 5.9 Hz, 1H), 4.70 (dt, J = 21.2, 6.4 Hz, 4H), 3.60 (q, J = 6.4 Hz, 1H), 3.49 - 3.30 (m, 4H), 2.66 - 2.37 (m, 7H) ppm. ESI-MS m/z calc. 426.16382, found 427.34 ($\text{M}+1$)⁺; Retention time: 2.03.

[00359] Table 3. Analytical Data

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
1	446.12	0.68	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.49 (d, J = 9.6 Hz, 2H), 7.37 (qd, J = 7.9, 3.5 Hz, 2H), 7.27 - 7.19 (m, 2H), 7.03 - 6.94 (m, 1H), 6.78 - 6.41 (m, 2H), 4.73 (d, J = 6.2 Hz, 4H), 3.67 (s, 5H), 2.49 (s, 4H) ppm.
2	463.94	0.7	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.50 (s, 2H), 7.25 (s, 1H), 7.06 (d, J = 6.2 Hz, 2H), 6.82 - 6.54 (m, 2H), 6.46 (s, 1H), 4.82 - 4.61 (m, 4H), 3.65 (d, J = 4.5 Hz, 4H), 3.60 - 3.44 (m, 1H), 2.46 (d, J = 4.6 Hz, 4H) ppm.
3	428.03	0.67	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.55 (dd, J = 14.0, 6.7 Hz, 4H), 7.42 (t, J = 7.6 Hz, 2H), 7.35 - 7.25 (m, 2H), 6.68 (d, J = 56.0 Hz, 1H), 6.44 (s, 1H), 4.83 - 4.60 (m, 4H), 3.79 - 3.49 (m, 5H), 2.57 - 2.35 (m, 4H) ppm.
4	340.06	0.81	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄ + CDCl ₃) δ 7.55 (d, J = 1.9 Hz, 1H), 7.36 (t, J = 5.4 Hz, 2H), 7.29 - 7.23 (m, 1H), 7.18 (s, 1H), 7.15 (s, 1H), 7.07 (s, 1H), 7.00 - 6.90 (m, 1H), 2.65 (q, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.26 (t, J = 7.6 Hz, 3H) ppm.
5	462.05	0.71	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.55 (t, J = 1.7 Hz, 1H), 7.51 (s, 2H), 7.46 - 7.40 (m, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.28 - 7.24 (m, 1H), 7.23 (d, J = 3.8 Hz, 1H), 6.68 (d, J = 56.0 Hz, 1H), 6.46 (s, 1H), 4.74 (d, J = 6.5 Hz, 4H), 3.70 (s, 5H), 2.53 (s, 4H) ppm.
6	405.28	0.64	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.61 - 7.49 (m, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.26 (d, J = 7.4 Hz, 1H), 7.17 (s, 1H), 7.03 (s, 1H), 6.93 (s, 1H), 6.79 (s, 1H), 6.47 (s, 1H), 4.71 (d, J = 5.5 Hz, 2H), 4.30 (d, J = 5.8 Hz, 2H), 3.49 - 3.18 (m, 4H), 2.74 - 2.45 (m, 4H), 2.35 (s, 3H) ppm.
7	391.05	0.64	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.59 - 7.51 (m, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.26 (d, J = 7.4 Hz, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 6.96 (s, 1H), 6.78 (s, 1H), 6.47 (s, 1H), 4.73 (d, J = 6.5 Hz, 4H), 3.70 - 3.55 (m, 1H), 3.41 - 3.25 (m, 4H), 2.68 - 2.50 (m, 4H), 2.35 (s, 3H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
8	446.08	0.67	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.59 - 7.42 (m, 4H), 7.12 (dd, J = 11.0, 6.4 Hz, 3H), 6.68 (d, J = 56.0 Hz, 1H), 6.45 (s, 1H), 4.74 (d, J = 6.4 Hz, 4H), 3.78 - 3.55 (m, 5H), 2.51 (s, 4H) ppm.
9	327.33	0.98	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.45 - 7.29 (m, 3H), 7.26 - 7.18 (m, 2H), 7.03 - 6.93 (m, 2H), 6.84 (s, 1H), 6.47 (s, 1H), 4.59 (dt, J = 12.1, 6.0 Hz, 1H), 2.35 (s, 3H), 1.38 (d, J = 6.1 Hz, 6H) ppm.
10	336.1	0.75	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.60 - 7.51 (m, 2H), 7.45 - 7.36 (m, 2H), 7.32 - 7.23 (m, 1H), 7.17 (s, 1H), 7.06 (d, J = 2.1 Hz, 2H), 6.78 (s, 1H), 6.46 (t, J = 1.7 Hz, 1H), 3.94 - 3.85 (m, 4H), 3.26 - 3.17 (m, 4H), 2.36 (s, 3H) ppm.
11	327.01	0.93	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.52 (ddd, J = 8.1, 5.2, 2.6 Hz, 2H), 7.18 - 7.04 (m, 3H), 6.97 (d, J = 2.0 Hz, 1H), 6.84 (s, 1H), 6.46 (s, 1H), 4.59 (dt, J = 12.1, 6.1 Hz, 1H), 2.35 (s, 3H), 1.37 (d, J = 6.1 Hz, 6H) ppm.
12	427.04	0.67	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.73 (d, J = 5.8 Hz, 1H), 7.59 - 7.48 (m, 2H), 7.18 - 7.07 (m, 3H), 7.02 (s, 1H), 6.47 (dd, J = 7.8, 1.6 Hz, 1H), 4.74 (d, J = 6.4 Hz, 4H), 3.68 (s, 1H), 3.22 (s, 4H), 2.63 (s, 4H), 2.37 (s, 3H) ppm.
13	427.09	0.67	Method E	¹ H NMR (300 MHz, CDCl ₃) δ 7.73 (d, J = 5.9 Hz, 1H), 7.43 - 7.31 (m, 2H), 7.28 - 7.19 (m, 2H), 7.08 (s, 1H), 7.03 - 6.92 (m, 1H), 6.53 - 6.43 (m, 1H), 4.74 (d, J = 5.9 Hz, 4H), 3.67 (s, 1H), 3.21 (s, 4H), 2.61 (s, 4H), 2.37 (s, 3H) ppm.
14	340.02	0.91	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄ + CDCl ₃) δ 7.61 - 7.52 (m, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.27 (t, J = 7.4 Hz, 1H), 7.16 (s, 1H), 6.92 (s, 1H), 6.83 (dt, J = 10.5, 2.0 Hz, 1H), 6.31 (dt, J = 11.9, 2.1 Hz, 1H), 3.95 - 3.79 (m, 4H), 3.27 - 3.14 (m, 4H) ppm.
15	479.91	0.74	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.63 (s, 1H), 7.55 (s, 2H), 7.44 (d, J = 7.8 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.24 (s, 2H), 6.51 (s, 1H), 4.74 (s, 4H), 3.71 (s, 5H), 2.51 (s, 4H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
16	421.06	0.65	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.83 (d, J = 2.8 Hz, 1H), 7.63 - 7.54 (m, 2H), 7.48 (s, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.32 - 7.24 (m, 1H), 7.19 (s, 1H), 6.40 (d, J = 2.7 Hz, 1H), 4.82 - 4.59 (m, 4H), 3.79 (s, 3H), 3.60 (p, J = 6.5 Hz, 1H), 3.37 - 3.18 (m, 4H), 2.68 - 2.44 (m, 4H), 2.32 (s, 3H) ppm.
17	427.09	0.68	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.75 (dd, J = 7.1, 1.3 Hz, 1H), 7.64 (td, J = 7.4, 2.2 Hz, 1H), 7.34 (d, J = 3.8 Hz, 1H), 7.28 - 7.07 (m, 4H), 6.48 (dd, J = 7.8, 1.5 Hz, 1H), 4.87 - 4.66 (m, 4H), 3.76 - 3.60 (m, 1H), 3.37 - 3.08 (m, 4H), 2.63 (s, 4H), 2.38 (s, 3H) ppm.
18	327.45	2.6	Method F	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.21 (s, 1H), 7.57 (d, J = 7.3 Hz, 2H), 7.44 (m, 3H), 7.27 (t, J = 7.4 Hz, 1H), 7.02 (s, 2H), 3.77 (s, 6H), 3.62 (s, 3H) ppm.
19	322.11	0.68	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 7.66 - 7.58 (m, 2H), 7.41 (dd, J = 14.6, 6.4 Hz, 4H), 7.36 - 7.26 (m, 2H), 7.09 - 7.02 (m, 1H), 6.85 (dd, J = 8.2, 1.8 Hz, 1H), 3.96 - 3.82 (m, 4H), 2.65 (s, 4H) ppm.
20	296.09	0.64	Method A	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 10.44 (s, 1H), 8.55 (d, J = 4.1 Hz, 1H), 7.85 (td, J = 7.8, 1.7 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.34 (t, J = 2.1 Hz, 1H), 7.29 - 7.21 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 9.0 Hz, 1H), 6.59 - 6.49 (m, 1H), 4.57 (sept, J = 6.0 Hz, 1H), 1.28 (d, J = 6.0 Hz, 6H) ppm.
21	427.34	0.63	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 7.42 (s, 1H), 7.31 - 7.12 (m, 3H), 6.90 - 6.74 (m, 2H), 6.57 (s, 1H), 5.48 (d, J = 2.5 Hz, 1H), 5.01 - 4.87 (m, 5H), 4.50 (dd, J = 12.3, 6.9 Hz, 1H), 3.52 (s, 4H), 3.38 (s, 3H), 2.32 (s, 3H), 1.41 - 1.12 (m, 3H), 0.97 - 0.83 (m, 1H) ppm.
22	428.33	0.61	Method A	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 10.40 (s, 1H), 7.67 (s, 1H), 7.34 - 7.19 (m, 2H), 7.19 - 7.06 (m, 1H), 6.98 (s, 1H), 6.27 (s, 1H), 4.52 (dt, J = 12.1, 6.3 Hz, 4H), 3.62 - 3.34 (m, 5H), 2.39 - 2.28 (m, 4H), 2.22 (s, 3H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
23	428.24	0.6	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 7.38 (s, 1H), 7.21 - 7.07 (m, 2H), 6.76 (tt, J = 9.1, 2.2 Hz, 1H), 6.42 (s, 1H), 6.34 (s, 1H), 4.71 (t, J = 6.6 Hz, 2H), 4.63 (t, J = 6.2 Hz, 2H), 3.61 - 3.38 (m, 5H), 2.53 - 2.42 (m, 4H), 2.36 (s, 3H) ppm.
24	309.15	0.93	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 7.82 - 7.68 (m, 2H), 7.66 - 7.51 (m, 2H), 7.52 - 7.39 (m, 2H), 7.25 (s, 1H), 7.17 (t, J = 2.3 Hz, 1H), 7.03 (s, 1H), 6.62 (s, 1H), 4.77 (ddd, J = 10.2, 8.1, 5.0 Hz, 1H), 2.52 (s, 3H), 1.55 (d, J = 6.1 Hz, 6H) ppm.
25	429.07	0.53	Method A	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 8.55 (d, J = 6.1 Hz, 2H), 8.09 (s, 1H), 7.84 (s, 1H), 7.68 (d, J = 6.1 Hz, 2H), 6.95 (dd, J = 79.8, 31.0 Hz, 2H), 4.54 (dt, J = 11.9, 6.2 Hz, 4H), 3.66 (s, 4H), 3.52 - 3.42 (m, 1H), 2.39 (s, 4H) ppm.
26	281.03	2.35	Method F	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.39 (s, 1H), 8.09 (d, J = 1.6 Hz, 1H), 7.70 (d, J = 1.6 Hz, 1H), 7.59 (dd, J = 8.6, 1.2 Hz, 2H), 7.56 - 7.48 (m, 2H), 7.41 (t, J = 7.9 Hz, 1H), 7.34 (t, J = 7.2 Hz, 1H), 6.46 (d, J = 7.5 Hz, 1H), 6.04 (d, J = 7.3 Hz, 1H), 4.40 (q, J = 7.0 Hz, 2H), 1.37 (t, J = 7.0 Hz, 3H) ppm.
27	281.07	2.1	Method F	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.21 (s, 1H), 8.07 (d, J = 1.7 Hz, 1H), 7.99 (d, J = 5.9 Hz, 1H), 7.74 (d, J = 1.7 Hz, 1H), 7.62 (dt, J = 8.6, 1.1 Hz, 2H), 7.51 (tt, J = 10.7, 5.2 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 6.46 (d, J = 2.1 Hz, 1H), 6.31 (dd, J = 5.9, 2.2 Hz, 1H), 4.02 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H) ppm.
28	251.2	2.11	Outsource LC-MS	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ ppm 2.43 (s, 3 H), 6.59 (d, J = 7.2 Hz, 1 H), 6.67 (d, J = 8.4 Hz, 1 H), 7.36 - 7.46 (m, 2 H), 7.50 - 7.60 (m, 4 H), 7.74 (s, 1 H), 7.94 (s, 1 H) ppm.
29	252.12	0.65	Method B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.80 (s, 1H), 8.35 (d, J = 5.1 Hz, 2H), 7.82 (m, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.55 (t, J = 8.0 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 6.73 (d, J = 5.0 Hz, 1H), 2.38 (s, 3H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
30	266.12	0.67	Method B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.07 (s, 1H), 8.74 (s, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.73 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.9 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 6.72 (s, 1H), 2.36 (s, 6H) ppm.
31	322.3	2.4	Outsource LC-MS	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ ppm 3.45 - 3.52 (m, 4 H), 3.78 - 3.84 (m, 4 H), 6.13 (d, J = 8.1 Hz, 1 H), 6.23 (d, J = 8.1 Hz, 1 H), 7.34 - 7.40 (m, 2 H), 7.48 - 7.58 (m, 4 H), 7.63 (s, 1 H), 7.91 (s, 1 H) ppm.
32	320.3	2.78	Outsource LC-MS	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ ppm 1.60 - 1.77 (m, 6 H), 3.49 - 3.61 (m, 4 H), 6.12 (d, J = 8.1 Hz, 1 H), 6.14 (d, J = 8.1 Hz, 1 H), 7.32 (t, J = 8.1 Hz, 1 H), 7.34 - 7.41 (m, 1 H), 7.48 - 7.57 (m, 4 H), 7.69 (d, J = 1.5 Hz, 1 H), 7.90 (d, J = 1.5 Hz, 1 H) ppm.
33	335.3	1.65	Outsource LC-MS	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ ppm 2.36 (s, 3 H), 2.52 - 2.67 (m, 4 H), 3.50 - 3.66 (m, 4 H), 6.14 (d, J = 8.1 Hz, 1 H), 6.21 (d, J = 8.1 Hz, 1 H), 7.31 - 7.44 (m, 2 H), 7.47 - 7.59 (m, 4 H), 7.64 (s, 1 H), 7.91 (s, 1 H) ppm.
34	265.2	1.57	Outsource LC-MS	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ ppm 2.23 (s, 3 H), 2.38 (s, 3 H), 6.47 (s, 1 H), 6.52 (s, 1 H), 7.35 - 7.42 (m, 1 H), 7.50 - 7.61 (m, 4 H), 7.68 (d, J = 1.5 Hz, 1 H), 7.94 (d, J = 1.5 Hz, 1 H) ppm.
35	379.3	1.93	Outsource LC-MS	¹ H NMR (300 MHz, CDCl ₃) δ ppm 1.45 (t, J = 7.2 Hz, 3 H), 1.52 - 1.65 (m, 4 H), 1.75 - 1.90 (m, 4 H), 3.58 - 3.75 (m, 4 H), 4.43 (q, J = 7.2 Hz, 2 H), 6.16 (d, J = 7.8 Hz, 1 H), 6.25 (d, J = 7.8 Hz, 1 H), 6.41 (s, 1 H), 6.56 (d, J = 5.7 Hz, 1 H), 6.92 (br s, 1 H), 7.42 (t, J = 7.8 Hz, 1 H), 7.67 (s, 1 H), 7.75 (s, 1 H), 8.19 (d, J = 5.7 Hz, 1 H) ppm.
36	295.3	2.26	Outsource LC-MS	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ ppm 1.38 (d, J = 6.3 Hz, 6 H), 5.28 (sept, J = 6.3 Hz, 1 H), 6.05 (d, J = 8.1 Hz, 1 H), 6.36 (d, J = 8.1 Hz, 1 H), 7.35 - 7.43 (m, 2 H), 7.50 - 7.59 (m, 4 H), 7.71 (d, J = 1.5 Hz, 1 H), 7.92 (d, J = 1.5 Hz, 1 H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
37	282.2	2.02	Outsource LC-MS	¹ H NMR (300 MHz, CDCl ₃) δ ppm 1.47 (t, J = 6.9 Hz, 3 H), 4.45 (q, J = 6.9 Hz, 2 H), 6.14 (d, J = 8.4 Hz, 1 H), 6.30 (d, J = 8.4 Hz, 1 H), 7.12 (br s, 1 H), 7.20 - 7.32 (m, 2 H), 7.43 (app t, J = 8.1 Hz, 1 H), 7.78 - 7.87 (m, 2 H), 8.25 (br s, 1 H), 8.43 - 8.49 (m, 1 H) ppm.
38	295.3	2.14	Outsource LC-MS	¹ H NMR (300 MHz, CDCl ₃) δ ppm 1.43 (t, J = 6.9 Hz, 3 H), 2.23 (s, 3 H), 4.38 (q, J = 6.9 Hz, 2 H), 5.99 (s, 1 H), 6.11 (s, 1 H), 6.76 (br. s, 1 H), 7.32 - 7.38 (m, 1 H), 7.39 - 7.44 (m, 2 H), 7.45 - 7.53 (m, 2 H), 7.57 (d, J = 1.2 Hz, 1 H), 7.64 (d, J = 1.2 Hz, 1 H) ppm.
39	366.3	2.05	Outsource LC-MS	¹ H NMR (300 MHz, CDCl ₃) δ ppm 1.48 (t, J = 7.0 Hz, 3 H), 2.99 - 3.02 (m, 4 H), 3.86 - 3.90 (m, 4 H), 4.50 (q, J = 7.0 Hz, 2 H), 6.27 (d, J = 8.2 Hz, 1 H), 6.60 (s, 1 H), 7.11 (d, J = 8.2 Hz, 1 H), 7.35 - 7.41 (m, 3 H), 7.46 - 7.51 (m, 3 H), 7.64 (d, J = 1.4 Hz, 1 H) ppm.
40	306.02	2.78	Outsource LC-MS	¹ H NMR (300 MHz, CDCl ₃) δ ppm 1.46 (t, J = 7.0 Hz, 3H), 4.40 (q, J = 7.1 Hz, 2H), 6.18 (d, J = 7.9 Hz, 1H), 6.28 (d, J = 7.9 Hz, 1H), 6.86 (bs, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.67 (bs, 1H), 7.74 (bs, 1H), 7.80 (d, J = 8.7 Hz, 2H) ppm.
41	282.2	0.66	Method B	
42	317.1	0.9	Method B	
43	358	0.74	Method B	
44	371	0.58	Method B	
45	370.1	0.89	Method B	
46	331.2	3.34	QC_PFP_2to98in_3p8_TF A	
47	335.1	0.72	Method B	

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
48	336.2	0.48	Method B	
49	323.12	0.57	Method B	
50	384.16	0.5	Method B	
51	335.1	2.81	UPLC	
52	384.21	0.45	Method B	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.83 - 8.74 (m, 1H), 8.73 - 8.61 (m, 1H), 8.50 - 8.38 (m, 2H), 8.17 - 8.03 (m, 3H), 8.02 - 7.88 (m, 1H), 7.63 (d, J = 1.6 Hz, 1H), 7.29 (dd, J = 9.0, 1.1 Hz, 1H), 7.11 (td, J = 5.9, 1.5 Hz, 2H), 7.01 - 6.92 (m, 1H), 5.59 - 5.48 (m, 1H), 4.04 (td, J = 8.2, 7.4, 4.8 Hz, 1H), 3.73 (td, J = 9.2, 6.8 Hz, 1H), 2.67 - 2.56 (m, 1H), 2.18 (ddt, J = 23.5, 19.2, 7.8 Hz, 4H) ppm.
53	336.18	0.8	Method B	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.71 - 8.61 (m, 2H), 8.51 (d, J = 1.9 Hz, 1H), 7.77 (q, J = 2.7, 2.2 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 6.45 (dd, J = 8.0, 0.6 Hz, 1H), 6.24 (dd, J = 8.0, 0.7 Hz, 1H), 5.20 (h, J = 6.2 Hz, 1H), 2.13 (tt, J = 8.4, 5.0 Hz, 1H), 1.39 (d, J = 6.2 Hz, 6H), 1.23 - 1.11 (m, 2H), 0.96 - 0.85 (m, 2H) ppm.
54	277.2	0.61	Method A	
55	286.25	0.67	Method A	
56	317.59	0.71	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.55 (d, J = 1.9 Hz, 1H), 7.81 - 7.67 (m, 2H), 7.60 - 7.44 (m, 3H), 6.44 (d, J = 7.9 Hz, 1H), 6.24 (d, J = 8.0 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H) ppm.
57	331.5	0.74	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.40 - 8.32 (m, 1H), 7.78 - 7.63 (m, 2H), 7.58 - 7.41 (m, 3H), 6.42 (dd, J = 8.0, 0.7 Hz, 1H), 6.18 (dd, J = 7.9, 0.7 Hz, 1H), 5.19 (hept, J = 6.2 Hz, 1H), 1.37 (d, J = 6.2 Hz, 6H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
58	296.2	0.62	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.98 - 8.88 (m, 1H), 8.80 (s, 1H), 8.71 (dd, J = 4.9, 1.4 Hz, 1H), 8.19 (ddd, J = 8.3, 2.7, 1.4 Hz, 1H), 7.70 (ddd, J = 8.3, 4.9, 0.7 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 6.48 (d, J = 8.0 Hz, 1H), 6.29 (d, J = 8.0 Hz, 1H), 5.16 (hept, J = 6.1 Hz, 1H), 1.39 (d, J = 6.2 Hz, 6H) ppm.
59	296.25	0.69	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.47 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 8.31 (d, J = 1.6 Hz, 1H), 8.03 (d, J = 1.6 Hz, 1H), 7.96 (ddd, J = 8.2, 7.4, 1.9 Hz, 1H), 7.58 (dd, J = 8.3, 1.0 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.32 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 6.37 (dd, J = 7.9, 0.7 Hz, 1H), 6.06 (dd, J = 7.8, 0.6 Hz, 1H), 5.35 (hept, J = 6.1 Hz, 1H), 1.41 (d, J = 6.2 Hz, 6H) ppm.
60	256.03	0.89	Method A	
61	256.03	0.89	Method A	
62	314.21	0.68	Method A	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 9.45 (s, 1H), 8.78 (s, 1H), 8.58 (s, 1H), 8.26 (s, 1H), 8.13 (d, J = 9.8 Hz, 1H), 7.71 (s, 1H), 7.42 (s, 1H), 6.46 (d, J = 8.2 Hz, 1H), 6.02 (d, J = 6.8 Hz, 1H), 5.31 (s, 1H), 1.33 (t, J = 10.3 Hz, 6H) ppm.
63	311.33	0.61	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.49 (dd, J = 4.9, 1.1 Hz, 1H), 8.40 (d, J = 1.1 Hz, 1H), 8.03 - 7.93 (m, 2H), 7.65 (d, J = 8.2 Hz, 1H), 7.36 (dd, J = 6.9, 4.9 Hz, 1H), 6.15 (d, J = 6.1 Hz, 1H), 5.44 (dq, J = 12.4, 6.1 Hz, 1H), 2.36 (d, J = 5.0 Hz, 3H), 1.40 (t, J = 6.5 Hz, 6H) ppm.
64	311.24	0.57	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.84 (d, J = 2.6 Hz, 1H), 8.57 (dd, J = 4.8, 1.3 Hz, 1H), 8.12 - 8.03 (m, 2H), 7.79 (d, J = 1.6 Hz, 1H), 7.61 (dd, J = 8.3, 4.8 Hz, 1H), 6.05 (s, 1H), 5.37 (dt, J = 12.4, 6.2 Hz, 1H), 2.31 (d, J = 3.0 Hz, 3H), 1.38 (d, J = 6.2 Hz, 6H) ppm.
65	300.25	0.69	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.36 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 7.66 (t, J = 8.1 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 6.35 (d, J = 8.1 Hz, 1H), 5.25 - 5.10 (m, 1H), 1.43 - 1.37 (m, 6H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
66	300.25	0.62	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.84 (d, J = 1.6 Hz, 1H), 7.87 (dd, J = 13.9, 5.6 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 8.2 Hz, 1H), 5.06 (dt, J = 12.3, 6.1 Hz, 1H), 1.44 (d, J = 6.1 Hz, 6H) ppm.
67	364.54	0.84	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.35 (s, 1H), 8.36 (t, J = 8.0 Hz, 1H), 8.22 (dd, J = 8.7, 5.1 Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.70 (t, J = 8.1 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.37 (d, J = 8.1 Hz, 1H), 5.20 (dq, J = 12.3, 6.1 Hz, 1H), 1.42 (d, J = 6.1 Hz, 6H) ppm.
68	322.31	0.66	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.30 (d, J = 2.2 Hz, 1H), 8.91 (t, J = 6.1 Hz, 1H), 8.83 (s, 1H), 8.74 (d, J = 8.5 Hz, 1H), 8.10 (dd, J = 8.5, 5.4 Hz, 1H), 7.88 (t, J = 8.3 Hz, 1H), 7.80 (d, J = 1.6 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 8.2 Hz, 1H), 5.28 - 5.19 (m, 1H), 2.15 - 1.62 (m, 8H) ppm.
69	280.31	0.56	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.40 (d, J = 2.3 Hz, 1H), 8.91 (dd, J = 7.9, 2.2 Hz, 2H), 8.55 (d, J = 1.6 Hz, 1H), 8.23 (dd, J = 13.8, 7.8 Hz, 1H), 8.04 (dt, J = 8.9, 5.1 Hz, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.14 (d, J = 8.9 Hz, 1H), 7.02 (d, J = 7.3 Hz, 1H), 2.94 (dd, J = 14.0, 6.5 Hz, 2H), 1.97 - 1.81 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H) ppm.
70	344.28	0.68	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.34 (d, J = 2.4 Hz, 1H), 9.12 (s, 1H), 8.97 (dd, J = 5.5, 1.0 Hz, 1H), 8.80 - 8.72 (m, 1H), 8.18 (dd, J = 8.5, 5.5 Hz, 1H), 7.84 - 7.74 (m, 1H), 7.44 (dd, J = 7.8, 1.5 Hz, 2H), 7.40 - 7.29 (m, 3H), 6.64 (d, J = 8.1 Hz, 1H), 6.54 (d, J = 8.1 Hz, 1H), 5.40 (d, J = 6.3 Hz, 2H) ppm.
71	344.28	0.74	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.45 (s, 1H), 8.64 - 8.58 (m, 1H), 8.10 (td, J = 7.9, 1.8 Hz, 2H), 7.76 (d, J = 8.2 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.57 (dd, J = 7.0, 4.9 Hz, 1H), 7.41 (d, J = 6.9 Hz, 2H), 7.37 - 7.23 (m, 3H), 6.51 (d, J = 7.9 Hz, 1H), 6.44 (d, J = 8.0 Hz, 1H), 5.41 (s, 2H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
72	278.24	0.55	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.47 (d, J = 2.3 Hz, 1H), 9.05 - 8.98 (m, 1H), 8.95 (d, J = 5.5 Hz, 1H), 8.63 (d, J = 1.5 Hz, 1H), 8.30 (dd, J = 8.6, 5.7 Hz, 1H), 7.99 (dd, J = 8.8, 7.6 Hz, 1H), 7.78 (d, J = 1.6 Hz, 1H), 7.09 (dd, J = 8.8, 0.6 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 2.39 - 2.23 (m, 1H), 1.44 - 1.32 (m, 2H), 1.18 (tt, J = 12.6, 6.2 Hz, 2H) ppm.
73	296.25	0.63	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.24 (d, J = 2.4 Hz, 1H), 8.98 (d, J = 1.6 Hz, 1H), 8.90 - 8.85 (m, 1H), 8.67 - 8.60 (m, 1H), 8.02 (dd, J = 8.5, 5.3 Hz, 1H), 7.87 - 7.75 (m, 2H), 6.62 (d, J = 8.2 Hz, 1H), 6.46 (d, J = 8.1 Hz, 1H), 4.32 - 4.22 (m, 2H), 1.96 - 1.78 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H) ppm.
74	308.31	0.64	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.36 (s, 1H), 8.98 - 8.89 (m, 2H), 8.82 (d, J = 8.3 Hz, 1H), 8.22 - 8.11 (m, 1H), 7.85 (dd, J = 9.3, 7.2 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.39 (d, J = 8.1 Hz, 1H), 5.08 (p, J = 7.1 Hz, 1H), 2.64 - 2.45 (m, 2H), 2.36 - 2.15 (m, 2H), 2.01 - 1.67 (m, 2H) ppm.
75	298.23	0.57	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.32 (s, 1H), 9.17 (dd, J = 8.1, 2.4 Hz, 2H), 8.94 - 8.86 (m, 2H), 8.83 (d, J = 5.5 Hz, 1H), 8.70 (d, J = 8.5 Hz, 1H), 8.57 - 8.50 (m, 1H), 8.18 (dd, J = 8.6, 5.6 Hz, 1H), 7.95 (dd, J = 8.4, 5.2 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.46 (d, J = 8.3 Hz, 1H), 5.15 (s, 1H), 4.00 (s, 5H), 3.88 (s, 3H), 3.80 (s, 3H) ppm.
76	326.27	0.85	Method B	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.22 (t, J = 8.6 Hz, 1H), 7.79 - 7.71 (m, 1H), 7.66 - 7.46 (m, 2H), 6.51 - 6.38 (m, 1H), 6.29 (dd, J = 11.4, 5.9 Hz, 1H), 5.25 - 5.11 (m, 1H), 3.99 - 3.91 (m, 3H), 1.49 - 1.32 (m, 7H) ppm.
77	326.18	0.66	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.00 (s, 1H), 8.57 (s, 1H), 8.47 (s, 1H), 7.87 (t, J = 2.3 Hz, 1H), 7.69 (t, J = 8.1 Hz, 1H), 6.55 (d, J = 7.9 Hz, 1H), 6.35 (dd, J = 10.3, 8.1 Hz, 1H), 5.11 (dq, J = 11.8, 5.9 Hz, 1H), 3.31 (dt, J = 3.2, 1.6 Hz, 3H), 1.47 - 1.33 (m, 6H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
78	286.25	0.7	Method B	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.21 (s, 1H), 8.25 (s, 1H), 8.18 (s, 1H), 7.95 (s, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.67 (dd, J = 15.7, 7.2 Hz, 2H), 7.05 (dt, J = 16.1, 8.0 Hz, 1H), 3.96 (s, 3H) ppm.
79	314.21	1.1	Method B	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.22 (d, J = 6.0 Hz, 1H), 8.51 (t, J = 1.7 Hz, 1H), 7.96 - 7.87 (m, 2H), 7.71 - 7.58 (m, 1H), 6.56 - 6.46 (m, 1H), 6.44 - 6.29 (m, 2H), 5.22 - 5.08 (m, 2H), 1.46 - 1.33 (m, 9H) ppm.
80	302.19	0.7	Method A	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 9.66 (s, 1H), 8.50 - 8.46 (m, 1H), 8.40 (d, J = 1.5 Hz, 1H), 8.01 (t, J = 2.1 Hz, 1H), 7.99 - 7.94 (m, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.33 (ddd, J = 7.4, 4.9, 0.8 Hz, 1H), 6.53 (d, J = 8.5 Hz, 1H), 4.07 (s, 3H) ppm.
81	336.31	0.78	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.26 (d, J = 1.5 Hz, 1H), 8.61 - 8.56 (m, 1H), 8.16 (d, J = 1.8 Hz, 1H), 8.13 - 8.05 (m, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.56 - 7.50 (m, 1H), 6.47 (d, J = 7.9 Hz, 1H), 6.31 (d, J = 8.0 Hz, 1H), 4.93 (td, J = 8.9, 4.1 Hz, 1H), 2.07 (d, J = 9.6 Hz, 2H), 1.85 - 1.74 (m, 2H), 1.67 - 1.43 (m, 5H), 1.40 - 1.24 (m, 1H) ppm.
82	280.26	0.64	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.73 (d, J = 1.5 Hz, 1H), 8.57 - 8.52 (m, 1H), 8.03 (ddd, J = 7.5, 5.9, 2.4 Hz, 2H), 7.80 (s, 1H), 7.77 (d, J = 1.5 Hz, 1H), 7.44 (dd, J = 7.4, 4.9 Hz, 1H), 7.09 (d, J = 8.9 Hz, 1H), 7.02 (d, J = 6.4 Hz, 1H), 7.02 (d, J = 7.4 Hz, 1H), 3.28 - 3.18 (m, 1H), 1.47 (d, J = 7.0 Hz, 6H) ppm.
83	310.29	0.87	Method B	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.07 (s, 1H), 8.47 - 8.34 (m, 1H), 7.64 (s, 1H), 7.57 (td, J = 8.0, 3.6 Hz, 1H), 7.32 (d, J = 5.1 Hz, 1H), 6.41 (dd, J = 20.4, 6.3 Hz, 1H), 6.33 - 6.22 (m, 1H), 5.28 - 5.10 (m, 1H), 2.57 - 2.43 (m, 3H), 1.50 - 1.26 (m, 7H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
84	310.25	0.72	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.13 (d, J = 11.9 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H), 7.94 - 7.84 (m, 1H), 7.78 (dd, J = 8.3, 1.7 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.57 (dd, J = 15.5, 7.7 Hz, 2H), 6.43 (t, J = 10.7 Hz, 1H), 6.27 (d, J = 8.0 Hz, 1H), 5.31 - 5.10 (m, 1H), 2.49 - 2.28 (m, 5H), 1.38 (t, J = 7.4 Hz, 6H) ppm.
85	302.23	0.67	Method A	¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.01 (d, J = 2.1 Hz, 1H), 8.11 (d, J = 1.4 Hz, 1H), 7.85 (d, J = 1.5 Hz, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 6.06 (d, J = 7.9 Hz, 1H), 5.31 (dt, J = 12.1, 6.1 Hz, 1H), 1.39 (d, J = 6.2 Hz, 6H) ppm.
86	426	0.56	Method A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.25 (s, 1H), 8.07 (s, 1H), 7.62 (d, J = 6.9 Hz, 2H), 7.39 (s, 1H), 7.19 (t, J = 9.3 Hz, 1H), 6.47 (s, 1H), 6.40 (s, 1H), 6.18 (s, 1H), 4.56 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.0 Hz, 2H), 3.53 - 3.37 (m, 1H), 3.10 (s, 4H), 2.38 (s, 4H), 2.20 (s, 3H) ppm.
87	427.43	0.57	Method A	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 8.83 (s, 1H), 8.17 (d, J = 1.6 Hz, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.48 (m, 2H), 7.19 (tt, J = 10.4, 8.2 Hz, 1H), 6.24 (m, 1H), 6.18 (m, 1H), 4.56 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.0 Hz, 2H), 3.49 - 3.38 (m, 1H), 3.23 (m, 4H), 2.41 - 2.33 (m, 4H), 2.31 (s, 3H) ppm.
88	299.02	0.66	Method A	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 11.34 (s, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.08 (s, 1H), 7.87 - 7.71 (m, 2H), 7.62 (t, J = 7.9 Hz, 1H), 7.23 - 7.14 (m, 1H), 6.63 (d, J = 7.8 Hz, 1H), 6.33 (d, J = 8.1 Hz, 1H), 4.54 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H) ppm.
89	389.2	0.91	Method A	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 11.28 (s, 1H), 7.96 (s, 1H), 7.33 - 7.16 (m, 2H), 7.10 (td, J = 9.3, 2.2 Hz, 1H), 6.24 (s, 2H), 3.85 - 3.68 (m, 4H), 3.66 - 3.44 (m, 4H), 2.20 (s, 3H) ppm.
90	444.31	0.68	Method B	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 11.01 (s, 1H), 7.91 (s, 1H), 7.29 (d, J = 7.1 Hz, 2H), 7.06 (t, J = 9.3 Hz, 1H), 6.46 (s, 1H), 6.27 (s, 1H), 4.57 (t, J = 6.5 Hz, 2H), 4.48 (t, J = 5.9 Hz, 2H), 3.50 - 3.40 (m, 1H), 3.30 (m, 8H), 2.39 - 2.36 (m, 3H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
91	409.26	0.56	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.74 (dd, J = 2.3, 0.9 Hz, 1H), 8.43 (dd, J = 4.8, 1.6 Hz, 1H), 7.72 (dt, J = 8.0, 1.9 Hz, 1H), 7.52 (s, 1H), 7.24 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 6.21 (d, J = 2.0 Hz, 2H), 4.60 (dt, J = 25.2, 6.4 Hz, 4H), 3.54 - 3.32 (m, 4H), 2.48 - 2.24 (m, 6H) ppm
92	410.41	0.54	Method A	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 8.50 (d, J = 5.0, 1.6 Hz, 1H), 8.07 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.77 (t, J = 7.7, 1.8 Hz, 1H), 7.27 - 7.12 (m, 1H), 6.07 (s, 1H), 4.52 (dt, J = 28.0, 6.2 Hz, 4H), 3.65 - 3.15 (m, 72H), 2.42 (s, 3H), 2.33 (t, J = 5.0 Hz, 4H) ppm.
93	367.32	0.54	Method A	¹ H NMR (300 MHz, CDCl ₃) δ 8.55 (ddd, J = 5.0, 1.8, 1.0 Hz, 1H), 7.88 (s, 1H), 7.72 - 7.60 (m, 1H), 7.55 (dt, J = 8.1, 1.1 Hz, 2H), 7.09 (ddd, J = 7.4, 5.0, 1.2 Hz, 1H), 6.26 (d, J = 2.0 Hz, 1H), 6.13 (s, 1H), 3.49 (s, 1H), 3.43 - 3.25 (m, 4H), 2.62 - 2.42 (m, 8H), 2.34 (s, 3H) ppm.
94	409.1	0.43	Method E	¹ H NMR (400 MHz, CDCl ₃) δ 8.84 (s, 1H), 8.50 (dd, J = 4.8, 1.6 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.41 - 7.30 (m, 1H), 6.30 (s, 1H), 6.04 (s, 1H), 4.69 (dt, J = 23.2, 6.4 Hz, 4H), 3.56 (p, J = 6.4 Hz, 1H), 3.38 (t, J = 5.1 Hz, 4H), 2.55 - 2.34 (m, 6H) ppm.
95	409.19	0.58	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.73 - 8.56 (m, 2H), 7.43 (d, J = 3.7 Hz, 1H), 7.33 - 7.30 (m, 2H), 6.93 (d, J = 3.7 Hz, 1H), 6.48 (d, J = 2.1 Hz, 1H), 6.01 (d, J = 2.1 Hz, 1H), 4.67 (dt, J = 29.1, 6.4 Hz, 4H), 3.53 (p, J = 6.3 Hz, 1H), 3.35 - 3.18 (m, 5H), 2.51 (s, 3H), 2.42 (dd, J = 6.1, 4.1 Hz, 4H) ppm.
96	327	0.82	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 9.48 (s, 1H), 8.84 (dd, J = 2.4, 0.9 Hz, 1H), 8.53 (dd, J = 4.8, 1.6 Hz, 1H), 7.83 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.69 (s, 1H), 7.57 (t, J = 7.9 Hz, 1H), 7.34 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 6.41 (ddd, J = 8.0, 4.3, 0.6 Hz, 2H), 4.37 (d, J = 6.8 Hz, 2H), 2.22 (hept, J = 6.7 Hz, 1H), 1.24 (d, J = 6.1 Hz, 0H), 1.11 (d, J = 6.7 Hz, 6H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
97	313.27	3.21	Method C	¹ H NMR (400 MHz, CDCl ₃) δ 8.57 (ddd, J = 4.9, 1.7, 1.0 Hz, 1H), 7.89 (s, 1H), 7.69 (ddd, J = 8.0, 7.4, 1.8 Hz, 1H), 7.64 - 7.52 (m, 2H), 7.14 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 6.45 (dd, J = 7.8, 0.7 Hz, 1H), 6.36 (dd, J = 8.0, 0.6 Hz, 1H), 5.64 (p, J = 6.1 Hz, 1H), 1.51 (d, J = 6.2 Hz, 6H) ppm.
98	313.2	3.06	Method C	¹ H NMR (400 MHz, CDCl ₃) δ 8.60 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H), 7.83 - 7.74 (m, 1H), 7.58 (dt, J = 8.0, 1.0 Hz, 1H), 7.23 (m, 1H), 6.66 - 6.54 (m, 1H), 6.46 - 6.30 (m, 1H), 4.62 (q, J = 7.0 Hz, 2H), 2.35 (t, J = 0.6 Hz, 3H), 1.53 (t, J = 7.0 Hz, 3H) ppm.
99	428.2	0.64	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.87 (dd, J = 2.4, 0.9 Hz, 1H), 8.55 (dd, J = 4.8, 1.6 Hz, 1H), 8.38 (s, 1H), 7.86 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.66 (s, 1H), 4.83 - 4.57 (m, 4H), 3.96 - 3.78 (m, 4H), 3.56 (p, J = 6.4 Hz, 1H), 2.53 (d, J = 0.8 Hz, 3H), 2.47 - 2.37 (m, 4H) ppm.
100				¹ H NMR (400 MHz, CDCl ₃) δ 10.51 (s, 1H), 8.74 (dd, J = 2.4, 0.9 Hz, 1H), 8.43 (dd, J = 4.8, 1.6 Hz, 1H), 8.13 (d, J = 0.9 Hz, 1H), 7.76 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.70 (s, 1H), 7.25 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 5.51 (hept, J = 6.1 Hz, 1H), 2.02 (d, J = 1.0 Hz, 3H), 1.40 (d, J = 6.2 Hz, 6H) ppm.
101	315.07	0.7	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 9.31 (s, 1H), 8.83 (dd, J = 2.4, 0.9 Hz, 1H), 8.53 (dd, J = 4.8, 1.6 Hz, 1H), 7.82 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.67 (s, 1H), 7.34 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 6.01 (d, J = 1.8 Hz, 1H), 5.96 (d, J = 1.8 Hz, 1H), 4.15 (s, 3H), 3.86 (s, 3H) ppm.
102	328.2	2.15	Method C	¹ H NMR (400 MHz, CDCl ₃) δ 8.84 (dd, J = 2.3, 0.8 Hz, 1H), 8.53 (dd, J = 4.8, 1.6 Hz, 1H), 8.23 (d, J = 1.0 Hz, 1H), 7.86 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.80 (s, 1H), 7.35 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 5.80 - 5.52 (m, 1H), 2.12 (d, J = 0.9 Hz, 3H), 1.50 (d, J = 6.2 Hz, 6H) ppm.
103	300.16	1.76	Method C	¹ H NMR (400 MHz, CDCl ₃) δ 8.67 (dd, J = 2.4, 0.9 Hz, 1H), 8.56 (dd, J = 4.9, 1.6 Hz, 1H), 8.35 (s, 1H), 8.15 (s, 1H), 7.68 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.38 - 7.32 (m, 1H), 4.06 (s, 3H), 2.54 (s, 3H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
104	440	0.81	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.86 (dd, J = 2.4, 0.9 Hz, 1H), 8.56 (dd, J = 4.8, 1.6 Hz, 1H), 7.85 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.65 (s, 1H), 7.36 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 6.40 - 6.21 (m, 2H), 4.97 (ddd, J = 6.4, 4.0, 2.4 Hz, 1H), 4.36 (ddd, J = 9.8, 6.4, 1.1 Hz, 2H), 4.04 (ddd, J = 9.8, 4.0, 1.1 Hz, 2H), 2.56 (s, 3H), 1.48 (s, 9H) ppm.
105	468	0.85	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.95 - 8.82 (m, 1H), 8.52 (dd, J = 4.8, 1.6 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.40 - 7.33 (m, 1H), 6.39 (s, 1H), 6.23 (s, 1H), 4.57 (dt, J = 7.2, 3.6 Hz, 1H), 3.71 (ddd, J = 12.0, 7.4, 3.8 Hz, 2H), 3.38 (ddd, J = 12.8, 7.6, 3.8 Hz, 2H), 2.55 (s, 3H), 1.95 (d, J = 4.8 Hz, 2H), 1.50 (s, 9H) ppm.
106	327.37	2.78	Method C	¹ H NMR (400 MHz, CDCl ₃) δ 8.97 - 8.77 (m, 2H), 8.53 (dd, J = 4.8, 1.6 Hz, 1H), 7.83 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.68 (s, 1H), 7.56 (t, J = 7.9 Hz, 1H), 7.34 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 6.40 (ddd, J = 7.8, 4.7, 0.7 Hz, 2H), 4.36 (d, J = 6.8 Hz, 2H), 2.22 (dt, J = 13.4, 6.7 Hz, 1H), 1.11 (d, J = 6.7 Hz, 6H) ppm.
107	341.13	0.83	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.79 (dd, J = 2.4, 0.9 Hz, 1H), 8.54 (dd, J = 4.8, 1.6 Hz, 1H), 7.79 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.60 (s, 1H), 7.34 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 7.19 (s, 1H), 5.40 (p, J = 6.2 Hz, 1H), 2.45 (t, J = 0.6 Hz, 3H), 2.14 (s, 3H), 1.36 (d, J = 6.2 Hz, 6H) ppm.
108	428.2	0.65	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 9.08 (s, 1H), 8.78 (dd, J = 2.3, 0.8 Hz, 1H), 8.45 (dd, J = 4.8, 1.6 Hz, 1H), 7.76 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.58 (s, 1H), 7.25 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 4.71 - 4.50 (m, 4H), 3.82 - 3.71 (m, 4H), 3.46 (p, J = 6.4 Hz, 1H), 2.44 (d, J = 0.8 Hz, 3H), 2.39 - 2.29 (m, 4H) ppm.
109	328.2	0.62	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.83 (dd, J = 2.4, 0.8 Hz, 1H), 8.53 (dd, J = 4.8, 1.6 Hz, 1H), 8.24 - 8.11 (m, 1H), 7.84 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.44 - 7.25 (m, 2H), 5.22 - 5.06 (m, 1H), 2.13 (d, J = 0.6 Hz, 3H), 1.49 (d, J = 6.9 Hz, 6H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
110	335.1	0.76	Method D	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.57 (ddd, J = 5.6, 1.7, 0.9 Hz, 1H), 8.26 (m, 2H), 8.11 - 8.01 (m, 1H), 6.80 (s, 1H), 7.6 (m, 1H), 6.81-6.71 (m, 1H), 6.61 (d, J = 1.1 Hz, 1H), 4.23 (s, 3H) ppm.
111	321.06	0.71	Method D	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 9.14 (dt, J = 2.2, 0.8 Hz, 1H), 8.84 - 8.76 (m, 1H), 8.71 (dt, J = 5.6, 1.1 Hz, 1H), 8.21 - 8.06 (m, 2H), 7.85 (t, J = 8.0 Hz, 1H), 7.74 (t, 1H), 6.93 (dd, J = 8.1, 0.6 Hz, 1H), 6.65 (dd, J = 7.9, 0.6 Hz, 1H) ppm.
112	419.18	0.85	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.62 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H), 7.79 (s, 1H), 7.73 (td, J = 7.8, 1.8 Hz, 1H), 7.67 - 7.59 (m, 1H), 7.38 (d, J = 2.1 Hz, 1H), 7.21 (ddd, J = 7.6, 4.9, 1.1 Hz, 1H), 7.05 - 6.94 (m, 2H), 6.56 (s, 1H), 5.09 (s, 2H), 3.86 (s, 3H), 2.60 (s, 3H), 2.29 (s, 3H) ppm.
113	341.1	2.38	Method A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.78 - 8.58 (m, 1H), 8.31 (sm 2H), 8.12 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 6.6 Hz, 1H), 6.99 (d, J = 2.3 Hz, 2H), 4.97 (s, 1H), 4.02 - 3.78 (m, 4H), 2.67 (s, 3H) ppm.
114	355.4	2.49	Method A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.60 (dt, J = 5.3, 0.9 Hz, 1H), 8.23 (s, 1H), 8.05 (s, 1H), 7.61 - 7.49 (m, 1H), 7.0 (S, 1H), 6.93 (S, 1H), 3.98 (m, 4H), 2.64 (d, J = 2.1 Hz, 3H), 1.61 (s, 3H) ppm.
115	341.4	2.68	Method A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.58 (dd, J = 5.2, 0.7 Hz, 1H), 8.18 (s, 1H), 8.00 (M, 2H), 7.48 (ddd, J = 7.4, 5.2, 1.3 Hz, 1H), 7.12 (s, 1H), 5.02-4.9 (M, 1H), 2.70 (s, 3H), 2.25 (s, 3H), 1.46 (d, J = 6.1 Hz, 6H) ppm.
116	327.4	2.66	Method A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.63 (ddd, J = 5.5, 1.7, 0.9 Hz, 1H), 8.33 - 8.14 (m, 2H), 8.08 (dt, J = 8.1, 1.0 Hz, 1H), 7.61 (ddd, J = 7.5, 5.4, 1.1 Hz, 1H), 6.87 (dd, J = 2.3, 0.9 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 4.93 (h, J = 6.1 Hz, 1H), 2.65 (s, 3H), 1.44 (d, J = 6.0 Hz, 6H) ppm.
117	410.2	0.63	Method D	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 9.07 (d, J = 2.1 Hz, 1H), 8.65 (dd, J = 5.5, 1.3 Hz, 1H), 8.07 (s, 1H), 6.74 (s, 1H), 5.03 - 4.92 (m, 2H), 4.79 - 4.53 (m, 2H), 2.61 (s, 3H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
118	424.32	0.64	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.87 (dd, J = 2.4, 0.8 Hz, 1H), 8.54 (dd, J = 4.8, 1.6 Hz, 1H), 7.85 (ddd, J = 7.9, 2.3, 1.6 Hz, 1H), 7.66 (s, 1H), 7.42 - 7.34 (m, 1H), 6.37 (d, J = 1.8 Hz, 1H), 4.66 (dt, J = 16.8, 6.4 Hz, 4H), 4.46 (dt, J = 7.0, 3.4 Hz, 1H), 3.58 - 3.36 (m, 1H), 2.54 (s, 5H), 2.22 (d, J = 8.3 Hz, 1H), 2.13 - 2.00 (m, 2H), 1.90 (dtd, J = 11.2, 7.6, 3.4 Hz, 2H) ppm.
119	408.2	0.74	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 7.66 - 7.53 (m, 3H), 7.40 (dd, J = 8.4, 7.0 Hz, 2H), 6.27 (d, J = 1.9 Hz, 1H), 6.13 (s, 1H), 4.68 (dt, J = 24.5, 6.4 Hz, 4H), 3.54 (p, J = 6.3 Hz, 1H), 3.38 (t, J = 5.0 Hz, 4H), 2.50 (s, 3H), 2.47 - 2.32 (m, 4H) ppm.
120	410.2	0.59	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.88 (d, J = 1.6 Hz, 1H), 8.51 (dd, J = 2.6, 1.6 Hz, 1H), 8.37 (d, J = 2.6 Hz, 1H), 7.93 (s, 1H), 6.35 - 6.19 (m, 1H), 4.87 - 4.46 (m, 4H), 3.57 (t, J = 6.4 Hz, 1H), 3.46 (t, J = 5.0 Hz, 4H), 2.64 - 2.39 (m, 8H), 2.15 (s, 2H) ppm.
121	432	2.1	Method A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.77 (dd, J = 2.4, 0.8 Hz, 1H), 8.43 (dd, J = 4.9, 1.6 Hz, 1H), 8.17 - 7.99 (m, 1H), 7.76 (s, 1H), 7.49 (ddd, J = 8.1, 4.9, 0.9 Hz, 1H), 6.43 (d, J = 2.1 Hz, 1H), 6.35 - 6.21 (m, 1H), 5.29 - 5.11 (m, 1H), 4.74 (d, J = 11.1 Hz, 1H), 4.37 (s, 2H), 4.02 - 3.73 (m, 4H), 2.63 - 2.38 (m, 4H) ppm.
122	396	2.05	Method B	¹ H NMR (400 MHz, CDCl ₃) δ 8.88 (dd, J = 2.3, 0.8 Hz, 1H), 8.53 (dd, J = 4.8, 1.6 Hz, 1H), 7.87 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.68 (s, 1H), 7.47 - 7.33 (m, 1H), 6.35 - 6.22 (m, 1H), 6.17 (s, 1H), 4.92 (p, J = 5.6 Hz, 1H), 4.73 (t, J = 6.7 Hz, 2H), 4.55 (dd, J = 6.7, 5.2 Hz, 2H), 3.98 - 3.75 (m, 3H), 3.45 - 3.24 (m, 2H), 2.55 (s, 3H) ppm.
123	397.2	0.8	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.78 (dd, J = 2.4, 0.9 Hz, 1H), 8.43 (dd, J = 4.8, 1.6 Hz, 1H), 7.76 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.60 (s, 1H), 7.24 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 6.24 (d, J = 1.9 Hz, 1H), 6.05 (d, J = 2.0 Hz, 1H), 4.14 - 3.85 (m, 1H), 3.28 - 2.99 (m, 4H), 2.67 (dt, J = 11.9, 6.9 Hz, 1H), 2.44 (s, 3H), 2.09 - 1.83 (m, 1H), 1.23 (s, 3H), 1.04 (s, 3H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
124	355.2	0.68	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.87 (dd, J = 2.4, 0.9 Hz, 1H), 8.52 (dd, J = 4.9, 1.6 Hz, 1H), 7.85 (dt, J = 8.0, 2.0 Hz, 1H), 7.67 (s, 1H), 7.34 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 6.35 (s, 1H), 6.18 (s, 1H), 4.99 (ddt, J = 6.2, 4.3, 2.1 Hz, 1H), 4.20 - 3.63 (m, 4H), 2.55 (s, 3H), 2.36 - 2.13 (m, 2H) ppm.
125	410.2	0.65	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.93 - 8.78 (m, 1H), 8.52 (dd, J = 4.8, 1.6 Hz, 1H), 7.86 (dt, J = 8.1, 1.9 Hz, 1H), 7.67 (s, 1H), 7.34 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 6.36 - 6.20 (m, 1H), 6.11 (s, 1H), 4.85 (p, J = 5.8 Hz, 1H), 4.01 - 3.53 (m, 6H), 3.29 - 3.02 (m, 3H), 2.54 (s, 3H), 2.10 - 1.84 (m, 2H) ppm.
126	357	2.27	Method A	¹ H NMR (400 MHz, CDCl ₃) δ 8.88 (dd, J = 2.4, 0.9 Hz, 1H), 8.52 (dd, J = 4.8, 1.6 Hz, 1H), 7.86 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.71 (s, 1H), 7.34 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 6.40 (s, 1H), 6.30 (s, 1H), 4.65 (td, J = 6.3, 4.3 Hz, 1H), 3.62 (dd, J = 10.3, 6.0 Hz, 1H), 3.52 (dd, J = 10.3, 4.2 Hz, 1H), 3.42 (s, 3H), 2.54 (s, 3H), 1.37 (d, J = 6.3 Hz, 3H) ppm.
127	327.2	2.9	Method A	¹ H NMR (400 MHz, CDCl ₃) δ 8.81 (dd, J = 2.3, 0.9 Hz, 1H), 8.53 (dd, J = 4.8, 1.6 Hz, 1H), 7.82 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.66 (s, 1H), 7.36 (dd, J = 4.8, 0.8 Hz, 1H), 6.21 (dt, J = 7.4, 1.0 Hz, 2H), 5.54 (h, J = 6.0 Hz, 1H), 2.30 (t, J = 0.7 Hz, 3H), 1.47 (d, J = 6.2 Hz, 6H) ppm.
128	341.2	2.58	Method A	¹ H NMR (400 MHz, CDCl ₃) δ 8.87 (dd, J = 2.4, 0.9 Hz, 1H), 8.56 (dd, J = 4.8, 1.6 Hz, 1H), 7.83 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.65 (s, 1H), 7.38 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 6.31 (dt, J = 4.1, 0.9 Hz, 2H), 5.94 (tt, J = 6.0, 4.9 Hz, 1H), 5.15 (ddd, J = 7.1, 6.1, 0.9 Hz, 2H), 4.80 (ddd, J = 7.5, 4.9, 0.9 Hz, 2H), 2.34 (d, J = 0.7 Hz, 3H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
129	357.2	4.09	Method A	¹ H NMR (400 MHz, CDCl ₃) δ 8.84 (dd, J = 2.3, 0.9 Hz, 1H), 8.54 (dd, J = 4.8, 1.6 Hz, 1H), 7.84 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.66 (s, 1H), 7.36 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 6.29 (dt, J = 12.3, 1.0 Hz, 2H), 5.70 - 5.52 (m, 1H), 3.77 (dd, J = 9.9, 5.7 Hz, 1H), 3.58 (dd, J = 9.9, 4.7 Hz, 1H), 3.45 (s, 3H), 2.31 (t, J = 0.7 Hz, 3H), 1.49 (d, J = 6.4 Hz, 3H) ppm.
130	440.2	4.47	Method A	¹ H NMR (400 MHz, CDCl ₃) δ 8.85 (dd, J = 2.4, 0.9 Hz, 1H), 8.56 (dd, J = 4.9, 1.6 Hz, 1H), 7.83 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.64 (s, 1H), 7.38 (ddd, J = 7.9, 4.9, 0.9 Hz, 1H), 6.32 (dt, J = 16.6, 0.9 Hz, 2H), 5.62 (tt, J = 6.4, 3.9 Hz, 1H), 4.44 (ddd, J = 9.9, 6.5, 1.1 Hz, 2H), 4.04 (ddd, J = 10.0, 4.0, 1.1 Hz, 2H), 2.34 (t, J = 0.7 Hz, 3H) ppm.
131	409.2	0.62	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.68 (dd, J = 2.4, 0.8 Hz, 1H), 8.41 (dd, J = 4.8, 1.6 Hz, 1H), 7.72 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.52 (s, 1H), 7.24 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 6.01 (s, 1H), 5.94 (s, 1H), 4.70 - 4.55 (m, 4H), 3.76 - 3.55 (m, 4H), 3.47 (t, J = 6.5 Hz, 1H), 2.50 - 2.33 (m, 4H), 2.19 (t, J = 0.6 Hz, 3H) ppm.
132	377.21	0.59	Method A	¹ H NMR (400 MHz, CDCl ₃) δ 8.79 (dd, J = 2.4, 0.8 Hz, 1H), 8.54 (dd, J = 4.8, 1.6 Hz, 1H), 7.81 (ddd, J = 8.0, 2.5, 1.6 Hz, 2H), 7.21 (s, 1H), 6.92 (s, 1H), 6.70 (s, 1H), 6.51 (s, 1H), 5.52 - 5.34 (m, 1H), 4.90 - 4.77 (m, 2H), 4.63 (dd, J = 7.7, 5.3 Hz, 2H) ppm.
133	286.13	0.63	Method D	¹ H NMR (400 MHz, Methanol-d ₄) δ 8.78 (dd, J = 2.3, 0.9 Hz, 1H), 8.55 (d, J = 1.0 Hz, 1H), 8.43 (dd, J = 4.9, 1.5 Hz, 1H), 8.05 (ddd, J = 8.0, 2.4, 1.5 Hz, 1H), 7.78 (s, 1H), 7.47 (ddd, J = 8.0, 4.9, 0.9 Hz, 1H), 6.38 (d, J = 1.0 Hz, 1H), 3.97 (s, 3H) ppm.
134	314.2	0.71	Method D	¹ H NMR (400 MHz, Methanol-d ₄) δ 8.87 (d, J = 2.2 Hz, 1H), 8.50 (dd, J = 5.1, 1.4 Hz, 1H), 8.35 - 8.18 (m, 1H), 7.85 (s, 1H), 7.63 (dd, J = 8.1, 5.1 Hz, 1H), 6.16 (d, J = 0.6 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.58 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
135	355.2	0.58	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.81 (dd, J = 2.3, 0.8 Hz, 1H), 8.53 (dd, J = 4.8, 1.6 Hz, 1H), 7.81 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.66 (d, J = 0.7 Hz, 1H), 7.43 - 7.33 (m, 1H), 6.35 - 6.23 (m, 2H), 4.93 (dd, J = 7.8, 6.2 Hz, 2H), 4.80 (d, J = 6.7 Hz, 2H), 4.66 (t, J = 6.0 Hz, 2H), 3.68 - 3.51 (m, 1H), 2.33 (s, 3H) ppm.
136	339.2	0.64	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.81 (dd, J = 2.4, 0.9 Hz, 1H), 8.52 (dd, J = 4.8, 1.6 Hz, 1H), 7.81 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.65 (s, 1H), 7.45 - 7.34 (m, 1H), 6.39 - 6.17 (m, 1H), 4.39 (d, J = 7.1 Hz, 2H), 2.31 (d, J = 0.7 Hz, 3H), 1.39 - 1.21 (m, 1H), 0.80 - 0.66 (m, 2H), 0.51 - 0.28 (m, 2H) ppm.
137	371.2	0.6	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.82 (dd, J = 2.4, 0.9 Hz, 1H), 8.51 (dd, J = 4.8, 1.6 Hz, 1H), 7.84 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.65 (s, 1H), 7.39 - 7.33 (m, 0H), 6.31 - 6.22 (m, 2H), 4.76 (t, J = 6.7 Hz, 2H), 2.31 (d, J = 0.7 Hz, 3H), 2.08 (t, J = 6.7 Hz, 2H), 1.38 (s, 6H) ppm.
138	371.2	0.76	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.86 (d, J = 2.3 Hz, 1H), 8.64 - 8.45 (m, 2H), 7.66 (s, 1H), 7.34 (d, J = 4.9 Hz, 0H), 6.45 (s, 1H), 6.22 (s, 1H), 3.88 (s, 2H), 3.32 (s, 3H), 2.55 (s, 3H), 1.33 (s, 6H) ppm.
139	369.2	0.63	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.87 (dd, J = 2.4, 0.9 Hz, 1H), 8.53 (dd, J = 4.8, 1.6 Hz, 1H), 7.89 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.67 (s, 1H), 7.40 - 7.34 (m, 1H), 6.28 (dt, J = 5.9, 1.0 Hz, 2H), 5.35 (tt, J = 7.2, 3.7 Hz, 1H), 4.21 (ddd, J = 11.2, 3.5, 1.5 Hz, 1H), 3.87 (dt, J = 10.2, 4.6 Hz, 1H), 3.67 (ddd, J = 11.5, 7.7, 2.7 Hz, 2H), 2.39 - 2.17 (m, 4H), 1.95 (dddd, J = 16.9, 12.6, 7.7, 3.8 Hz, 2H) ppm.
140	300.17	0.65	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.87 (s, 1H), 8.58 (d, J = 4.7 Hz, 1H), 7.88 (ddd, J = 7.9, 2.3, 1.6 Hz, 1H), 7.66 (s, 1H), 7.45 - 7.35 (m, 1H), 6.15 (s, 1H), 4.00 (s, 3H), 2.67 (d, J = 0.5 Hz, 3H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
141	376.2	2.43	Method A	¹ H NMR (400 MHz, CDCl ₃) δ 8.85 (d, J = 2.3 Hz, 1H), 8.69 - 8.54 (m, 1H), 7.96 - 7.80 (m, 1H), 7.69 (s, 1H), 7.48 - 7.39 (m, 1H), 6.63 (s, 1H), 5.72 (s, 1H), 4.27 - 3.91 (m, 5H), 2.45 - 2.26 (m, 2H) ppm.
142	426.3	0.76	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 7.73 (d, J = 1.7 Hz, 1H), 7.56 - 7.44 (m, 1H), 7.16 - 7.03 (m, 3H), 6.20 (s, 1H), 6.01 (s, 1H), 4.61 (dt, J = 21.1, 6.4 Hz, 4H), 3.47 (p, J = 6.4 Hz, 1H), 3.35 - 3.26 (m, 4H), 2.47 - 2.33 (m, 7H) ppm.
143	413.2	0.62	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 8.87 (dd, J = 2.3, 0.9 Hz, 1H), 8.52 (dd, J = 4.8, 1.6 Hz, 2H), 7.99 (d, J = 5.7 Hz, 1H), 7.86 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.68 (s, 1H), 7.33 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 6.51 (t, J = 6.1 Hz, 1H), 4.70 (dt, J = 22.0, 6.4 Hz, 4H), 3.60 (t, J = 6.4 Hz, 1H), 3.47 - 3.31 (m, 4H), 2.63 - 2.42 (m, 4H) ppm.
144	373.23	0.51	Method D	¹ H NMR (400 MHz, Methanol-d ₄) δ 8.74 (dd, J = 2.3, 0.9 Hz, 1H), 8.38 (dd, J = 4.9, 1.6 Hz, 1H), 8.02 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.76 (s, 1H), 7.44 (ddd, J = 8.0, 4.9, 0.9 Hz, 1H), 4.38 (d, J = 11.1 Hz, 1H), 4.08 (d, J = 11.1 Hz, 1H), 3.68 - 3.47 (m, 2H), 2.54 (d, J = 0.7 Hz, 3H), 1.44 (s, 3H) ppm.
145	442.36	1.91	Method C	¹ H NMR (300 MHz, CDCl ₃) δ 8.64 (dd, J = 2.4, 0.8 Hz, 1H), 8.52 (dd, J = 4.8, 1.5 Hz, 1H), 7.61 (ddd, J = 8.0, 2.4, 1.5 Hz, 1H), 7.35 - 7.30 (m, 2H), 7.13 (d, J = 0.9 Hz, 1H), 4.64 (d, J = 5.5 Hz, 2H), 4.28 (d, J = 5.6 Hz, 2H), 3.97 - 3.77 (m, 4H), 2.57 - 2.38 (m, 7H), 1.38 (s, 3H) ppm.
146	427.34	2.03	Method C	¹ H NMR (400 MHz, CDCl ₃) δ 8.95 - 8.77 (m, 1H), 8.52 (dd, J = 4.9, 1.6 Hz, 1H), 8.33 (s, 1H), 7.86 (ddd, J = 7.9, 2.4, 1.6 Hz, 1H), 7.66 (s, 1H), 7.33 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 6.33 (d, J = 5.9 Hz, 1H), 4.70 (dt, J = 21.2, 6.4 Hz, 4H), 3.60 (q, J = 6.4 Hz, 1H), 3.49 - 3.30 (m, 4H), 2.66 - 2.37 (m, 7H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
147	382.2	0.62	Method D	¹ H NMR (400 MHz, CDCl ₃) δ 10.81 (s, 1H), 8.78 (dd, J = 2.4, 0.9 Hz, 1H), 8.45 (dd, J = 4.8, 1.6 Hz, 1H), 7.78 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.62 (s, 1H), 7.34 - 7.25 (m, 1H), 6.76 - 6.57 (m, 2H), 3.63 (d, J = 63.6 Hz, 6H), 3.35 (s, 3H) ppm.
148	394.2	0.69	Method D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.65 (s, 1H), 9.29 (t, J = 6.3 Hz, 1H), 8.86 (dd, J = 2.4, 0.8 Hz, 1H), 8.45 (dd, J = 4.8, 1.6 Hz, 1H), 8.11 - 7.86 (m, 2H), 7.43 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 7.36 - 7.11 (m, 2H), 4.27 - 3.98 (m, 3H), , 2.59 (s, 3H) ppm.
149	376.2	0.66	Method D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.64 (s, 1H), 9.03 (t, J = 5.9 Hz, 1H), 8.86 (dd, J = 2.4, 0.8 Hz, 1H), 8.45 (dd, J = 4.8, 1.6 Hz, 1H), 8.08 - 7.84 (m, 2H), 7.43 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 7.33 - 7.17 (m, 2H), 6.21 (dt, J = 55.9, 3.9 Hz, 1H), 3.68 (tdd, J = 15.7, 6.0, 4.0 Hz, 2H), 2.58 (s, 3H) ppm.
150	388.2	0.69	Method D	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.96 (d, J = 2.2 Hz, 1H), 8.64 - 8.44 (m, 2H), 8.01 - 7.77 (m, 2H), 6.98 (d, J = 0.7 Hz, 2H), 3.21 (p, J = 1.7 Hz, 4H), 2.56 (d, J = 0.6 Hz, 3H).
151	408.2	2.4	Method C	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.78 (dd, J = 2.4, 0.9 Hz, 1H), 8.47 (dd, J = 4.9, 1.5 Hz, 1H), 8.05 (ddd, J = 8.0, 2.3, 1.5 Hz, 1H), 7.80 (s, 1H), 7.49 (ddd, J = 8.0, 4.9, 0.9 Hz, 1H), 6.62 (s, 1H), 6.29 (d, J = 2.2 Hz, 1H), 3.93 (t, J = 7.2 Hz, 2H), 3.63 (s, 7H), 2.51 (s, 3H) ppm.
152	382.1	2.49	Method C	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.78 (dd, J = 2.4, 0.9 Hz, 1H), 8.47 (d, J = 4.9 Hz, 1H), 8.21 - 7.98 (m, 1H), 7.81 (s, 1H), 7.60 - 7.40 (m, 1H), 6.63 (s, 1H), 6.29 (s, 1H), 3.78 (s, 2H), 3.41 (s, 3H), 2.51 (s, 3H) ppm.
153	425.1	2.28	Method C	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.76 (dd, J = 2.4, 0.9 Hz, 1H), 8.42 (dd, J = 4.9, 1.6 Hz, 1H), 8.03 (ddd, J = 8.0, 2.4, 1.5 Hz, 1H), 7.74 (s, 1H), 7.47 (ddd, J = 8.1, 4.9, 0.9 Hz, 1H), 6.50 (d, J = 2.0 Hz, 1H), 6.27 (d, J = 2.1 Hz, 1H), 3.51 (t, J = 6.1 Hz, 4H), 3.37 (s, 3H), 2.84 (d, J = 46.6 Hz, 6H), 2.49 (s, 3H) ppm.

Cmpd No.	M+1	Ret time	LCMS method	¹ H-NMR
154	395.19	2.27	Method C	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄ -d) δ 8.90 (d, J = 2.5 Hz, 1H), 8.58 (dd, J = 5.1, 1.5 Hz, 1H), 8.39 - 8.20 (m, 1H), 7.95 (d, J = 2.6 Hz, 1H), 7.69 (dd, J = 8.1, 5.1 Hz, 1H), 6.81 (d, J = 2.4 Hz, 1H), 6.55 (d, J = 2.6 Hz, 1H), 4.33 (d, J = 13.9 Hz, 2H), 3.66 - 3.49 (m, 1H), 3.22 (t, J = 13.3 Hz, 2H), 2.90 (s, 4H), 2.64 (d, J = 1.1 Hz, 1H), 2.55 (d, J = 3.6 Hz, 3H), 2.26 (d, J = 12.8 Hz, 2H), 1.93 - 1.47 (m, 2H) ppm.
155	340.14	0.63	Method D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.56 (s, 1H), 8.86 (dd, J = 2.4, 0.8 Hz, 1H), 8.45 (dd, J = 4.7, 1.5 Hz, 1H), 8.12 - 7.85 (m, 2H), 7.43 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 2.99 (s, 3H), 2.89 (s, 3H), 2.55 (s, 3H) ppm.
156	370.2	0.65	Method D	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.99 (d, J = 2.2 Hz, 1H), 8.69 - 8.45 (m, 3H), 7.97 (s, 1H), 7.83 (dd, J = 8.2, 5.4 Hz, 1H), 7.19 (d, J = 11.6 Hz, 2H), 3.58 (d, J = 2.3 Hz, 4H), 3.39 (s, 3H), 2.65 (d, J = 2.0 Hz, 3H) ppm.
157	409.2	0.67	Method D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.00 (s, 1H), 8.81 (dd, J = 2.4, 0.9 Hz, 1H), 8.42 (dd, J = 4.7, 1.6 Hz, 1H), 8.06 - 7.74 (m, 2H), 7.40 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 5.93 (d, J = 1.7 Hz, 1H), 5.82 (d, J = 1.9 Hz, 1H), 3.94 (t, J = 7.5 Hz, 2H), 3.78 - 3.50 (m, 7H), 2.36 (s, 7H) ppm.

ASSAYS FOR DETECTING AND MEASURING REMYELINATION
PROPERTIES OF COMPOUNDS

5 ***In vivo* Mouse Cuprizone Assay:**

[00360] Cuprizone Feeding Protocol:

[00361] 2 month old female C57BL/6 mice (Stock Number: 000664) are purchased from Jackson Labs and fed for 4-10 months with a 0.2% cuprizone chow (provided by Research Diets, Product # D10020701R, Description AIN-76A Rodent Diet with 0.2% cuprizone) using cuprizone purchased from Sigma (Cat# 14690-

100G). Chow is provided *ad libitum*, and refreshed every 4 days to ensure stability of

the cuprizone. Mice are maintained on this diet for 4 -10 months before initiation of the experiments.

[00362] Dosing and PK:

5 **[00363]** 1) 24 hours prior to the start of dosing, 6 to 10 mice are switched from cuprizone chow to normal chow (Picolab rodent diet 20 EXT IRR 5053, irradiated) without added cuprizone. These mice are maintained on normal chow throughout the course of dosing.

10 **[00364]** 2) 6 to 10 mice per group are randomized into new cages such that mice that are housed in one cage during the cuprizone diet are not housed together in one dose group during the study.

15 **[00365]** 3) Mice can be dosed with compound in one of two regimens:

Regimen A: mice are dosed QD or BID for 14 days via oral gavage. **Regimen B:** mice are dosed QD or BID for 14 days via IP injection. However, other dosing schedules and/or routes of administration may also be used.

20 **[00366]** 4) On the last day of dosing, dried blood spots are collected at multiple time points following the last dose. Often this is 30 minutes, 2, 6 and 24 hours following the final dose on day 14 via the tail vein.

25 **[00367]** Perfusion and sectioning:

30 **[00368]** 1) The day after the last day of dosing, mice are transcardially perfused with 12 ml of PBS (Sigma, P4417) followed by 20 ml of 3.2% paraformaldehyde in PBS (Electron Microscopy Sciences # 15714-S). The brains are removed via standard dissection techniques and each is postfixed in 3.2% paraformaldehyde (20 ml) for 24-48 hours at room temperature in sealed scintillation vials.

35 **[00369]** 2) Serial 50 micron sections are collected through the anterior posterior extent of the brain, from just behind the olfactory bulb, through visual cortex using a vibrating microtome, the V-STAR (described in International Publication No. WO 2013/012799 and US Patent number US 8,967,024 both of which are incorporated herein by reference in their entirety). Sections are collected in phosphate buffered saline (PBS). Vibratome speed is set to 1.1 mm/s and amplitude was set to 0.8 mm.

40 **[00370]** 3) A series of every 24th section is removed for staining yielding 5 sections per brain.

45 **[00371]** Staining:

- [00372]** 1) Tissue sections are stained using an automated system for processing blots (hereinafter the “blotinator”) (described in WO2011/087646 and US Patent numbers US 8,337,754 and US 8,679,406 each of which is incorporated herein by reference in its entirety). Brain sections are placed in the blotinator plate and
- 5 bathed in PBS. The blotinator applies primary antibodies (MOG and MBP together) and Hoechst nuclear stain for 12 hours at room temperature with constant shaking.
- [00373]** The following stains are diluted in blocking buffer (described below):
- [00374]** Hoechst nuclear stain (0.5 mg/ml)(bisBenzimide H 33342 trihydrochloride Sigma # 33342).
- 10 **[00375]** Myelin basic Protein (MBP) antibody (Abcam Cat # ab7349) is diluted at a 1:750 ratio in blocking buffer).
- [00376]** Myelin Oligodendrocyte Glycoprotein (MOG) (R&D systems Cat # AF2439) is diluted at a 1:250 ratio in blocking buffer.
- [00377]** Antibodies are diluted in blocking buffer, which consists of 0.3% Triton X-100 (Sigma Cat # 234729), 0.02% Sodium Azide (Sigma Cat# S2002) and
- 15 8% fetal bovine serum in PBS (Sigma Cat# F2442).
- [00378]** 2) The blotinator washes the samples 4 times for 5 minutes each with a wash buffer (0.2% Triton X-100 in PBS).
- [00379]** 3) The blotinator applies secondary antibodies diluted in blocking
- 20 buffer and incubates them for 2 hours with constant shaking.
- [00380]** Alexa 488 donkey anti-rat secondary (Life technologies Cat# A-21208) is diluted at 1:1000 in blocking buffer.
- [00381]** Alexa 568 donkey anti-goat secondary (Life technologies Cat# A-11057) is diluted at 1:1000 in blocking buffer.
- 25 **[00382]** Antibodies are also diluted in blocking buffer described above.
- [00383]** 4) The samples are then washed 4 times for 5 minutes each with wash buffer (0.2% Triton X-100 in PBS).
- [00384]** 5) All 5 sections are mounted on a slide (Fisherbrand Superfrost Plus microscope slide Cat# 12-550-15) and coverslip with 50 microliters Fluormount
- 30 (Sigma cat# F4680-25ml) in preparation for scanning.
- [00385]** Scanning:
- [00386]** Images are scanned using an Olympus CS120 fluorescent scanning microscope. Entire sections are scanned at 10x magnification, with 500 millisecond

exposures for the 488 and 568 nanometer fluorescent channels. The Hoechst signal is detected using a 100 millisecond exposure.

In vivo Myelin Detection Software:

5 **[00387]** A custom algorithm, developed in house, is used to quantify the amount of new myelin in mice that has been demyelinated with cuprizone and subsequently is treated with compounds. Conceptually, the software can subtract a mature myelin marker from a pan-myelin (young and old myelin) marker, and measure the area of the remaining “new” myelin. Myelin oligodendrocyte glycoprotein (“MOG”) is specific to old myelin, while myelin basic protein (“MBP”) is a pan myelin marker, expressed in more immature myelin as well as more mature myelin. This process accounts for the variability inherent in the demyelination process, in which some animals experience more demyelination than others. It more accurately measures myelin generated in response to compound treatment.

15 **[00388]** The algorithm is written using Definiens Tissue Studio and Definiens Developer XD. There are several steps to the algorithm, each of which is discussed below.

20 **[00389]** Three channels of information for each sample are loaded. The intensity levels of the three images are summed, and the resulting image is used to determine the “tissue” area. Subsequent analyses are done exclusively on the tissue area.

25 **[00390]** The MOG channel is loaded and the Definiens “Auto Threshold” function is used to distinguish MOG positive regions from background. Regions of putative white matter with areas < 50 pixels are returned to the tissue class. Thus, remaining white matter tracts that resist demyelination from cuprizone are excluded from subsequent analyses.

30 **[00391]** The ratio of MBP signal to MOG signal is calculated. This consists of the mean MBP intensity value divided by the mean MOG intensity value over the entirety of the image. This MBP:MOG ratio is used to normalize the intensity between the MBP and MOG channels. The normalized MOG signal multiplied by 0.5 is subtracted from the MBP signal, creating a new image, “MBP-MOG”. The “Auto Threshold” function is used on the MBP-MOG image, and the ‘new’ myelin consisting of pixels with intensities above the threshold is delineated. Regions of

putative new myelin with areas <2 pixels are returned to the tissue class, and the number of pixels positive for “new” myelin is measured.

[00392] The algorithm returns the area of the tissue and the MBP positive, MOG negative ‘new’ myelin. Each section is normalized by area relative to its comparable tissue (e.g., the first). Most anterior sections are normalized relative to other first anterior sections. The 5 normalized MBP+/MOG- areas are summed, yielding a total positive area per sample. This yields a representation of myelin synthesis over the whole extent of the brain, excluding the olfactory bulb and the cerebellum.

10 [00393] Compound of the present invention may be tested in the *in vivo* Mouse Cuprizone assay described above.

***In vitro* Myelination Assay**

[00394] Compounds were screened for their ability to induce myelination using a primary rat mixed cortical cell culture assay, which contains neurons, oligodendrocyte precursor cells, oligodendrocytes, astrocytes and microglia. The assay quantifies myelination by measuring myelin basic protein (MBP) immunofluorescent positive myelin strands from images taken using a Cellomics Array Scan (model Arrayscan VTI HCS Reader) or a Molecular Devices Image Xpress (model IXM XL) high content imager. The myelin strands were quantitated using a custom created myelin detection software program. Test compounds were dissolved in DMSO to make a 10 mM initial stock solution. Dilutions were made in myelination medium to obtain the final solutions for the assay and were tested in primary rat mixed cortical cells at selected doses.

[00395] Primary rat mixed cortical cells were prepared from harvested cerebral cortices from postnatal day 1 (P1) rats (P1 Rat CD® IGS pups) were purchased from Charles River) in Complete Dissociation Medium, wherein the meninges were removed and the cortical tissue chopped with a razor blade into ~1 mm³ pieces. Tissue from 1-3 pups was collected and placed into 15 ml conical tubes in a total volume of 5 ml of Complete Dissociation Medium. Activated papain (3 ml) was added to each 15 ml conical tube and tissue was incubated at 37°C for 30 minutes. After the 30 minute incubation, DNase (Sigma D4527; 75 µl of a 1 mg/ml stock) was added to each tube, followed by mechanical trituration using a 2 ml serological pipette and autopipettor to gently dissociate the tissue. Following trituration, larger tissue

pieces were allowed to settle by gravity, and the supernatant containing dissociated cells was transferred to a 50 ml conical tube with 4 ml of trypsin inhibitor. Cells were pelleted by centrifugation, resuspended in myelination medium and filtered through a 40 µm filter. Cells were then seeded in 96-well plates (BD Biosciences, Black, PDL-coated, Cat. No. 356640) or in some cases in 384-well plates at 87,500-95,000 cells/well in a final volume of 200 µl of Myelination Medium in the presence or absence of compound and cultured for 14 days in a humidified 37°C incubator with 5% CO₂. Half the medium was removed and replaced with fresh medium containing 1X compound on days 6 and 10. Using a Biotek automatic plate washer (model Biomek® FXP Laboratory Automation Workstation), cells were fixed with 4% paraformaldehyde on day 14, washed with PBS and blocked in 5% normal goat serum (Vector Laboratories, S-1000) in 0.1% PBS-TritonX-100 (PBST) for 1 hour. Cells were stained with 1:500 anti-MBP (Covance, cat #SMI99) primary antibody in 1% normal goat serum in 0.1% PBST for 2 hours at room temperature followed by 2 washes with PBST. A final incubation in secondary antibody (1:1000, Invitrogen, Alexa-488 anti-mouse IgG2b) and 1:10,000 Hoechst dye in 1% normal goat serum in 0.1% PBST was performed for 2 hours at room temperature. Plates were washed with PBS and then scanned on a Cellomics Array Scan using a 10X objective (25 images per well) or the Image Xpress using a 10X objective (9 image per well). Images were analyzed using Vertex myelin detection software (described below) to quantify total MBP myelin pixels per well. Fold myelin pixels above background at two concentrations (1.0 µM and 10.0 µM) relative to baseline of no added compound are reported below in Table 4. Standard deviation for each compound concentration was calculated using all replicates and using a standard deviation formula commonly used in the art.

[00396] One of skill in the art would recognize that for this type of primary neuronal mixed cell assay variability between different assay runs is to be expected even though the protocol is the same for each assay run. For instance, variability may be due to small differences in cell viability, cell density, age of the animals, etc.

30 [00397] Vertex Myelin Detection Software:

[00398] The Vertex myelin detection software was used to quantify the amount of myelin wrapping axons in a digital image that was obtained from our in-house microscope. Conceptually, the software identified and traced MBP positive ridge like

structures in the image that were indicative of myelinating axons. A confounding factor in the analysis was the large debris fields typically occurring in the images. These fields resulted from the assay conditions required to achieve myelination. Special care was taken to ensure that noise in the image induced by the debris field was appropriately suppressed so that the signal that arose from the myelination could be recovered. The software was written in the Jython programming language and made significant utilization of the Fiji image analysis toolkits (see, Schindelin, J.; Arganda-Carreras, I. & Frise, E. et al., "Fiji: an open-source platform for biological-image analysis", *Nature Methods* **9**(7): 676-682, 2012). There were several steps to the algorithm, each of which are discussed below.

[00399] Initially the image was loaded and converted to a 256-bit grey scale representation. Image contrast was enhanced by performing standard histogram stretching. The saturation parameter for the enhancement was set at 0.35, meaning the upper and lower 3.5% of the distribution of the gray scale values present in the image were removed prior to enhancement. The Frangi[2] vesselness measure, which computes the likelihood of a pixel belonging to a ridge-like structure, was applied to the resulting image (see, Frangi AF, Niessen WJ, Vincken KL, Viergever MA "Multiscale vessel enhancement filtering", *Proceedings of Medical Image Computer-Assisted Intervention (MICCAI)*, Lecture notes in computer science 1496: 130–137, 1998). The Frangi process created a "vessel likeness image" which was then converted to a binary image mask. The threshold of the Frangi measure for conversion to the mask was adjusted so that appropriate regions of the input image were selected. Once the mask was created, morphological closing was applied to remove small holes. Small structures were removed from the mask by deleting regions containing less than 40 connected pixels. The resulting mask overlaps regions of the original image that had a high likelihood of containing myelin strands.

[00400] Morphological skeletonization was applied to the binary mask and the resulting image was then converted to a graph data structure. Each node of the graph represented a pixel of the image. Owing to the skeletonization process, each node was connected to at most 4 neighboring pixels. Nodes connected to one other node indicated the end of a myelin strand ("end nodes"); nodes connected to exactly two other nodes indicated a pixel contained in a myelin strand ("myelin node"); while nodes connected to 3 or 4 other nodes indicated regions where myelin strands

intersect (“join nodes”). Neighboring ‘myelin nodes’ that were adjacent to the same “join node” were merged into longer strands of myelin. This process was done in a greedy fashion. The longest strand of myelin originating from an “end node” in the graph was identified. If this strand terminated in an end node the strand was extracted
5 from the graph. If the strand terminated at a “join node” then it was joined with one of the other myelin strands adjacent to the same join node. The largest angle between the growing strand and all other strands adjacent to the join node was determined. If this angle was greater or equal to 140 degrees, then the growing strand and the strand that made this large angle were merged into one strand. The two strands that were
10 merged were removed from being adjacent to the “join node”. If the angle was less than 140 degrees, the growing strand was extracted from the graph and removed as being adjacent to the join node. The entire process was repeated until all strands were removed from the graph. Various geometric properties of the strand such as length and maximum curvature were computed from the number of pixels in the strand and
15 the connectivity of the graph.

[00401] Before a putative myelin strand was quantified as myelin it was subjected to several quality control measures. The strand needed to be of a sufficient length (at least greater than 40 pixels). To ensure the strand was not overly curved, the ratio of the geometric distance between strand endpoints to the length of the strand needed to
20 be greater than or equal to 0.8. Finally, to ensure the strand was not overly thick, the gray scale gradient at each point on the strand in the directions orthogonal to the strand direction needed to decay sufficiently rapidly. Specifically, the gray scale needed to decrease by 25% from the gray scale value of pixel intersected by the orthogonal line and the putative myelin strand. This decrease needed to occur within
25 5 pixels. If a strand passes all quality checks it was quantified as myelin.

[00402] Reagent and media preparation and animal source for the *in vitro* Myelination Assay

[00403] 10x Dissociation Media (DM): 10x DM was prepared on a 1 liter scale by combining 900 mM Na₂SO₄, 300 mM K₂SO₄, 58 mM MgCl₂, 2.5 mM CaCl₂, 10 mM
30 HEPES and 20 mL of a phenol red solution (0.5%). The pH was adjusted with .1N NaOH by eye until orange-red. The solution was then sterilized by filtration through a 0.2uM filter (prewashed with 100 ml of deionized sterile water which was discarded prior to filtration of the DM media solution.

[00404] 10x KyMg Stock: KyMg stock was prepared on a 200 mL scale as follows. To a 250 mL flask was added 190 mL of water, 1 mL of phenol red (Sigma P0290), stock, 1.75 mL of 1N NaOH, 378 mg of kynurenic acid, and 2 mL 500 mM HEPES. The mixture was then sonicated to dissolve the kynurenate and then MgCl₂ (4.1 ml of
5 a 4.9 M solution) was added. The pH was adjusted to 7.4 by adding up to 1 ml of 0.1N NaOH and the mixture sterilized by filtration through a prewashed nylon filter (0.2 µm pore).

[00405] Complete dissociation medium (DM): 5 mL Ky Mg to 45 mL 1X DM media

[00406] Papain Enzyme Solution (Worthington Biochemical, LK003178): A 10
10 units/mL stock solution was made fresh the day of dissection by adding 1mL of 10mM NaOH and Complete Dissociation Medium to one vial of papain (~100 units) to give a 10 units/mL final concentration. The papain was activated at 37 °C for 10-15 minutes prior to use.

[00407] Trypsin Inhibitor Solution: 9.6mL of Complete Dissociation Medium was
15 added to 100 mg of trypsin inhibitor (type II-O; Sigma T-9253) and the mixture was sonicated. The pH was adjusted to ~5.75 using 1N NaOH and pH strips. Aliquots (4 mL) were measured out and stored at -20 °C.

[00408] DNase I Solution 1mg/mL: Added 25 mL DMEM/F12 medium (Corning, 10-092-CM) to 20 KU DNase I (Sigma D4527) and aliquoted into one time use
20 aliquots stored at -20° C.

Myelination Medium:

DMEM (Invitrogen, Cat #11960-051)

1:50 B27 (Invitrogen, Cat #17504-044)

1% FBS (HyClone)

25 2 mM Glutamax (1:100) (Cat # Gibco 25030081)

Pen Strep (1:100) 10,000 units/mL (Cat # Gibco 15140122)

PDGF/FGF 0.3 ng/mL each (3 µL per 100 mL; PeproTech, cat #100-13A and cat #100-18B)

Myelination medium was made fresh the day of use from a stock bottle of DMEM
30 containing penicillin/streptomycin and Glutamax, which was stored at 4° C for up to one month. On the day of use, 1:50 B27, 1% FBS and 0.3ng/mL of PDGF and FGF were added to the DMEM containing penicillin/streptomycin and Glutamax.

[00409] Other *in vitro* and *in vivo* assays and models known in the art may also be used to show induction of remyelination in response to treatment with compounds such as those of the present invention (see, Nalm, F. J. et al., *Nature* (Letter), published online 20 April 2015, doi:10.1038/nature14335 and Macklin, W.B. et al.,
 5 *Developmental Cell*, 32, pp 447-458 (2015))

[00410] The activities of the compounds below in Table 4 below have between less than 1 fold to greater than 10,000 fold myelin pixels above background at two concentrations (1.0 μ M and 10.0 μ M) relative to baseline of no added compound.

Table 4. Remyelination in vitro data.

Cmpd No.	10 uM Score	1 uM Score
1	++	+++
2	ND	ND
3	+++	+++
4	-	++
5	++	++
6	+	++
7	-	++
8	++	++
9	+++	++
10	+++	+++
11	++	+
12	+++	+
13	++	+
14	++	-
15	+	+
16	-	+
17	+	+
18	-	+
19	+	-
20	++	-
21	+	+
22	-	-
23	+	-
24	++	+
25	ND	ND
26	++	++
27	ND	ND
28	-	-
29	-	-
30	-	+
31	++	++
32	-	-

33	+++	-
34	+	-
35	++	-
36	-	+++
37	+++	++
38	-	++
39	+	+
40	++	++
41	+++	+
42	+++	-
43	++	++
44	++	-
45	+	-
46	++	++
47	+	-
48	+	-
49	-	+
50	++	-
51	ND	ND
52	+	-
53	+	+
54	-	-
55	++	+
56	++	+
57	-	+
58	+++	++
59	++	+++
60	+	-
61	-	-
62	++	+
63	+++	-
64	++	-
65	++	+++
66	++	++
67	+	-
68	+++	++
69	++	-
70	++	-
71	++	-
72	+++	++
73	+++	++
74	+	++
75	+	-
76	+++	-
77	++	-
78	-	-
79	+++	-

80	-	-
81	+++	++
82	+	+
83	+++	-
84	++	+
85	++	+++
86	+	-
87	+	-
88	+++	+++
89	++	+
90	+	-
91	-	+++
92	++	+++
93	-	++
94	-	++
95	-	-
96	++	++
97	+++	+++
98	++	+++
99	-	-
100	+	-
101	++	++
102	+	+
103	-	-
104	++	+
105	+	+
106	+	++
107	++	+
108	-	+
109	++	+
110	++	++
111	+	-
112	+	+
113	+	+++
114	-	++
115	+++	+
116	++	+
117	-	+++
118	-	+
119	+++	+++
120	-	+
121	++	+
122	++	++
123	++	+
124	-	++
125	++	+
126	+	+

127	++	+++
128	++	++
129	-	+++
130	+	+
131	ND	ND
132	ND	ND
133	ND	ND
134	ND	ND
135	ND	ND
136	ND	ND
137	ND	ND
138	ND	ND
139	ND	ND
140	ND	ND
141	ND	ND
142	ND	ND
143	ND	ND
144	ND	ND
145	ND	ND
146	ND	ND
147	ND	ND
148	ND	ND
149	ND	ND
150	ND	ND
151	ND	ND
152	ND	ND
153	ND	ND
154	ND	ND
155	ND	ND
156	ND	ND

Fold relative to baseline

ND

≤1

>1 to 10x

>10 to 100x

>100 to 1000x

>1000 to 10,000x

Activity

not determined

-

+

++

+++

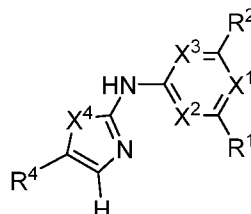
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- [00411]** All publications and patents referred to in this disclosure are incorporated
- 5 herein by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Should the meaning of the terms in any of the patents or publications incorporated by reference conflict with the meaning of the terms used in this

disclosure, the meaning of the terms in this disclosure are intended to be controlling. Furthermore, the foregoing discussion discloses and describes merely exemplary embodiments of the invention. One skilled in the art will readily recognize from such discussion and from the accompanying drawings and claims, that various changes, 5 modifications and variations can be made therein without departing from the spirit and scope of the invention as defined in the following claims.

We claim:

1. A compound of formula (I)



5

(I)

or a pharmaceutically acceptable salt thereof,

wherein:

X¹ is CR^{X1} or N;

X² is CR^{X2} or N;

10 X³ is CR^{X3} or N;

X⁴ is O or S;

provided that X¹ is not N simultaneously with X² and X³;

R¹ is selected from the group consisting of -OC₁₋₆alkyl, -OC₁₋₆haloalkyl, -O-C₂-

6alkylene-OC₁₋₄alkyl, -O-C₂₋₆alkylene-OH, -NHC(O)(C₁₋₄alkyl), -N(C₁-

15 4alkyl)C(O)(C₁₋₄alkyl), -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁-

4alkyl), -C(O)NH(C₁₋₄haloalkyl), -C(O)NH(-C₂₋₆alkylene-OC₁₋₄alkyl), -

C(O)N(C₁₋₄alkyl)(-C₂₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₂₋₆alkylene-OH), -

C(O)N(C₁₋₄alkyl)(-C₂₋₆alkylene-OH), -L¹-G¹-R⁶, -L¹-G², -L¹-G³, and -L²-G⁴;

R² is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄haloalkyl,

20 halogen, and -OC₁₋₄alkyl;

R^{X1} is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, C₁-
4haloalkyl, and -O-C₁₋₄alkyl;

R^{X2} is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, and C₁-
4haloalkyl;

25 R^{X3} is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, C₁-
4haloalkyl, and -O-C₁₋₄alkyl;

L¹ is a bond, -O-, -O-C₁₋₄alkylene-, -NR⁵-, -NR⁵-C₁₋₄alkylene-, or -C(O)-
, wherein R⁵ is hydrogen or C₁₋₄alkyl;

L² is -O-C₁₋₄alkylene-;

G¹ is a 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C₁₋₃alkylene bridge between two non-adjacent ring atoms, G¹ being optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, and oxo;

R⁶ is

- a) a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the heterocycle being optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, -CH₂S(O)₂phenyl, halogen, hydroxyl, oxo, -OC₁₋₄alkyl, -C₁₋₆alkylene-OC₁₋₄alkyl, and -C₁₋₆alkylene-OH; or
- b) a 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, -C(O)OC₁₋₄alkyl, -C(O)OH, oxo, -OC₁₋₄alkyl, -C₁₋₆alkylene-OC₁₋₄alkyl, and -C₁₋₆alkylene-OH;

G² is a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, G² being optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, oxo, cyano, -C₁₋₆alkylene-cyano, -C(O)C₁₋₄alkyl, -C(O)-C₁₋₆alkylene-OC₁₋₄alkyl, -C(O)-C₁₋₆alkylene-OH, -C(O)C₃₋₆cycloalkyl, -C(O)OC₁₋₄alkyl, -C(O)OC₁₋₄haloalkyl, -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -NH(-C₁₋₆alkylene-OH), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -C(O)C₁₋₄haloalkyl, -OC₁₋₄alkyl, -OC₁₋₄haloalkyl, -C₁₋₆alkylene-OC₁₋₄alkyl, -C₁₋₆alkylene-OH, -C₁₋₆alkylene-NH₂, -C₁₋₆alkylene-NH(C₁₋₄alkyl), -C₁₋₆alkylene-N(C₁₋₄alkyl)(C₁₋₄alkyl), -O-C₁₋₆alkylene-NH₂, -O-C₁₋₆alkylene-NH(C₁₋₄alkyl), -O-C₁₋₆alkylene-N(C₁₋₄alkyl)(C₁₋₄alkyl), -O-C₁₋₆alkylene-OC₁₋₄alkyl, -O-C₁₋₆alkylene-OH, -C₁₋₄alkylene-O-C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₄alkylene-O-C₁₋₄alkylene-OH, -C₁₋₄alkylene-C(O)OC₁₋₄alkyl, -C₁₋₄alkylene-C(O)OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NH₂, -NH(C₁₋

4alkyl), $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-S(O)_{1-2}C_{1-4}alkyl$, $-C_{1-6}alkylene-S(O)_{1-2}C_{1-4}alkyl$, and a $-C_{1-6}alkylene$ substituted by 2 groups independently selected from hydroxyl, halogen, $-OC(O)C_{1-4}alkyl$, $-OC_{1-4}alkyl$, $-NH_2$, $-NH(C_{1-4}alkyl)$, and $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$;

- 5 G^3 is 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, halogen, hydroxyl, oxo, cyano, $-C(O)C_{1-4}alkyl$, $-C(O)C_{3-6}cycloalkyl$, $-C(O)OC_{1-4}alkyl$, $-C(O)OC_{1-4}haloalkyl$, $-C(O)NH_2$, $-C(O)NH(C_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-C(O)NH(-C_{1-6}alkylene-OC_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)(-C_{1-6}alkylene-OC_{1-4}alkyl)$, $-C(O)NH(-C_{1-6}alkylene-OH)$, $-C(O)N(C_{1-4}alkyl)(-C_{1-6}alkylene-OH)$, $-NH(-C_{1-6}alkylene-OC_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(-C_{1-6}alkylene-OC_{1-4}alkyl)$, $-NH(-C_{1-6}alkylene-OH)$, $-N(C_{1-4}alkyl)(-C_{1-6}alkylene-OH)$, $-C(O)C_{1-4}haloalkyl$, $-OC_{1-4}alkyl$, $-C_{1-4}alkylene-OC_{1-4}alkyl$, $-C_{1-6}alkylene-OH$, $-C_{1-6}alkylene$ substituted by 2 groups independently selected from hydroxyl and $-OC(O)C_{1-4}alkyl$, $-C_{1-4}alkylene-C(O)OC_{1-4}alkyl$, $-C_{1-4}alkylene-C(O)OH$, $-NHC(O)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl)$, $-NH_2$, $-NH(C_{1-4}alkyl)$, and $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$;

- G^4 is phenyl optionally substituted with 1-4 substituents independently selected from the group consisting of $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, halogen, hydroxyl, cyano, phenyl, $-C(O)C_{1-4}alkyl$, $-C(O)C_{3-6}cycloalkyl$, $-C(O)OC_{1-4}alkyl$, $-C(O)OC_{1-4}haloalkyl$, $-C(O)NH_2$, $-C(O)NH(C_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-C(O)NH(-C_{1-6}alkylene-OC_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)(-C_{1-6}alkylene-OC_{1-4}alkyl)$, $-C(O)NH(-C_{1-6}alkylene-OH)$, $-C(O)N(C_{1-4}alkyl)(-C_{1-6}alkylene-OH)$, $-NH(-C_{1-6}alkylene-OC_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(-C_{1-6}alkylene-OC_{1-4}alkyl)$, $-NH(-C_{1-6}alkylene-OH)$, $-N(C_{1-4}alkyl)(-C_{1-6}alkylene-OH)$, $-C(O)C_{1-4}haloalkyl$, $-OC_{1-4}alkyl$, $-C_{1-4}alkylene-OC_{1-4}alkyl$, $-C_{1-6}alkylene-OH$, $-C_{1-6}alkylene$ substituted by 2 groups independently selected from hydroxyl and $-OC(O)C_{1-4}alkyl$, $-C_{1-4}alkylene-C(O)OC_{1-4}alkyl$, $-C_{1-4}alkylene-C(O)OH$, $-NHC(O)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl)$, $-NH_2$, $-NH(C_{1-4}alkyl)$, and $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$; and

- 30 R^4 is phenyl or a 5- or 6-membered heteroaryl containing 1-3 heteroatoms independently selected from oxygen, nitrogen and sulfur, R^4 being optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, $-S(O)_2C_{1-4}alkyl$, $-S(O)C_{1-4}alkyl$, $-SC_{1-4}alkyl$, C_{1-}

4alkyl, C₁₋₄haloalkyl, -OC₁₋₄alkyl, -OC₁₋₄haloalkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₄alkylene-N(C₁₋₄alkyl)(C₁₋₄alkyl), -NH(C₁₋₄alkylene-OC₁₋₄alkyl), -NH(C₁₋₄alkylene-OH), -N(C₁₋₄alkyl)(C₁₋₄alkylene-OC₁₋₄alkyl), -N(C₁₋₄alkyl)(C₁₋₄alkylene-OH), -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)(C₁₋₄alkyl), C₃₋₆cycloalkyl, C₅₋₆cycloalkenyl, or a 4- to 8-membered monocyclic heterocycle containing 1-2 nitrogen atoms, the C₃₋₆cycloalkyl, the C₅₋₆cycloalkenyl, and the 4- to 8-membered monocyclic heterocycle being independently optionally substituted with 1-2 substituents independently selected from the group consisting of pyridyl, halogen, hydroxyl, -OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄haloalkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, and -C₁₋₄alkylene-OH;

provided that when X⁴ is S then

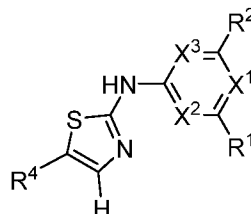
- (i) R¹ is not -O-C₂₋₆alkylene-OC₁₋₄alkyl, -O-C₂₋₆alkylene-OH, G², -O-G², or -O-C₁₋₄alkylene-G², where G² is an optionally substituted monocyclic heterocycle containing at least one nitrogen atom, when X¹ is N, X³ is N, X² is CH, and R⁴ is optionally substituted phenyl;
- (ii) R¹ is not -OC₁₋₄alkyl when R⁴ is optionally substituted phenyl or thiophene, and X¹ is CR^{X1};
- (iii) R² is other than H, when R¹ is G² or -O-G², G² is an optionally substituted monocyclic heterocycle containing at least one nitrogen atom, X¹ is CH, X² is CH and X³ is N;
- (iv) R² is other than H, when R¹ is G² or -NR⁵-C₁₋₄alkylene-G², G² is an optionally substituted monocyclic heterocycle containing at least one nitrogen atom, X¹ is CH, X³ is CH and X² is N; or
- (v) the compound of formula (I) is not N-(4-chloro-6-(4-methylpiperazin-1-yl)pyridin-2-yl)-5-(pyridin-4-yl)thiazol-2-amine;

and provided that when X⁴ is O then

- (i) G² is not morpholino when R⁴ is phenyl substituted with cyano;
- (ii) R¹ is not -O-C₁₋₄alkyl when R⁴ is optionally substituted phenyl; or

(iii) R^1 is not $-NHC(O)(C_{1-4}alkyl)$ when R^4 is pyridinyl.

2. The compound of claim 1 of formula (II)



5 (II)

or a pharmaceutically acceptable salt thereof,

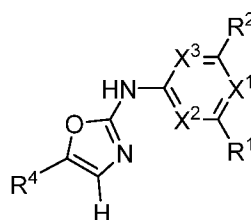
wherein:

R^1 is selected from the group consisting of $-OC_{1-6}alkyl$, $-OC_{1-6}haloalkyl$, $-O-C_{2-6}alkylene-OC_{1-4}alkyl$, $-O-C_{2-6}alkylene-OH$, $-C(O)NH_2$, $-C(O)NH(C_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-C(O)NH(C_{1-4}haloalkyl)$, $-C(O)NH(-C_{2-6}alkylene-OC_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)(-C_{2-6}alkylene-OC_{1-4}alkyl)$, $-C(O)NH(-C_{2-6}alkylene-OH)$, $-C(O)N(C_{1-4}alkyl)(-C_{2-6}alkylene-OH)$, $-L^1-G^1-R^6$, $-L^1-G^2$, $-L^1-G^3$, and $-L^2-G^4$; and

R^2 , R^4 , X^1 , X^2 , and X^3 are as defined in claim 1.

15

3. The compound of claim 1 of formula (III)



(III)

or a pharmaceutically acceptable salt thereof,

20 wherein:

R^1 is selected from the group consisting of $-OC_{1-6}alkyl$, $-OC_{1-6}haloalkyl$, $-O-C_{2-6}alkylene-OC_{1-4}alkyl$, $-NHC(O)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl)$, $-L^1-G^1-R^6$, $-L^1-G^2$, $-L^1-G^3$, and $-L^2-G^4$;

L^1 is a bond, $-O-$, or $-O-C_{1-4}alkylene-$; and

25 R^2 , R^4 , X^1 , X^2 , and X^3 are as defined in claim 1.

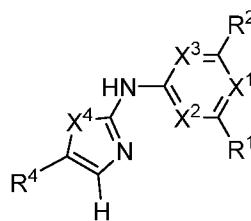
4. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-L^1-G^1-R^6$.
5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein L^1 is a bond or $-O-$.
6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein L^1 is a bond and G^1 is a 4- to 8-membered optionally substituted monocyclic heterocycle containing a first nitrogen atom and optionally a second heteroatom independently selected from oxygen and nitrogen, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms, G^1 being connected to L^1 through the first nitrogen atom.
7. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein L^1 is $-O-$ and G^1 is a 4- to 8-membered optionally substituted monocyclic heterocycle containing a first nitrogen atom and optionally a second heteroatom independently selected from oxygen and nitrogen, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms, G^1 being attached to L^1 at a ring carbon atom of G^1 .
8. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-L^1-G^2$.
9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein L^1 is a bond, $-O-$, $-O-C_{1-4}$ alkylene-, $-NR^5-$, or $-C(O)-$.
10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein L^1 is a bond or $-C(O)-$ and G^2 is attached to L^1 at a ring nitrogen atom of G^2 .
11. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein L^1 is $-O-$, $-O-C_{1-4}$ alkylene-, or $-NR^5-$ and G^2 is attached to L^1 at a ring carbon atom of G^2 .

12. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-L^1-G^3$ and L^1 is $-O-$ or $-O-C_{1-4}alkylene-$.
13. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^1 is L^2-G^4 .
14. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of $-OC_{1-6}alkyl$, $-OC_{1-6}haloalkyl$, $-O-C_{1-6}alkylene-OC_{1-4}alkyl$, $-O-C_{1-6}alkylene-OH$, $-NHC(O)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl)$, $-C(O)NH_2$, $-C(O)NH(C_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-C(O)NH(C_{1-4}haloalkyl)$, $-C(O)NH(-C_{1-6}alkylene-OC_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)(-C_{1-6}alkylene-OC_{1-4}alkyl)$, $-C(O)NH(-C_{1-6}alkylene-OH)$, and $-C(O)N(C_{1-4}alkyl)(-C_{1-6}alkylene-OH)$.
15. The compound of any of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen, $C_{1-4}alkyl$, or $C_{1-4}haloalkyl$.
16. The compound of any of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^{X1} is hydrogen.
17. The compound of any of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^{X2} is hydrogen or halogen.
18. The compound of any of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^{X3} is hydrogen or $-OC_{1-4}alkyl$.
19. The compound of any of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^4 is phenyl or a 6-membered heteroaryl containing 1-3 nitrogen atoms, R^4 being optionally substituted with 1-3 halogen.
20. The compound of claim 1, or a pharmaceutically acceptable salt thereof, selected from Table 2.

21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any of claims 1-20, or a pharmaceutically acceptable salt thereof.

5

22. A method of treating a disease or disorder selected from a demyelinating disease, central pontine myelinolysis, a nerve injury disease or disorder, a leukoencephalopathy, and a leukodystrophy, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a composition or pharmaceutically acceptable salt thereof, as defined in any of claims 1-21, or a compound of formula (I)



(I)

wherein:

15 X¹ is CR^{X1} or N;

X² is CR^{X2} or N;

X³ is CR^{X3} or N;

X⁴ is O or S;

provided that X¹ is not N simultaneously with X² and X³;

20 R¹ is selected from the group consisting of -OC₁₋₆alkyl, -OC₁₋₆haloalkyl, -O-C₂₋₆alkylene-OC₁₋₄alkyl, -O-C₂₋₆alkylene-OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(C₁₋₄haloalkyl), -C(O)NH(-C₂₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₂₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₂₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₂₋₆alkylene-OH), -L¹-G¹-R⁶, -L¹-G², -L¹-G³, and -L²-G⁴;

25 R² is selected from the group consisting of hydrogen, C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, and -OC₁₋₄alkyl;

R^{X1} is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, C₁₋₄haloalkyl, and -O-C₁₋₄alkyl;

R^{X2} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{X3} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, and $-O-C_{1-4}$ alkyl;

5 L^1 is a bond, $-O-$, $-O-C_{1-4}$ alkylene-, $-NR^5-$, $-NR^5-C_{1-4}$ alkylene-, or $-C(O)-$, wherein R^5 is hydrogen or C_{1-4} alkyl;

L^2 is $-O-C_{1-4}$ alkylene-;

G^1 is a 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms, G^1 being optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, and oxo;

R^6 is

- 15 a) a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the heterocycle being optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, $-CH_2S(O)_2$ phenyl, halogen, hydroxyl, oxo, $-OC_{1-4}$ alkyl, $-C_{1-6}$ alkylene- OC_{1-4} alkyl, and $-C_{1-6}$ alkylene-OH; or
- 20 b) a 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, $-C(O)OC_{1-4}$ alkyl, $-C(O)OH$, oxo, $-OC_{1-4}$ alkyl, $-C_{1-6}$ alkylene- OC_{1-4} alkyl, and $-C_{1-6}$ alkylene-OH;

G^2 is a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, G^2 being optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, oxo, cyano, $-C_{1-6}$ alkylene-cyano, $-C(O)C_{1-4}$ alkyl, $-C(O)-C_{1-6}$ alkylene- OC_{1-4} alkyl, $-C(O)-C_{1-6}$ alkylene-OH, $-C(O)C_{3-6}$ cycloalkyl, $-C(O)OC_{1-4}$ alkyl, $-C(O)OC_{1-4}$ haloalkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-4}$ alkyl), $-C(O)N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $-C(O)NH(-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-C(O)N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-C(O)NH(-C_{1-6}$ alkylene-OH), $-C(O)N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene-OH), $-NH(-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-NH(-C_{1-6}$ alkylene-OH), $-N(C_{1-4}$ alkyl)($-C_{1-6}$ alkylene-

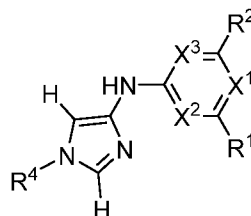
OH), $-\text{C}(\text{O})\text{C}_{1-4}\text{haloalkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{OC}_{1-4}\text{haloalkyl}$, $-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-6}\text{alkylene}-\text{OH}$, $-\text{C}_{1-6}\text{alkylene}-\text{NH}_2$, $-\text{C}_{1-6}\text{alkylene}-\text{NH}(\text{C}_{1-4}\text{alkyl})$, $-\text{C}_{1-6}\text{alkylene}-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$, $-\text{O}-\text{C}_{1-6}\text{alkylene}-\text{NH}_2$, $-\text{O}-\text{C}_{1-6}\text{alkylene}-\text{NH}(\text{C}_{1-4}\text{alkyl})$, $-\text{O}-\text{C}_{1-6}\text{alkylene}-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$, $-\text{O}-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl}$, $-\text{O}-\text{C}_{1-6}\text{alkylene}-\text{OH}$, $-\text{C}_{1-4}\text{alkylene}-\text{O}-\text{C}_{1-4}\text{alkylene}-\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{O}-\text{C}_{1-4}\text{alkylene}-\text{OH}$, $-\text{C}_{1-4}\text{alkylene}-\text{C}(\text{O})\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{C}(\text{O})\text{OH}$, $-\text{NHC}(\text{O})(\text{C}_{1-4}\text{alkyl})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})\text{C}(\text{O})(\text{C}_{1-4}\text{alkyl})$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-4}\text{alkyl})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$, $-\text{S}(\text{O})_{1-2}\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{1-6}\text{alkylene}-\text{S}(\text{O})_{1-2}\text{C}_{1-4}\text{alkyl}$, and a $-\text{C}_{1-6}\text{alkylene}$ substituted by 2 groups independently selected from hydroxyl, halogen, $-\text{OC}(\text{O})\text{C}_{1-4}\text{alkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-4}\text{alkyl})$, and $-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$;

G^3 is a 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{haloalkyl}$, halogen, hydroxyl, oxo, cyano, $-\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$, $-\text{C}(\text{O})\text{C}_{3-6}\text{cycloalkyl}$, $-\text{C}(\text{O})\text{OC}_{1-4}\text{alkyl}$, $-\text{C}(\text{O})\text{OC}_{1-4}\text{haloalkyl}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}(\text{C}_{1-4}\text{alkyl})$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$, $-\text{C}(\text{O})\text{NH}(-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{alkyl})(-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{C}(\text{O})\text{NH}(-\text{C}_{1-6}\text{alkylene}-\text{OH})$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{alkyl})(-\text{C}_{1-6}\text{alkylene}-\text{OH})$, $-\text{NH}(-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{NH}(-\text{C}_{1-6}\text{alkylene}-\text{OH})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(-\text{C}_{1-6}\text{alkylene}-\text{OH})$, $-\text{C}(\text{O})\text{C}_{1-4}\text{haloalkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-6}\text{alkylene}-\text{OH}$, $-\text{C}_{1-6}\text{alkylene}$ substituted by 2 groups independently selected from hydroxyl and $-\text{OC}(\text{O})\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{C}(\text{O})\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{C}(\text{O})\text{OH}$, $-\text{NHC}(\text{O})(\text{C}_{1-4}\text{alkyl})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})\text{C}(\text{O})(\text{C}_{1-4}\text{alkyl})$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-4}\text{alkyl})$, and $-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$;

G^4 is phenyl optionally substituted with 1-4 substituents independently selected from the group consisting of $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{haloalkyl}$, halogen, hydroxyl, cyano, phenyl, $-\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$, $-\text{C}(\text{O})\text{C}_{3-6}\text{cycloalkyl}$, $-\text{C}(\text{O})\text{OC}_{1-4}\text{alkyl}$, $-\text{C}(\text{O})\text{OC}_{1-4}\text{haloalkyl}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}(\text{C}_{1-4}\text{alkyl})$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$, $-\text{C}(\text{O})\text{NH}(-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{alkyl})(-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{C}(\text{O})\text{NH}(-\text{C}_{1-6}\text{alkylene}-\text{OH})$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{alkyl})(-\text{C}_{1-6}\text{alkylene}-\text{OH})$, $-\text{NH}(-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(-\text{C}_{1-6}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{NH}(-\text{C}_{1-6}\text{alkylene}-\text{OH})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(-\text{C}_{1-6}\text{alkylene}-\text{OH})$, $-\text{C}(\text{O})\text{C}_{1-4}\text{haloalkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-6}\text{alkylene}-\text{OH}$, $-\text{C}_{1-6}\text{alkylene}$ substituted by 2 groups

- independently selected from hydroxyl and $-\text{OC}(\text{O})\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{C}(\text{O})\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{C}(\text{O})\text{OH}$, $-\text{NHC}(\text{O})(\text{C}_{1-4}\text{alkyl})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})\text{C}(\text{O})(\text{C}_{1-4}\text{alkyl})$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-4}\text{alkyl})$, and $-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$; and R^4 is phenyl or a 5- or 6-membered heteroaryl containing 1-3 heteroatoms
- 5 independently selected from oxygen, nitrogen and sulfur, R^4 being optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, $-\text{S}(\text{O})_2\text{C}_{1-4}\text{alkyl}$, $-\text{S}(\text{O})\text{C}_{1-4}\text{alkyl}$, $-\text{SC}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{haloalkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{OC}_{1-4}\text{haloalkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{OC}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$, $-\text{NH}(\text{C}_{1-4}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{NH}(\text{C}_{1-4}\text{alkylene}-\text{OH})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkylene}-\text{OC}_{1-4}\text{alkyl})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkylene}-\text{OH})$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-4}\text{alkyl})$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$, $\text{C}_{3-6}\text{cycloalkyl}$, $\text{C}_{5-6}\text{cycloalkenyl}$, or a 4- to 8-membered monocyclic heterocycle containing 1-2 nitrogen atoms, the $\text{C}_{3-6}\text{cycloalkyl}$, the $\text{C}_{5-6}\text{cycloalkenyl}$, and the 4- to 8-membered monocyclic heterocycle being independently optionally substituted
- 10 with 1-2 substituents independently selected from the group consisting of pyridyl, halogen, hydroxyl, $-\text{OC}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{haloalkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{OC}_{1-4}\text{alkyl}$, and $-\text{C}_{1-4}\text{alkylene}-\text{OH}$.

23. A compound of formula (IV), or a pharmaceutically acceptable salt thereof,



(IV)

wherein:

X^1 is CR^{X^1} or N;

X^2 is CR^{X^2} or N;

25 X^3 is CR^{X^3} or N;

provided that X^1 is not N simultaneously with X^2 or X^3 ;

R^1 is selected from the group consisting of hydrogen, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{haloalkyl}$, $-\text{O}-\text{C}_{1-4}\text{alkyl}$, OH , $-\text{NH}-\text{C}_{1-4}\text{alkyl}$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$, $-\text{NH}_2$, $-\text{L}^1-\text{G}^1-\text{R}^6$, $-\text{L}^1-\text{G}^2$, $-\text{L}^1-\text{G}^3$, $-\text{L}^2-\text{G}^4$, $-\text{L}^2-\text{G}^5$, and G^5 ;

- R^2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;
 R^{X1} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, $-O-C_{1-4}$ alkyl, and G^2 ;
 provided that R^1 and R^{X1} do not simultaneously contain G^2 ;
- 5 R^{X2} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, and $-OC_{1-4}$ alkyl;
 R^{X3} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;
 L^1 is a bond, $-O-$, or $-O-C_{1-4}$ alkylene-;
- 10 L^2 is $-O-$ or $-O-C_{1-4}$ alkylene-;
 G^1 is a 4- to 8-membered monocyclic heterocycle containing 1-2 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the monocyclic heterocycle optionally containing one double bond and/or a C_{1-3} alkylene bridge between two non-adjacent ring atoms, G^1 being optionally substituted with 1-4
- 15 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, and oxo;
- R^6 is
- a) a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, the heterocycle being optionally
- 20 substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, $-CH_2S(O)_2$ phenyl, halogen, hydroxyl, oxo, $-OC_{1-4}$ alkyl, $-C_{1-6}$ alkylene- OC_{1-4} alkyl, and $-C_{1-6}$ alkylene-OH; or
- b) a 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl,
- 25 halogen, hydroxyl, $-C(O)OC_{1-4}$ alkyl, $-C(O)OH$, oxo, $-OC_{1-4}$ alkyl, $-C_{1-6}$ alkylene- OC_{1-4} alkyl, and $-C_{1-6}$ alkylene-OH;
- G^2 is a 4- to 12-membered heterocycle containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, G^2 being optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, halogen, hydroxyl, oxo, cyano, $-C_{1-6}$ alkylene-cyano, $-C(O)C_{1-4}$ alkyl,
- 30 $-C(O)-C_{1-6}$ alkylene- OC_{1-4} alkyl, $-C(O)-C_{1-6}$ alkylene-OH, $-C(O)C_{3-6}$ cycloalkyl, $-C(O)OC_{1-4}$ alkyl, $-C(O)OC_{1-4}$ haloalkyl, $-C(O)NH_2$, $-C(O)NH(C_{1-4}$ alkyl), $-C(O)N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $-C(O)NH(-C_{1-6}$ alkylene- OC_{1-4} alkyl), $-C(O)N(C_{1-6}$ alkylene- OC_{1-4} alkyl), and $-C(O)N(C_{1-6}$ alkylene- OC_{1-4} alkyl);

4alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -NH(-C₁₋₆alkylene-OH), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -C(O)C₁₋₄haloalkyl, -OC₁₋₄alkyl, -OC₁₋₄haloalkyl, -C₁₋₆alkylene-OC₁₋₄alkyl, -C₁₋₆alkylene-OH, -C₁₋₆alkylene-NH₂, -C₁₋₆alkylene-NH(C₁₋₄alkyl), -C₁₋₆alkylene-N(C₁₋₄alkyl)(C₁₋₄alkyl), -O-C₁₋₆alkylene-NH₂, -O-C₁₋₆alkylene-NH(C₁₋₄alkyl), -O-C₁₋₆alkylene-N(C₁₋₄alkyl)(C₁₋₄alkyl), -O-C₁₋₆alkylene-OC₁₋₄alkyl, -O-C₁₋₆alkylene-OH, -C₁₋₄alkylene-O-C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₄alkylene-O-C₁₋₄alkylene-OH, -C₁₋₄alkylene-C(O)OC₁₋₄alkyl, -C₁₋₄alkylene-C(O)OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)(C₁₋₄alkyl), -S(O)₁₋₂C₁₋₄alkyl, -C₁₋₆alkylene-S(O)₁₋₂C₁₋₄alkyl, and a -C₁₋₆alkylene substituted by 2 groups independently selected from hydroxyl, -OC(O)C₁₋₄alkyl, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)(C₁₋₄alkyl);

15 G³ is a 3- to 8-membered cycloalkyl optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, oxo, cyano, -C(O)C₁₋₄alkyl, -C(O)C₃₋₆cycloalkyl, -C(O)OC₁₋₄alkyl, -C(O)OC₁₋₄haloalkyl, -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -NH(-C₁₋₆alkylene-OH), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -C(O)C₁₋₄haloalkyl, -OC₁₋₄alkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₆alkylene-OH, -C₁₋₆alkylene substituted by 2 groups independently selected from hydroxyl and -OC(O)C₁₋₄alkyl, -C₁₋₄alkylene-C(O)OC₁₋₄alkyl, -C₁₋₄alkylene-C(O)OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)(C₁₋₄alkyl);

25 G⁴ is phenyl optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, cyano, phenyl, -C(O)C₁₋₄alkyl, -C(O)C₃₋₆cycloalkyl, -C(O)OC₁₋₄alkyl, -C(O)OC₁₋₄haloalkyl, -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -NH(-C₁₋₆alkylene-

OC₁₋₄alkyl), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -NH(-C₁₋₆alkylene-OH), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -C(O)C₁₋₄haloalkyl, -OC₁₋₄alkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₆alkylene-OH, -C₁₋₆alkylene substituted by 2 groups independently selected from hydroxyl and -OC(O)C₁₋₄alkyl, -C₁₋₄alkylene-C(O)OC₁₋₄alkyl, -C₁₋₄alkylene-C(O)OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)(C₁₋₄alkyl);

G⁵ is a monocyclic 5- or 6-membered heteroaryl containing 1-4 heteroatoms independently selected from oxygen, nitrogen, and sulfur, G⁵ being optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄haloalkyl, halogen, hydroxyl, cyano, phenyl, -C(O)C₁₋₄alkyl, -C(O)C₃₋₆cycloalkyl, -C(O)OC₁₋₄alkyl, -C(O)OC₁₋₄haloalkyl, -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(C₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -C(O)NH(-C₁₋₆alkylene-OH), -C(O)N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -NH(-C₁₋₆alkylene-OC₁₋₄alkyl), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OC₁₋₄alkyl), -NH(-C₁₋₆alkylene-OH), -N(C₁₋₄alkyl)(-C₁₋₆alkylene-OH), -C(O)C₁₋₄haloalkyl, -OC₁₋₄alkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₆alkylene-OH, -C₁₋₆alkylene substituted by 2 groups independently selected from hydroxyl and -OC(O)C₁₋₄alkyl, -C₁₋₄alkylene-C(O)OC₁₋₄alkyl, -C₁₋₄alkylene-C(O)OH, -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NH₂, -NH(C₁₋₄alkyl), and -N(C₁₋₄alkyl)(C₁₋₄alkyl); and

R⁴ is phenyl or a 5- or 6-membered heteroaryl containing 1-3 heteroatoms independently selected from oxygen, nitrogen and sulfur, R⁴ being optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, -S(O)₂C₁₋₄alkyl, -S(O)C₁₋₄alkyl, -SC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄haloalkyl, -OC₁₋₄alkyl, -OC₁₋₄haloalkyl, -C₁₋₄alkylene-OC₁₋₄alkyl, -C₁₋₄alkylene-N(C₁₋₄alkyl)(C₁₋₄alkyl), -NH(C₁₋₄alkylene-OC₁₋₄alkyl), -NH(C₁₋₄alkylene-OH), -N(C₁₋₄alkyl)(C₁₋₄alkylene-OC₁₋₄alkyl), -N(C₁₋₄alkyl)(C₁₋₄alkylene-OH), -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)(C₁₋₄alkyl), C₃₋₆cycloalkyl, C₅₋₆cycloalkenyl, or a 4- to 8-membered monocyclic heterocycle containing 1-2 nitrogen atoms, the C₃₋₆cycloalkyl, the C₅₋₆cycloalkenyl, and the 4- to 8-membered monocyclic heterocycle being independently optionally substituted with 1-2 substituents independently selected from the group consisting of pyridyl,

halogen, hydroxyl, $-\text{OC}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{haloalkyl}$, $-\text{C}_{1-4}\text{alkylene}-\text{OC}_{1-4}\text{alkyl}$, and $-\text{C}_{1-4}\text{alkylene}-\text{OH}$.

24. The compound of claim 23, or a pharmaceutically acceptable salt thereof,
5 wherein R^1 is $-\text{L}^1-\text{G}^1-\text{R}^6$; L^1 is a bond; and G^1 is a 4- to 8-membered optionally substituted monocyclic heterocycle containing a first nitrogen atom and optionally a second heteroatom independently selected from oxygen and nitrogen, the monocyclic heterocycle optionally containing one double bond and/or a $\text{C}_{1-3}\text{alkylene}$ bridge between two non-adjacent ring atoms, G^1 being connected to L^1 through the first
10 nitrogen atom.

25. The compound of claim 23, or a pharmaceutically acceptable salt thereof,
wherein R^1 is L^1-G^2 ; L^1 is a bond; and G^2 is an optionally substituted 4- to 8-
15 membered monocyclic heterocycle containing a first nitrogen atom and optionally a second nitrogen atom, an oxygen or sulfur atom, and optionally containing one double bond and/or a $\text{C}_{1-3}\text{alkylene}$ bridge between two non-adjacent ring atoms, G^2 being connected to L^1 through the first nitrogen atom.

26. The compound of claim 23, or a pharmaceutically acceptable salt thereof,
20 wherein R^1 is $-\text{L}^1-\text{G}^3$ and L^1 is a bond or $-\text{O}-$.

27. The compound of claim 23, or a pharmaceutically acceptable salt thereof,
wherein R^1 is $-\text{L}^2-\text{G}^4$.

25 28. The compound of claim 23, or a pharmaceutically acceptable salt thereof,
wherein R^1 is $-\text{L}^2-\text{G}^5$.

29. The compound of claim 23, or a pharmaceutically acceptable salt thereof,
wherein R^1 is G^5 .

30 30. The compound of claim 23, or a pharmaceutically acceptable salt thereof,
wherein R^1 is selected from the group consisting of hydrogen, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{haloalkyl}$,
 $-\text{O}-\text{C}_{1-4}\text{alkyl}$, OH , $-\text{NH}-\text{C}_{1-4}\text{alkyl}$, $-\text{N}(\text{C}_{1-4}\text{alkyl})(\text{C}_{1-4}\text{alkyl})$, and $-\text{NH}_2$.

31. The compound of claim 23, or a pharmaceutically acceptable salt thereof, selected from Table 2.

5

32. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any of claims 23-31, or a pharmaceutically acceptable salt thereof.

10 33. A method of treating a disease or disorder selected from a demyelinating disease, central pontine myelinolysis, a nerve injury disease or disorder, a leukoencephalopathy, and a leukodystrophy, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of formula (IV), or a composition or pharmaceutically acceptable salt thereof, as defined in any of claims
15 23-32.

34. The method of claim 22 or 33, wherein the disease or disorder is a demyelinating disease selected from multiple sclerosis, acute disseminated encephalomyelitis, neuromyelitis optica, optic neuritis, and transverse myelitis.

20

35. The method of claim 34, wherein the demyelinating disease is multiple sclerosis.

36. The method of claim 35, wherein the type of multiple sclerosis is primary
25 progressive multiple sclerosis, relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis or progressive relapsing multiple sclerosis.

37. The method of claim 22 or 33, wherein the disease or disorder is a leukodystrophy selected from the group consisting of adrenoleukodystrophy,
30 Alexander's disease, Pelizaeus Merzbacher disease, Globoid cell Leucodystrophy (Krabbe's disease), cerebrotendineous xanthomatosis, hereditary CNS demyelinating

disease, metachromatic leukodystrophy, Canavan disease, adrenoleukodystrophy, Refsum disease, and xenobefantosis.

38. The method of claim 22 or 33, wherein the disease or disorder is a
5 leukoencephalopathy selected from progressive multifocal leukoencephalopathy.

39. The method of claim 22 or 33, wherein the disease or disorder is a nerve injury
disease or disorder selected from spinal cord injury, cerebral palsy, periventricular
leukomalacia and Wallerian degeneration.

10

40. A method of promoting remyelination of demyelinated axons comprising
administering to a patient in need thereof a therapeutically effective amount of a
compound of formula (I) or (IV), or pharmaceutical composition or pharmaceutically
acceptable salt thereof, as defined in any of claims 1-32.

15

41. A method of differentiating endogenous oligodendrocyte precursor cells,
comprising administering to a patient in need thereof a therapeutically effective
amount of a compound of formula (I) or (IV), or pharmaceutical composition or
pharmaceutically acceptable salt thereof, as defined in any of claims 1-32.

20

42. A method of treating, preventing, or reducing the severity of one or more
symptoms of multiple sclerosis or another neurodegenerative disease comprising
administering to a patient in need thereof a therapeutically effective amount of a
compound of formula (I) or (IV), or pharmaceutical composition or pharmaceutically
25 acceptable salt thereof, as defined in any of claims 1-32.

43. The method of claim 42, wherein the one or more symptoms of multiple
sclerosis or another neurodegenerative disease is selected from auditory impairment,
optic neuritis, decreased visual acuity, diplopia, nystagmus, ocular dysmetria,
30 internuclear ophthalmoplegia, movement and sound phosphenes, afferent pupillary
defect, paresis, monoparesis, paraparesis, hemiparesis, quadraparesis, plegia,
paraplegia, hemiplegia, tetraplegia, quadraplegia, spasticity, dysarthria, motor
dysfunction, walking impairment, muscle atrophy, spasms, cramps, hypotonia, clonus,

myoclonus, myokymia, restless leg syndrome, gait disturbances, footdrop, dysfunctional reflexes, paraesthesia, anaesthesia, neuralgia, neuropathic and neurogenic pain, L'hermitte's, proprioceptive dysfunction, trigeminal neuralgia, ataxia, intention tremor, dysmetria, vestibular ataxia, vertigo, speech ataxia, dystonia,
 5 disability progression, dysdiadochokinesia, frequent micturation, bladder spasticity, flaccid bladder, detrusor- sphincter dyssynergia, erectile dysfunction or anorgasmy.

44. The method of claim 22 or 33, wherein the disease or disorder is selected from spinal cord injury, stroke, multiple sclerosis, progressive multifocal
 10 leukoencephalopathy, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelolysis, hypoxic demyelination, ischemic demyelination, neuromyelitis optica, adrenoleukodystrophy, Alexander's disease, Niemann-Pick disease, Pelizaeus Merzbacher disease, periventricular leukomalacia, globoid cell leukodystrophy (Krabbe's disease), Wallerian degeneration,
 15 optic neuritis, transverse myelitis, amyotrophic lateral sclerosis (Lou Gehrig's disease), Huntington's disease, Alzheimer's disease, Parkinson's disease, Tay-Sacks disease, Gaucher's disease, Hurler Syndrome, traumatic brain injury, post radiation injury, neurologic complications of chemotherapy, neuropathy, acute ischemic optic neuropathy, neuromyelitis optica, vitamin B12 deficiency, isolated vitamin E
 20 deficiency syndrome, Bassen-Kornzweig syndrome, Leber's hereditary optic atrophy/Leber congenital amaurosis, Marchiafava-Bignami syndrome, metachromatic leukodystrophy, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, schizophrenia, cerebral ischemia, multiple system atrophy, traumatic glaucoma, tropical spastic paraparesis/human T-lymphotropic virus 1 (HTLV-1) associated
 25 myelopathy, essential tremor or osmotic hyponatremia.

45. A compound of formula (I) or (IV), or a pharmaceutical composition or pharmaceutically acceptable salt thereof, as defined in any of claims 1-32, for use in the manufacture of a medicament for the treatment of a disease or disorder selected
 30 from a demyelinating disease, central pontine myelinolysis, a nerve injury disease or disorder, a leukoencephalopathy, a leukodystrophy, or multiple sclerosis; or for the promotion of remyelination of demyelinated axons; or for the differentiation of endogenous oligodendrocyte precursor cells.

46. A compound of formula (I) or (IV), or a pharmaceutical composition or pharmaceutically acceptable salt thereof, as defined in any of claims 1-32, for use in treating or lessening the severity of, in a subject, a disease or disorder selected from a demyelinating disease, central pontine myelinolysis, a nerve injury disease or disorder, a leukoencephalopathy, a leukodystrophy, or multiple sclerosis; or for use in promoting remyelination of demyelinated axons; or for use in differentiating endogenous oligodendrocyte precursor cells.
47. A kit comprising the compound of formula (I) or (IV), or a pharmaceutical composition or pharmaceutically acceptable salt thereof, as defined in any of claims 1-32, and instructions for use thereof.
48. The kit of claim 47, further comprising one or more additional therapeutic agent(s).
49. The kit of claim 47 or 48, wherein the compound of formula (I) or (IV) and the one or more additional therapeutic agent(s) are in separate containers.
50. The kit of claim 47 or 48 wherein the compound of formula (I) or (IV) and the one or more additional therapeutic agent(s) are in the same container.
51. The kit of claim 49 or 50 wherein the container is a bottle, vial, or blister pack, or combinations thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/064629

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D403/12 C07D401/14 C07D413/14 C07D401/12 C07D403/14 C07D413/12 C07D417/12 C07D417/14 C07D263/48 C07D277/42 A61P25/28 A61K31/422 A61K31/427		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/014170 A1 (AB SCIENCE [FR]; BENJAHAD ABDELLAH [FR]; MOUSSY ALAIN [FR]; CHEVENIER) 31 January 2013 (2013-01-31) claims 1, 15 pages 33-50, compounds: 107, 111, 127, 138, 146, 150, 160, 163, 170, 172, 181, 182, 185, 188, 193, 209, 210 -----	1,3-22, 34-51
X	WO 2006/106437 A2 (AB SCIENCE [FR]; CENTRE NAT RECH SCIENT [FR]; INST CURIE [FR]; GRIERSO) 12 October 2006 (2006-10-12) claims 1,15 examples on pages 9 to 14 -----	1,3-22, 34-51
X	WO 2016/124747 A1 (AB SCIENCE [FR]) 11 August 2016 (2016-08-11) compound 1 -----	1,3-21
☐ 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 1 March 2018		Date of mailing of the international search report 16/05/2018
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Panday, Narendra

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/064629

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.:
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 additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of 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.:

3(completely); 1, 4-22, 34-51(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3(completely); 1, 4-22, 34-51(partially)

compound of formula (I), with $X_4 = O$, pharmaceutical composition comprising it, its application in therapy

2. claims: 2(completely); 1, 4-22, 34-51(partially)

compound of formula (I), with $X_4 = S$, pharmaceutical composition comprising it, its application in therapy

3. claims: 23-33(completely); 34-51(partially)

compound of formula (IV), pharmaceutical composition comprising it, its application in therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/064629

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