TYK2 INHIBITORS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of US Provisional Application No. 63/151,287 filed on February 19, 2021 and US Provisional Application No. 63/193,514 filed on May 26, 2021, each of which is incorporated herein by reference in its entirety.

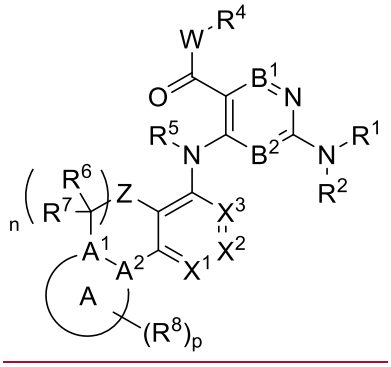
BACKGROUND OF THE INVENTION

[0002] The present invention relates to compounds that bind to the pseudokinase domain (JH2) of the non-receptor tyrosine-protein kinase 2 (TYK2). Compounds of the present disclosure may inhibit certain cytokine signaling, for example IL-12, IL-23, and IFNα signaling. Additional aspects of the invention include pharmaceutical compositions comprising the compounds described herein, methods of using the compounds to treat certain diseases, and intermediates and processes useful in the synthesis of the compounds.

[0003] TYK2 is a non-receptor tyrosine kinase member of the Janus kinase (JAKs) family of protein kinases. The mammalian JAK family consists of four members, TYK2, JAK1, JAK2, and JAK3. JAK proteins, including TYK2, are integral to cytokine signaling. TYK2 associates with the cytoplasmic domain of type I and type II cytokine receptors, as well as interferon types I and III receptors, and is activated by those receptors upon cytokine binding. Cytokines implicated in TYK2 activation include interferons (e.g. IFN-a, IFN-β, IFN-K, IFN-δ, IFN-ε, IFN-τ, IFN-co, and IFN-ζ (also known as limitin), and interleukins (e.g. IL-4, IL-6, IL-10, IL-1 1, IL-12, IL-13, IL-22, IL-23, IL-27, IL-31, oncostatin M, ciliary neurotrophic factor, cardiotrophin 1, cardiotrophin-like cytokine, and LIF). The activated TYK2 then goes on to phosphorylate further signaling proteins such as members of the STAT family, including STAT1, STAT2, STAT4, and STAT6.

SUMMARY ~~OF THE INVENTION~~

[0003a] In an aspect of the present disclosure, there is provided a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

Ring A is an unsubstituted or substituted 6-membered heterocyclic ring wherein A^1 and A^2 are independently N or C, wherein if Ring A is substituted then Ring A is substituted with p instances of R^8;

each R^8 is independently hydrogen, halogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 deuteroalkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted C_1-C_6 heteroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, -CN, -OH, $-OR^{17}$, $-C(=O)R^{16}$, $-CO_2R^{16}$, $-C(=O)N(R^{16})_2$, $-N(R^{16})_2$, $-NR^{16}C(=O)R^{17}$, $-SR^{16}$, $-S(=O)R^{17}$, $-SO_2R^{17}$, or $-SO_2N(R^{16})_2$; wherein if R^8 is attached to a nitrogen atom, then R^8 is hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 deuteroalkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted C_1-C_6 heteroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, $-C(=O)R^{16}$, $-CO_2R^{16}$, $-C(=O)N(R^{16})_2$, $-S(=O)R^{17}$, $-SO_2R^{17}$, or $-SO_2N(R^{16})_2$; or two R^8 attached to the same carbon atom are taken together to form =O, =S, or =NH;

Z is $-NR^{10}$-, -O-, -S-, -S(=O)-, or $-SO_2$-;

R^{10} is hydrogen, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or monocyclic heterocycle;

X^1, X^2, and X^3 are each independently CR^{11} or N;

each R^{11} is independently hydrogen, halogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted C_1-C_6 heteroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, -CN, -OH, $-OR^{17}$, $-C(=O)R^{16}$, $-CO_2R^{16}$, $-C(=O)N(R^{16})_2$, $-N(R^{16})_2$, $-NR^{16}C(=O)R^{17}$, $-SR^{16}$, $-S(=O)R^{17}$, $-SO_2R^{17}$, or $-SO_2N(R^{16})_2$;

B^1 is N or CR^{12a};

B^2 is N or CR^{12b};

R^{12a} and R^{12b} are each independently hydrogen, halogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted C_1-C_6 heteroalkyl, unsubstituted or substituted

carbocycle, unsubstituted or substituted heterocycle, -CN, -OH, -OR^{17}, -$C(=O)R^{16}$, -CO_2R^{16}, -$C(=O)N(R^{16})_2$, -$N(R^{16})_2$, -$NR^{16}C(=O)R^{17}$, -SR^{16}, -$S(=O)R^{17}$, -SO_2R^{17}, or -$SO_2N(R^{16})_2$;

R^1 is hydrogen, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl;

R^2 is a Ring B that is an unsubstituted or substituted heterocycle or unsubstituted or substituted carbocycle, wherein if Ring B is substituted then Ring B is substituted with q instances of R^{13};

each R^{13} is independently halogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted C_1-C_6 heteroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, -CN, -OH, -OR^{17}, -$C(=O)R^{16}$, -CO_2R^{16}, -$C(=O)N(R^{16})_2$, -$N(R^{16})_2$, -$NR^{16}C(=O)R^{17}$, -SR^{16}, -$S(=O)R^{17}$, -SO_2R^{17}, or -$SO_2N(R^{16})_2$;

or two R^{13} groups on adjacent atoms of Ring B are taken together with the intervening atoms to which they are attached to form an unsubstituted or substituted 5- or 6-membered monocyclic carbocycle or an unsubstituted or substituted 5- or 6-membered monocyclic heterocycle;

or R^2 is -$C(=O)R^{14}$, -$C(=O)NR^{14}R^{15}$, or -$C(=O)OR^{14}$;

R^{14} is hydrogen, unsubstituted or substituted C_1-C_6 alkyl, C_1-C_6 deuteroalkyl unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted C_1-C_6 heteroalkyl, unsubstituted or substituted monocyclic carbocycle, unsubstituted or substituted bicyclic carbocycle, unsubstituted or substituted monocyclic heterocycle, or unsubstituted or substituted bicyclic heterocycle;

R^{15} is hydrogen, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl;

or R^{14} and R^{15} are taken together with the intervening atoms to which they are attached to form an unsubstituted or substituted 4- to 6-membered monocyclic heterocycle;

or R^1 and R^{15} are taken together with the intervening atoms to which they are attached to form an unsubstituted or substituted 5- or 6-membered monocyclic heterocycle;

W is -NR^3- or -O-;

R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or monocyclic heterocycle;

R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or monocyclic heterocycle;

or R^3 and R^4 are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

or R^3 and R^{12a} are taken together with the intervening atoms to which they are attached to form a substituted or unsubstituted 5- or 6-membered heterocycle;

R^5 is hydrogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or monocyclic heterocycle;

each R^6 and R^7 is independently hydrogen, deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or monocyclic heterocycle, -CN, -OH, $-OR^{17}$, $-C(=O)R^{16}$, $-CO_2R^{16}$, $-C(=O)N(R^{16})_2$, $-N(R^{16})_2$, $-NR^{16}C(=O)R^{17}$, $-SR^{16}$, $-S(=O)R^{17}$, $-SO_2R^{17}$, or $-SO_2N(R^{16})_2$;

or one R^6 and one R^7 attached to the same carbon atom are taken together with the carbon atom to which they are attached to form C=O or C_3-C_4 cycloalkyl;

each R^{16} is independently hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 fluoroalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^{16} on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle; and

each R^{17} is independently substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 fluoroalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl;

wherein each substituted alkyl, substituted fluoroalkyl, substituted deuteroalkyl, substituted alkoxy, substituted fluoroalkoxy, substituted heteroalkyl, substituted carbocycle, and substituted heterocycle is substituted with one or more R^s groups independently selected from the group consisting of deuterium, halogen, C_1-C_6 alkyl, monocyclic carbocycle, monocyclic heterocycle, -CN, $-CH_2CN$, $-OR^{18}$, $-CH_2OR^{18}$, $-CO_2R^{18}$, $-CH_2CO_2R^{18}$, $-C(=O)N(R^{18})_2$, $-CH_2C(=O)N(R^{18})_2$, $-N(R^{18})_2$, $-CH_2N(R^{18})_2$, $-NR^{18}C(=O)R^{18}$, $-CH_2NR^{18}C(=O)R^{18}$, $-NR^{18}SO_2R^{19}$, $-CH_2NR^{18}SO_2R^{19}$, $-SR^{18}$, $-CH_2SR^{18}$, $-S(=O)R^{19}$, $-CH_2S(=O)R^{19}$, $-SO_2R^{19}$, $-CH_2SO_2R^{19}$, $-SO_2N(R^{18})_2$, or $-CH_2SO_2N(R^{18})_2$;

each R^{18} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, C_2-C_6 heterocycloalkyl, phenyl, benzyl, 5-membered heteroaryl and 6-membered heteroaryl;

or two R^{18} groups are taken together with the N atom to which they are attached to form a N-containing heterocycle;

each R^{19} is independently selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, C_2-C_6 heterocycloalkyl, phenyl, benzyl, 5-membered heteroaryl, and 6-membered heteroaryl;

n is 1, 2, or 3;

p is 0, 1, 2, 3, or 4; and

q is 0, 1, 2, 3, or 4.

[0003b] In another aspect of the present disclosure, there is provided a compound selected from:

1: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)pyridazine-3-carboxamide;

2: 6-((5-fluoropyridin-2-yl)amino)-N-(methyl-d3)-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)pyridazine-3-carboxamide; and

3: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)nicotinamide;

4: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrimido[5,4-c]quinolin-7-yl)amino)nicotinamide;

5: 6-(cyclopropanecarboxamido)-4-((3-fluoro-6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)-N-(methyl-d3)nicotinamide;

6: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrimido[5,4-c]quinolin-7-yl)amino)pyridazine-3-carboxamide;

7: 6-(cyclopropanecarboxamido)-4-((3-fluoro-6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

8: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrazino[2,3-c]quinolin-7-yl)amino)nicotinamide;

9: 6-(cyclopropanecarboxamido)-4-((2,6-dimethyl-1-oxo-1,2,5,6-tetrahydrobenzo[c][2,6]naphthyridin-7-yl)amino)-N-(methyl-d3)nicotinamide;

10: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrazino[2,3-c]quinolin-7-yl)amino)pyridazine-3-carboxamide;

11: 6-(cyclopropanecarboxamido)-4-((2,6-dimethyl-1-oxo-1,2,5,6-tetrahydrobenzo[c][2,6]naphthyridin-7-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

12: 4-((3-cyano-6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)-6-(cyclopropanecarboxamido)-N-(methyl-d3)nicotinamide;

13: 4-((3-cyano-6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)-6-(cyclopropanecarboxamido)-N-(methyl-d3)pyridazine-3-carboxamide;

14: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrazino[2,3-c][1,7]naphthyridin-7-yl)amino)nicotinamide;

15: 6-(cyclopropanecarboxamido)-N-methyl-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)nicotinamide;

16: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrazino[2,3-c]quinolin-7-yl)amino)pyridazine-3-carboxamide;

17: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-(methyl-d3)-5,6-dihydropyrazino[2,3-c]quinolin-7-yl)amino)nicotinamide;

18: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-(methyl-d3)-5,6-dihydropyrazino[2,3-c]quinolin-7-yl)amino)pyridazine-3-carboxamide;

19: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrido[3,4-h][1,6]naphthyridin-7-yl)amino)nicotinamide;

20: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)nicotinamide;

21: 6-(cyclopropanecarboxamido)-4-((3-fluoro-6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

22: 6-(cyclopropanecarboxamido)-4-((3-fluoro-6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)-N-(methyl-d3)nicotinamide;

23: 6-(cyclopropanecarboxamido)-4-((2,6-dimethyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

24: 6-(cyclopropanecarboxamido)-4-((2,6-dimethyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)-N-(methyl-d3)nicotinamide;

25: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-2-(trifluoromethyl)-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)nicotinamide;

26: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-2-(trifluoromethyl)-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)pyridazine-3-carboxamide;

27: 6-(cyclopropanecarboxamido)-4-((2,6-dimethyl-1-oxo-1,2,5,6-tetrahydropyridazino[4,5-c]quinolin-7-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

28: 6-(cyclopropanecarboxamido)-4-((2,6-dimethyl-1-oxo-1,2,5,6-tetrahydropyridazino[4,5-c]quinolin-7-yl)amino)-N-(methyl-d3)nicotinamide;

29: 6-(cyclopropanecarboxamido)-N-methyl-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)pyridazine-3-carboxamide;

30: 6-(cyclopropanecarboxamido)-N-methyl-4-((6-methyl-5,6-dihydropyrazino[2,3-c]quinolin-7-yl)amino)nicotinamide;

31: 6-(cyclopropanecarboxamido)-4-((10-fluoro-5-methyl-5,6-dihydrophenanthridin-4-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

32: (R)-6-(cyclopropanecarboxamido)-4-((5,6-dimethyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide; and

33: (S)-6-(cyclopropanecarboxamido)-4-((5,6-dimethyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

[0003c] In a further aspect of the present disclosure, there is provided a compound selected from:

3: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)nicotinamide;

15: 6-(cyclopropanecarboxamido)-N-methyl-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)nicotinamide;

34: 6-(cyclopropanecarboxamido)-4-((2,5-dimethyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinolin-6-yl)amino)-N-methylpyridazine-3-carboxamide;

35: 4-((2,5-dimethyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinolin-6-yl)amino)-6-((5-fluoropyridin-2-yl)amino)-N-methylnicotinamide;

36: 4-((2,5-dimethyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinolin-6-yl)amino)-6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methylnicotinamide;

37: 6-(cyclopropanecarboxamido)-4-((2,5-dimethyl-4,5-dihydro-2H-[1,2,3]triazolo[4,5-c]quinolin-6-yl)amino)-N-methylnicotinamide; and

38: 6-(cyclopropanecarboxamido)-4-((2,5-dimethyl-4,5-dihydropyrazolo[1,5-a]quinoxalin-6-yl)amino)-N-methylpyridazine-3-carboxamide;

or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

[0003d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, and a pharmaceutically acceptable excipient.

[0003e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, in the manufacture of a medicament for treating a TYK2-mediated disease or condition in a patient in need thereof.

[0003f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, in the manfacture of a medicament for treating an inflammatory disease or condition or autoimmune disease or condition in a patient in need thereof.

[0003g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, in the manufacture of a medicament for treating a disease or condition of the eye in a patient in need thereof.

[0003h] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, for use in therapy.

[0004] Compounds described herein are modulators of the JAK family of kinases. More specifically, the compounds of the present disclosure are inhibitors of TYK2. In some ~~embodiment~~examples, compounds are selective for TYK2 over other JAKs. For example, compounds may bind specifically to the pseudokinase domain (JH2) of TYK2 thereby enhancing selectivity over JAK family members. In some ~~embodiment~~examples, a compound of the present disclosure may be an allosteric modulator or noncompetitive inhibitor of TYK2. In additional ~~embodiment~~examples, a compound described herein may be useful in the treatment of TYK2 mediated diseases or disorders.

[0005] In one ~~aspect~~example, described herein is a compound of Formula (I):

wherein each substituted alkyl, substituted fluoroalkyl, substituted deuteroalkyl, substituted alkoxy, substituted fluoroalkoxy, substituted heteroalkyl, substituted carbocycle, and substituted heterocycle is substituted with one or more R^s groups independently selected from the group consisting of deuterium, halogen, C_1-C_6 alkyl, monocyclic carbocycle, monocyclic heterocycle, -CN, -CH_2CN, -OR^{18}, -CH_2OR^{18}, -CO_2R^{18}, -$CH_2CO_2R^{18}$, -$C(=O)N(R^{18})_2$, -$CH_2C(=O)N(R^{18})_2$, -$N(R^{18})_2$, -$CH_2N(R^{18})_2$, -$NR^{18}C(=O)R^{18}$, -$CH_2NR^{18}C(=O)R^{18}$, -$NR^{18}SO_2R^{19}$, -$CH_2NR^{18}SO_2R^{19}$, -SR^{18}, -CH_2SR^{18}, -$S(=O)R^{19}$, -$CH_2S(=O)R^{19}$, -SO_2R^{19}, -$CH_2SO_2R^{19}$, -$SO_2N(R^{18})_2$, or -$CH_2SO_2N(R^{18})_2$;

each R^{18} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, C_2-C_6 heterocycloalkyl, phenyl, benzyl, 5-membered heteroaryl and 6-membered heteroaryl;

or two R^{18} groups are taken together with the N atom to which they are attached to form a N-containing heterocycle;

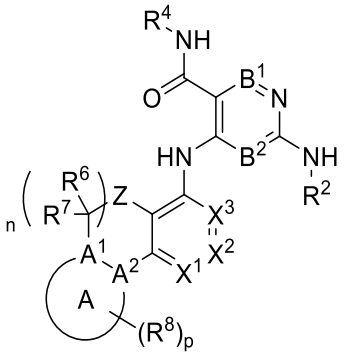
each R^{19} is independently selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, C_2-C_6 heterocycloalkyl, phenyl, benzyl, 5-membered heteroaryl, and 6-membered heteroaryl;

n is 1, 2, or 3;

p is 0, 1, 2, 3, or 4; and

q is 0, 1, 2, 3, or 4.

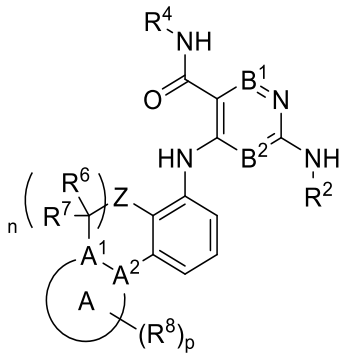
[0006] In some ~~embodiment~~examples, the compound is a compound of Formula (II):



Formula (II),

or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

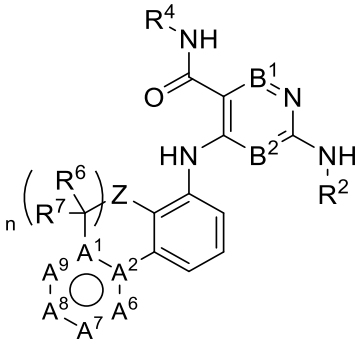
[0007] In some ~~embodiment~~examples, the compound is a compound of Formula (IV):



Formula (IV),

or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

[0008] In some ~~embodiment~~examples, the compound is a compound of Formula (VI):



Formula (VI),

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

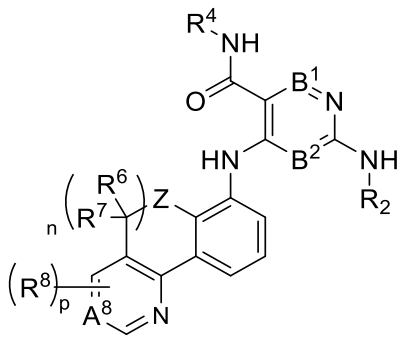
(i) A^1 and A^2 are each C; and A^6, A^7, A^8, and A^9 are each independently CR^8 or N;

(ii) A^1 is N; A^2 is C; A^6, A^7, and A^8 are each independently CR^8 or N; and A^9 is C(=O);

(iii) A^1 is C; A^2 is N; A^6 is C(=O); and A^7, A^8, and A^9 are each independently CR^8 or N; or

(iv) A^1 and A^2 are each C; one of A^6, A^7, A^8, and A^9 is NR^8, wherein A^6, A^7, A^8, or A^9 adjacent to the NR^8 is C(=O) and the remaining members of A^6, A^7, A^8, and A^9 are each independently CR^8 or N.

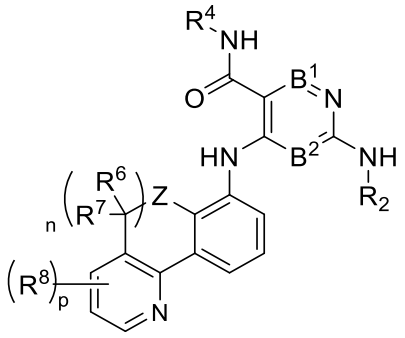
[0009] In some ~~embodiment~~examples, the compound is a compound of Formula (VIa):



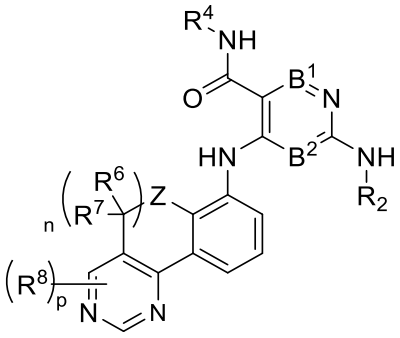
Formula (VIa),

or a pharmaceutically acceptable salt, tautomer, or solvate thereof; wherein A^8 is CR^8 or N.

[0010] In some ~~embodiment~~examples, the compound is a compound of Formula (VIb) or Formula (VIc):



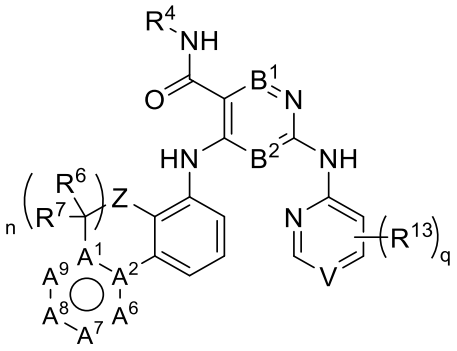
Formula (VIb)



Formula (VIc)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

[0011] In some ~~embodiment~~examples, the compound is a compound of Formula (VIII):



Formula (VIII)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

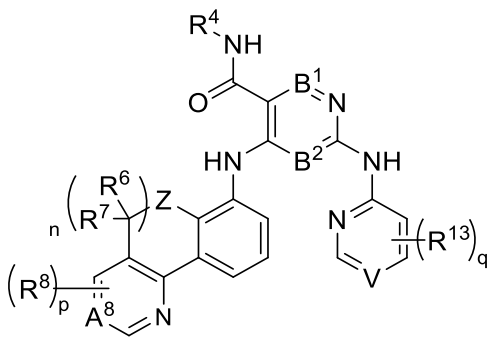
V is N, CH, or CR^{13};

q is 1, 2, 3, or 4;

A^1 and A^2 are each C; and

A^6, A^7, A^8, and A^9 are each independently CR^8 or N.

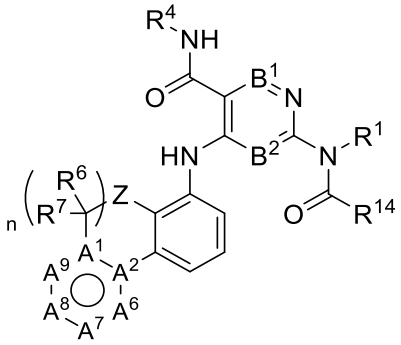
[0012] In some ~~embodiment~~examples, the compound is a compound of Formula (VIIIa):



Formula (VIIIa)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein A^8 is CR^8 or N.

[0013] In some ~~embodiment~~examples, the compound is a compound of Formula (IX):



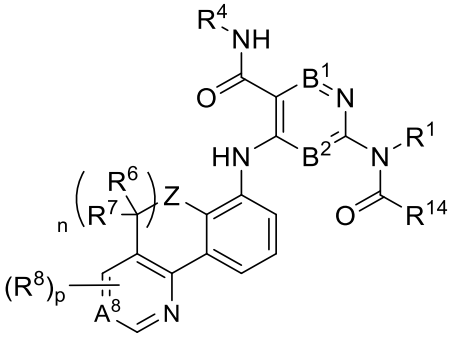
Formula (IX),

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

A^1 and A^2 are each C; and

each of A^6, A^7, A^8, and A^9 are independently CR^8 or N.

[0014] In some ~~embodiment~~examples, the compound is a compound of Formula (IXa):



Formula (IXa)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein A^8 is CR^8 or N.

[0015] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0016] Also described herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, and a pharmaceutically acceptable excipient. In some ~~embodiment~~examples, the pharmaceutical composition is formulated for administration to a mammal by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration. In some ~~embodiment~~examples, the pharmaceutical composition is formulated for administration to a mammal by oral administration. In some ~~embodiment~~examples, the pharmaceutical composition is in the form of a tablet, a pill, a capsule, a liquid, a suspension, a

gel, a dispersion, a solution, an emulsion, an ointment, or a lotion. In some ~~embodiment~~examples, the pharmaceutical composition is in the form of a tablet, a pill, or a capsule. In some ~~embodiment~~examples, the pharmaceutical composition in the form of an ointment, a lotion, a cream, an oil, a gel, a transdermal patch, or other topical formulation. In additional ~~embodiment~~examples, the pharmaceutical composition is in the form of a liquid solution, suspension, gel, depot, or other preparation that can be administered to the eye or surrounding tissue (e.g., eye drops).

[0017] Described herein are compounds of Formula (A1), or a pharmaceutically acceptable salt, tautomer, or solvate thereof useful in the treatment of TYK2-mediated disorders. Described herein are compounds of Formula (A1), or a pharmaceutically acceptable salt, tautomer, or solvate thereof, useful in the treatment of an inflammatory or autoimmune disease. In some ~~embodiment~~examples, the disease is selected from rheumatoid arthritis, multiple sclerosis, psoriasis, psoriatic arthritis, lupus, systemic lupus erythematosus, Sjögren's syndrome, ankylosing spondylitis, vitiligo, atopic dermatitis, scleroderma, alopecia, hidradenitis suppurativa, uveitis, dry eye, intestinal bowel disease, Crohn's disease, ulcerative colitis, celiac disease, Bechet's disease, type 1 diabetes, systemic sclerosis, and idiopathic pulmonary fibrosis. In some ~~embodiment~~examples, the disease is selected from psoriasis, psoriatic arthritis, vitiligo, atopic dermatitis, alopecia, and hidradenitis suppurativa. In some ~~embodiment~~examples, the disease is selected from interferonopathies such as, by way of example, Alcardi-Goutieres syndrome.

[0018] In any of the aforementioned ~~aspect~~examples are further ~~embodiment~~examples in which the effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt, or solvate thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by inhalation; and/or (e) administered by nasal administration; or and/or (f) administered by injection to the mammal; and/or (g) administered topically to the mammal; and/or (h) administered by ophthalmic administration; and/or (i) administered rectally to the mammal; and/or (j) administered non-systemically or locally to the mammal.

[0019] In any of the aforementioned ~~aspect~~examples are further ~~embodiment~~examples comprising single administrations of the effective amount of the compound, including further ~~embodiment~~examples in which the compound is administered once a day to the mammal or the compound is administered to the mammal multiple times over the span of one day. In some ~~embodiment~~examples, the compound is administered on a continuous dosing schedule. In some ~~embodiment~~examples, the compound is administered on a continuous daily dosing schedule.

[0020] In any of the ~~embodiment~~examples disclosed herein, the mammal is a human.

[0021] In some ~~embodiment~~examples, compounds provided herein are topically administered to a human.

[0022] Articles of manufacture, which include packaging material, a compound described herein, or a pharmaceutically acceptable salt thereof, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, tautomers, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is used for modulating TYK2, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from modulating TYK2, are provided.

[0023] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific ~~embodiment~~example<u>s</u>, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0024] TYK2 activation has been linked to many diseases and disorders, including inflammatory diseases and disorders, autoimmune diseases and disorders, respiratory diseases and disorders, and cancer.

[0025] In particular, IL-23 activation of TYK2 is associated with inflammatory diseases such as inflammatory bowel disease (IBD), Crohn's disease, celiac disease, and ulcerative colitis. As the downstream effector of IL-23, TYK2 also plays a role in psoriasis, ankylosing spondylitis, and Behcet's disease. TYK2 has also been associated with diseases and conditions of the skin, such as psoriasis, vitiligo, atopic dermatitis, hidradenitis suppurativa, scleroderma; or diseases and conditions of the eye, such as Sjögren’s syndrome, uveitis, and dry eye.

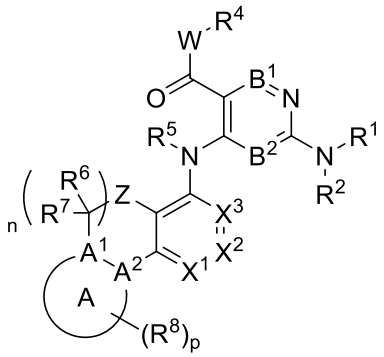
[0026] TYK2 is associated with respiratory diseases and conditions such as asthma, chronic obstructive pulmonary disease (COPD), lung cancer, and cystic fibrosis. Goblet cell hyperplasia (GCH) and mucous hypersecretion is mediated by IL-13-induced activation of the TYK2/STAT6 pathway.

[0027] TYK2 is also associated with autoimmune diseases and conditions, such as multiple sclerosis (MS), lupus, and systemic lupus erythematosus (SLE). Loss of function mutation in TYK2, leads to decreased demyelination and increased remyelination of neurons, further suggesting a role for TYK2 inhibitors in the treatment of MS and other CNS demyelination disorders. Various type I IFN signaling pathways dependent on TYK2 signaling have implicated TYK2 in SLE and other autoimmune diseases and conditions.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

Ring A is an unsubstituted or substituted 6-membered heterocyclic ring wherein A^1 and A^2 are independently N or C, wherein if Ring A is substituted then Ring A is substituted with p instances of R^8;

each R^8 is independently hydrogen, halogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 deuteroalkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted C_1-C_6 heteroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, -CN, -OH, $-OR^{17}$, $-C(=O)R^{16}$, $-CO_2R^{16}$, $-C(=O)N(R^{16})_2$, $-N(R^{16})_2$, $-NR^{16}C(=O)R^{17}$, $-SR^{16}$, $-S(=O)R^{17}$, $-SO_2R^{17}$, or $-SO_2N(R^{16})_2$; wherein if R^8 is attached to a nitrogen atom, then R^8 is hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 deuteroalkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted C_1-C_6 heteroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, $-C(=O)R^{16}$, $-CO_2R^{16}$, $-C(=O)N(R^{16})_2$, $-S(=O)R^{17}$, $-SO_2R^{17}$, or $-SO_2N(R^{16})_2$; or two R^8 attached to the same carbon atom are taken together to form =O, =S, or =NH;

Z is $-NR^{10}$-, -O-, -S-, -S(=O)-, or $-SO_2$-;

R^{10} is hydrogen, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or monocyclic heterocycle;

X^1, X^2, and X^3 are each independently CR^{11} or N;

each R^{11} is independently hydrogen, halogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-

C_6 alkynyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted C_1-C_6 heteroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, -CN, -OH, $-OR^{17}$, $-C(=O)R^{16}$, $-CO_2R^{16}$, $-C(=O)N(R^{16})_2$, $-N(R^{16})_2$, $-NR^{16}C(=O)R^{17}$, $-SR^{16}$, $-S(=O)R^{17}$, $-SO_2R^{17}$, or $-SO_2N(R^{16})_2$;

B^1 is N or CR^{12a};

B^2 is N or CR^{12b};

R^{12a} and R^{12b} are each independently hydrogen, halogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted C_1-C_6 heteroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, -CN, -OH, $-OR^{17}$, $-C(=O)R^{16}$, $-CO_2R^{16}$, $-C(=O)N(R^{16})_2$, $-N(R^{16})_2$, $-NR^{16}C(=O)R^{17}$, $-SR^{16}$, $-S(=O)R^{17}$, $-SO_2R^{17}$, or $-SO_2N(R^{16})_2$;

R^1 is hydrogen, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl;

R^2 is a Ring B that is an unsubstituted or substituted heterocycle or unsubstituted or substituted carbocycle, wherein if Ring B is substituted then Ring B is substituted with q instances of R^{13};

each R^{13} is independently halogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted C_1-C_6 heteroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, -CN, -OH, $-OR^{17}$, $-C(=O)R^{16}$, $-CO_2R^{16}$, $-C(=O)N(R^{16})_2$, $-N(R^{16})_2$, $-NR^{16}C(=O)R^{17}$, $-SR^{16}$, $-S(=O)R^{17}$, $-SO_2R^{17}$, or $-SO_2N(R^{16})_2$;

or two R^{13} groups on adjacent atoms of Ring B are taken together with the intervening atoms to which they are attached to form an unsubstituted or substituted 5- or 6-membered monocyclic carbocycle or an unsubstituted or substituted 5- or 6-membered monocyclic heterocycle;

or R^2 is $-C(=O)R^{14}$, $-C(=O)NR^{14}R^{15}$, or $-C(=O)OR^{14}$;

R^{14} is hydrogen, unsubstituted or substituted C_1-C_6 alkyl, C_1-C_6 deuteroalkyl unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted C_1-C_6 heteroalkyl, unsubstituted or substituted monocyclic carbocycle, unsubstituted or substituted bicyclic

carbocycle, unsubstituted or substituted monocyclic heterocycle, or unsubstituted or substituted bicyclic heterocycle;

R^{15} is hydrogen, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl;

or R^{14} and R^{15} are taken together with the intervening atoms to which they are attached to form an unsubstituted or substituted 4- to 6-membered monocyclic heterocycle;

or R^1 and R^{15} are taken together with the intervening atoms to which they are attached to form an unsubstituted or substituted 5- or 6-membered monocyclic heterocycle;

W is $-NR^3-$ or -O-;

R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or monocyclic heterocycle;

R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or monocyclic heterocycle;

or R^3 and R^4 are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

or R^3 and R^{12a} are taken together with the intervening atoms to which they are attached to form a substituted or unsubstituted 5- or 6-membered heterocycle;

R^5 is hydrogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or monocyclic heterocycle;

each R^6 and R^7 is independently hydrogen, deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or monocyclic heterocycle, -CN, -OH, $-OR^{17}$, $-C(=O)R^{16}$, $-CO_2R^{16}$, $-C(=O)N(R^{16})_2$, $-N(R^{16})_2$, $-NR^{16}C(=O)R^{17}$, $-SR^{16}$, $-S(=O)R^{17}$, $-SO_2R^{17}$, or $-SO_2N(R^{16})_2$;

or one R^6 and one R^7 attached to the same carbon atom are taken together with the carbon atom to which they are attached to form C=O or C_3-C_4 cycloalkyl;

each R^{16} is independently hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 fluoroalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^{16} on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle; and

each R^{17} is independently substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 fluoroalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl,

substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl;

wherein each substituted alkyl, substituted fluoroalkyl, substituted deuteroalkyl, substituted alkoxy, substituted fluoroalkoxy, substituted heteroalkyl, substituted carbocycle, and substituted heterocycle is substituted with one or more R^s groups independently selected from the group consisting of deuterium, halogen, C_1-C_6 alkyl, monocyclic carbocycle, monocyclic heterocycle, -CN, -CH_2CN, -OR^{18}, -CH_2OR^{18}, -CO_2R^{18}, -$CH_2CO_2R^{18}$, -$C(=O)N(R^{18})_2$, -$CH_2C(=O)N(R^{18})_2$, -$N(R^{18})_2$, -$CH_2N(R^{18})_2$, -$NR^{18}C(=O)R^{18}$, -$CH_2NR^{18}C(=O)R^{18}$, -$NR^{18}SO_2R^{19}$, -$CH_2NR^{18}SO_2R^{19}$, -SR^{18}, -CH_2SR^{18}, -$S(=O)R^{19}$, -$CH_2S(=O)R^{19}$, -SO_2R^{19}, -$CH_2SO_2R^{19}$, -$SO_2N(R^{18})_2$, or -$CH_2SO_2N(R^{18})_2$;

each R^{18} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, C_2-C_6 heterocycloalkyl, phenyl, benzyl, 5-membered heteroaryl and 6-membered heteroaryl;

or two R^{18} groups are taken together with the N atom to which they are attached to form a N-containing heterocycle;

each R^{19} is independently selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, C_2-C_6 heterocycloalkyl, phenyl, benzyl, 5-membered heteroaryl, and 6-membered heteroaryl;

n is 1, 2, or 3;

p is 0, 1, 2, 3, or 4; and

q is 0, 1, 2, 3, or 4.

2. The compound of claim 1, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is hydrogen or C_1-C_4 alkyl;

W is -NR^3-;

R^3 is hydrogen, C_1-C_4 alkyl, or C_1-C_4 deuteroalkyl;

R^4 is hydrogen, C_1-C_4 alkyl, or C_1-C_4 deuteroalkyl; and

R^5 is hydrogen or C_1-C_4 alkyl.

~~3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein R^5 is hydrogen or C_1-C_4 alkyl.~~

~~4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein R^5 is hydrogen.~~

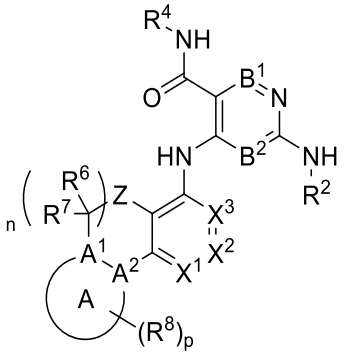
~~5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein W is -NR^3-.~~

~~6. The compound of claim 5, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein R^3 is hydrogen, C$_1$-C$_4$ alkyl, or C$_1$-C$_4$ deuteroalkyl.~~

~~7. The compound of claim 5 or claim 6, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein R^3 is hydrogen.~~

~~8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein R^4 is hydrogen, C$_1$-C$_4$ alkyl, or C$_1$-C$_4$ deuteroalkyl.~~

~~9.~~3. The compound of claim 1 having a structure of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

~~10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:~~

~~X^1 is CR^{11}, X^2 is CR^{11}, and X^3 is CR^{11};~~

~~or X^1 is CR^{11}, X^2 is CR^{11}, and X^3 is N;~~

~~or X^1 is CR^{11}, X^2 is N, and X^3 is CR^{11};~~

~~or X^1 is CR^{11}, X^2 is N, and X^3 is N;~~

~~or X^1 is N, X^2 is CR^{11}, and X^3 is CR^{11};~~

~~or X^1 is N, X^2 is CR^{11}, and X^3 is N;~~

~~or X^1 is N, X^2 is N, and X^3 is CR^{11}.~~

~~11.~~4. The compound of any one of claims 1-~~10~~3, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

X^1 is CR^{11}, X^2 is CR^{11}, and X^3 is CR^{11};

or X^1 is CR^{11}, X^2 is CR^{11}, and X^3 is N;

or X^1 is CR^{11}, X^2 is N, and X^3 is CR^{11};

or X^1 is N, X^2 is CR^{11}, and X^3 is CR^{11}; and

each R^{11} is independently hydrogen, halogen, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ fluoroalkyl, -CN, -OH, -OR^{17}, or -N(R^{16})$_2$.

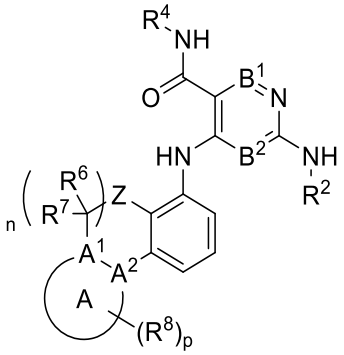
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

X^1 is CR^{11}, X^2 is CR^{11}, and X^3 is CR^{11}.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein each R^{11} is independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, -CN, -OH, $-OR^{17}$, or $-N(R^{16})_2$.

14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein each R^{11} is independently hydrogen or fluoro.

15.5. The compound of claim 1 having a structure of Formula (IV):



Formula (IV)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

16.6. The compound of any one of claims 1-515, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein Ring A is an unsubstituted or substituted 6-membered heteroaryl ring wherein A^1 and A^2 are independently N or C, wherein if Ring A is substituted then Ring A is substituted with p instances of R^8.

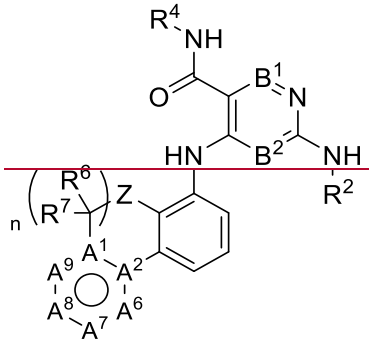
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein Ring A is an unsubstituted or substituted pyridine, unsubstituted or substituted pyridazine, unsubstituted or substituted pyrimidine, unsubstituted or substituted pyrazine, unsubstituted or substituted triazine, or unsubstituted or substituted pyridone, wherein if Ring A is substituted then Ring A is substituted with p instances of R^8.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein Ring A is an unsubstituted or substituted pyridine, unsubstituted or substituted pyrimidine, unsubstituted or substituted pyrazine, or unsubstituted or substituted pyridone, wherein if Ring A is substituted then Ring A is substituted with p instances of R^8.

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein Ring A is an unsubstituted or substituted pyridone; wherein if Ring A is substituted then Ring A is substituted with p instances of R^8.

20. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein Ring A is an unsubstituted or substituted pyridine, or unsubstituted or substituted pyrimidine, wherein if Ring A is substituted then Ring A is substituted with p instances of R^8.

21. The compound of claim 1 having a structure of Formula (VI):



Formula (VI)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

(i) A^1 and A^2 are each C; and A^6, A^7, A^8, and A^9 are each independently CR^8 or N;

(ii) A^1 is N; A^2 is C; A^6, A^7, and A^8 are each independently CR^8 or N; and A^9 is C(=O);

(iii) A^1 is C; A^2 is N; A^6 is C(=O); and A^7, A^8, and A^9 are each independently CR^8 or N;

or

(iv) A^1 and A^2 are each C; one of A^6, A^7, A^8, and A^9 is NR^8, wherein A^6, A^7, A^8, or A^9 adjacent to the NR^8 is C(=O) and the remaining members of A^6, A^7, A^8, and A^9 are each independently CR^8 or N.

22. The compound of claim 21, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

A^1 is C; A^2 is C; A^6 is N; A^7 is CR^8; A^8 is CR^8; and A^9 is CR^8;

or A^1 is C; A^2 is C; A^6 is CR^8; A^7 is N; A^8 is CR^8; and A^9 is CR^8;

or A^1 is C; A^2 is C; A^6 is CR^8; A^7 is CR^8; A^8 is N; and A^9 is CR^8;

or A^1 is C; A^2 is C; A^6 is CR^8; A^7 is CR^8; A^8 is CR^8; and A^9 is N;

or A^1 is N; A^2 is C; A^6 is CR^8; A^7 is CR^8; A^8 is CR^8; and A^9 is C(=O);

or A^1 is C; A^2 is N; A^6 is C(=O); A^7 is CR^8; A^8 is CR^8; and A^9 is CR^8;

or A^1 is C; A^2 is C; A^6 is NR^8; A^7 is C(=O); A^8 is CR^8; and A^9 is CR^8;

or A^1 is C; A^2 is C; A^6 is C(=O); A^7 is NR^8; A^8 is CR^8; and A^9 is CR^8;

or A^1 is C; A^2 is C; A^6 is CR^8; A^7 is NR^8; A^8 is C(=O); and A^9 is CR^8;

~~or A^1 is C; A^2 is C; A^6 is CR^8; A^7 is C(=O); A^8 is NR^8; and A^9 is CR^8;~~

~~or A^1 is C; A^2 is C; A^6 is CR^8; A^7 is CR^8; A^8 is NR^8; and A^9 is C(=O);~~

~~or A^1 is C; A^2 is C; A^6 is CR^8; A^7 is CR^8; A^8 is C(=O); and A^9 is NR^8;~~

~~or A^1 is C; A^2 is C; A^6 is N; A^7 is N; A^8 is CR^8; and A^9 is CR^8;~~

~~or A^1 is C; A^2 is C; A^6 is N; A^7 is CR^8; A^8 is N; and A^9 is CR^8;~~

~~or A^1 is C; A^2 is C; A^6 is N; A^7 is CR^8; A^8 is CR^8; and A^9 is N;~~

~~or A^1 is C; A^2 is C; A^6 is CR^8; A^7 is N; A^8 is N; and A^9 is CR^8;~~

~~or A^1 is C; A^2 is C; A^6 is CR^8; A^7 is N; A^8 is CR^8; and A^9 is N;~~

~~or A^1 is C; A^2 is C; A^6 is CR^8; A^7 is CR^8; A^8 is N; and A^9 is N.~~

~~23. The compound of claim 21, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:~~

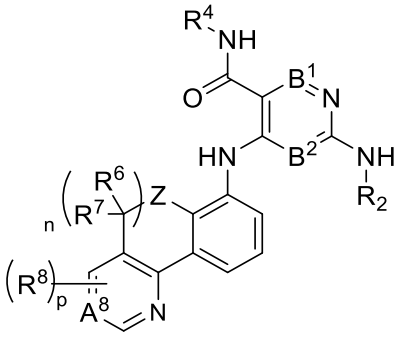
~~A^1 is C; A^2 is C; A^6 is N; A^7 is CR^8; A^8 is CR^8; and A^9 is CR^8;~~

~~or A^1 is C; A^2 is C; A^6 is N; A^7 is CR^8; A^8 is N; and A^9 is CR^8;~~

~~or A^1 is C; A^2 is C; A^6 is N; A^7 is CR^8; A^8 is CR^8; and A^9 is N;~~

~~or A^1 is C; A^2 is C; A^6 is C(=O); A^7 is NR^8; A^8 is CR^8; and A^9 is CR^8.~~

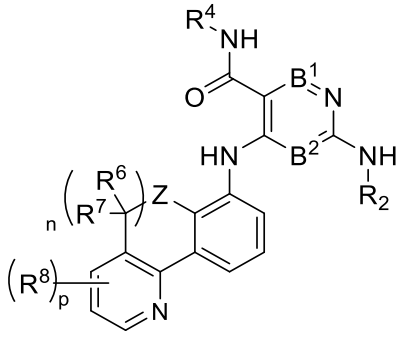
~~24.~~7. The compound of claim ~~21~~ 1 having a structure of Formula (VIa):



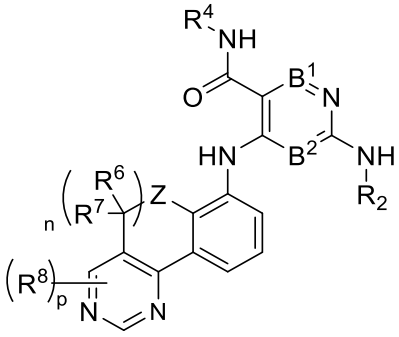
Formula (VIa)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof; wherein A^8 is CR^8 or N.

~~25.~~8. The compound of claim 1~~21~~ having a structure of Formula (VIb) or Formula (VIc):



Formula (VIb)



Formula (VIc)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

~~26.~~9. The compound of any one of claims 1-~~8~~25, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein each R^8 is independently hydrogen, halogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 deuteroalkyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, -CN, -OH, $-OR^{17}$, $-C(=O)R^{16}$, $-CO_2R^{16}$, or $-C(=O)N(R^{16})_2$; wherein if R^8 is attached to a nitrogen atom, then R^8 is hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 deuteroalkyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, $-C(=O)R^{16}$, $-CO_2R^{16}$, or $-C(=O)N(R^{16})_2$.

~~27.~~10. The compound of any one of claims 1-~~9~~26, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein each R^8 is independently hydrogen, -Cl, -F, methyl, ethyl, isopropyl, $-CD_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, oxetanyl, azetidinyl, -CN, -OH, $-CO_2H$, or $-CO_2CH_3$; wherein if R^8 is attached to a nitrogen atom, then R^8 is hydrogen, methyl, ethyl, isopropyl, $-CD_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, oxetanyl, azetidinyl, $-CO_2H$, or $-CO_2CH_3$.

~~28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein each R^8 is independently hydrogen, methyl, $-CD_3$, -OH, $-CH_2OH$, $-CF_3$, oxetanyl, -CN, or $-CO_2CH_3$; wherein if R^8 is attached to a nitrogen atom, then R^8 is hydrogen, methyl, $-CD_3$, $-CH_2OH$, oxetanyl, or $-CO_2CH_3$.~~

~~29.~~11. The compound of any one of claims 1-~~28~~10, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

each R^6 and R^7 is independently hydrogen, deuterium, halogen, C_1-C_4 alkyl, or C_1-C_4 deuteroalkyl;

Z is $-NR^{10}$- or -O-; and

R^{10} is hydrogen, C_1-C_4 alkyl, C_1-C_4 deuteroalkyl, or cyclopropyl.

~~30. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein each R^6 and R^7 is independently hydrogen, deuterium, F, or methyl.~~

~~31. The compound of any one of claims 1-30, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein Z is $-NR^{10}$-, -O-, or $-SO_2$-.~~

~~32. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein Z is $-NR^{10}$- or -O-.~~

~~33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein Z is $-NR^{10}$-.~~

34. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein R^{10} is hydrogen, C_1-C_4 alkyl, C_1-C_4 deuteroalkyl, or cyclopropyl.

35. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein Z is -O-.

36. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein R^2 is a Ring B that is an unsubstituted or substituted heterocycle or unsubstituted or substituted carbocycle, wherein if Ring B is substituted then Ring B is substituted with q instances of R^{13}.

37. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^2 is a Ring B that is an unsubstituted or substituted monocyclic carbocycle, unsubstituted or substituted bicyclic carbocycle, unsubstituted or substituted monocyclic heterocycle, or unsubstituted or substituted bicyclic heterocycle, wherein if Ring B is substituted then Ring B is substituted with q instances of R^{13}.

38. The compound of any one of claims 1-37, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^2 is a Ring B that is an unsubstituted or substituted phenyl, unsubstituted or substituted monocyclic 6-membered heteroaryl, or unsubstituted or substituted monocyclic 5-membered heteroaryl, wherein if Ring B is substituted then Ring B is substituted with q instances of R^{13}.

39. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^2 is a Ring B that is an unsubstituted or substituted phenyl or unsubstituted or substituted monocyclic 6-membered heteroaryl, wherein if Ring B is substituted then Ring B is substituted with q instances of R^{13}.

40. The compound of any one of claims 1-39, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^2 is a Ring B that is an unsubstituted or substituted phenyl, unsubstituted or substituted pyridinyl, unsubstituted or substituted pyrimidinyl, unsubstituted or substituted pyrazinyl, or unsubstituted or substituted pyridazinyl, wherein if Ring B is substituted then Ring B is substituted with q instances of R^{13}.

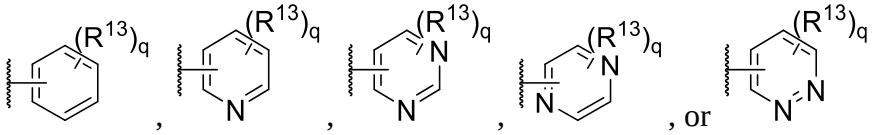
41. The compound of any one of claims 1-40, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

~~R^2 is a Ring B that is an unsubstituted or substituted pyridinyl or unsubstituted or substituted pyrimidinyl, wherein if Ring B is substituted then Ring B is substituted with q instances of R^{13}.~~

~~42. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:~~

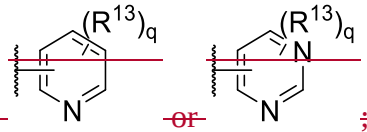
~~R^2 is a Ring B that is an unsubstituted or substituted pyridinyl, wherein if Ring B is substituted then Ring B is substituted with q instances of R^{13}.~~

~~43.~~12. The compound of any one of claims 1-~~39~~11, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

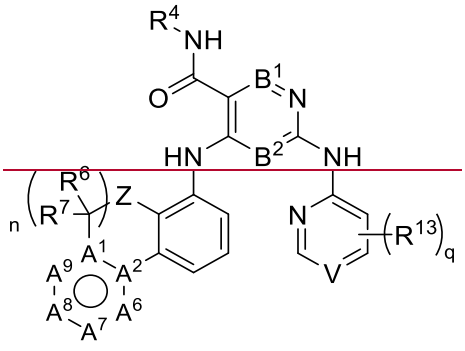
R^2 is ; and q is 0, 1, 2, 3, or 4; and

each R^{13} is independently halogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, -CN, -OH, -OR^{17}, -$C(=O)R^{16}$, -CO_2R^{16}, -$C(=O)N(R^{16})_2$, -$N(R^{16})_2$, -$NR^{16}C(=O)R^{17}$, -SO_2R^{17}, or -$SO_2N(R^{16})_2$.

~~44. The compound of any one of claims 1-39, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:~~

~~Ring B is~~  ~~; and q is 0, 1, 2, 3, or 4.~~

~~45. The compound of claim 1 having a structure of Formula (VIII):~~



~~Formula (VIII)~~

~~or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:~~

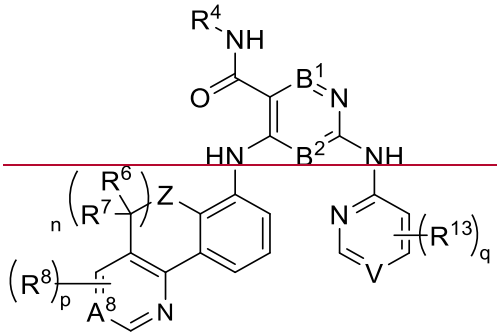
~~V is N, CH, or CR^{13};~~

~~q is 1, 2, 3, or 4;~~

~~A^1 and A^2 are each C; and~~

~~A^6, A^7, A^8, and A^9 are each independently CR^8 or N.~~

~~46. The compound of claim 45 having a structure of Formula (VIIIa):~~



~~Formula (VIIIa)~~

~~or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein A^8 is CR^8 or N.~~

~~47. The compound of any one of claims 45-46, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein V is N.~~

~~48. The compound of any one of claims 45-46, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein V is CH or CR^{13}.~~

~~49. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein each R^{13} is independently halogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, -CN, -OH, $-OR^{17}$, $-C(=O)R^{16}$, $-CO_2R^{16}$, $-C(=O)N(R^{16})_2$, $-N(R^{16})_2$, $-NR^{16}C(=O)R^{17}$, $-SO_2R^{17}$, or $-SO_2N(R^{16})_2$.~~

~~50. The compound of any one of claims 1-49, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein each R^{13} is independently -F, -Cl, $-CH_3$, or $-CF_3$.~~

~~51.~~13. The compound of any one of claims 1-~~35~~11, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^2 is $-C(=O)R^{14}$, $-C(=O)NR^{14}R^{15}$, or $-C(=O)OR^{14}$;

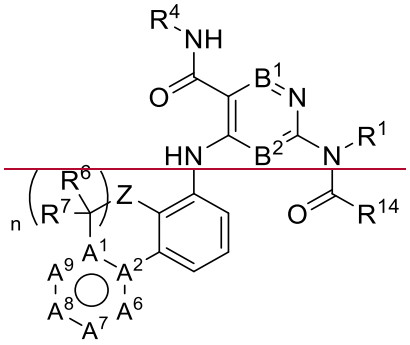
R^{14} is unsubstituted or substituted C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, unsubstituted or substituted C_3-C_6 cycloalkyl, or unsubstituted or substituted 4- to 6-membered heterocycloalkyl; wherein the substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, or substituted heterocycloalkyl is substituted with one or more R^s groups independently selected from the group consisting of deuterium, halogen, C_1-C_6 alkyl, -CN, $-OR^{18}$, and $-N(R^{18})_2$; and

R^{15} is hydrogen, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl;

or R^{14} and R^{15} are taken together with the intervening atoms to which they are attached to form an unsubstituted or substituted 4- to 6-membered monocyclic heterocycle.

52.14. The compound of claim 5113, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein R^2 is -C(=O)R^{14} and R^{14} is unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_3-C_4 cycloalkyl, or unsubstituted or substituted 4-membered heterocycloalkyl; wherein the substituted alkyl, substituted cycloalkyl, or substituted heterocycloalkyl is substituted with one or more R^s groups independently selected from the group consisting of deuterium, halogen, -CN, -NH_2, -OH, -NH(CH_3), -N(CH_3)$_2$, -CH_3, -CH_2CH_3, -CHF_2, -CF_3, -OCH_3, -$OCHF_2$, and -OCF_3.

53. The compound of claim 51, having a structure of Formula (IX):



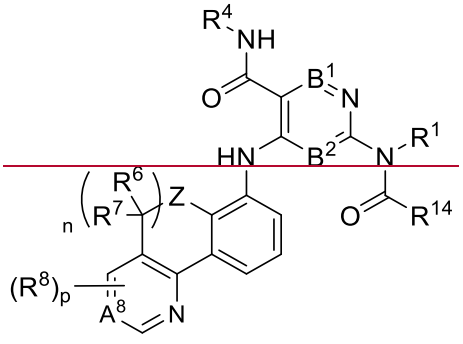
Formula (IX)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

A^1 and A^2 are each C; and

each of A^6, A^7, A^8, and A^9 are independently CR^8 or N.

54. The compound of claim 53, having a structure of Formula (IXa):



Formula (IXa)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein A^8 is CR^8 or N.

55. The compound of any one of claims 51-54, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein R^{14} is unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_3-C_4 cycloalkyl, or unsubstituted or substituted 4-membered heterocycloalkyl; wherein the substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, or substituted heterocycloalkyl is substituted with one or more R^s groups

~~independently selected from the group consisting of deuterium, halogen, -CN, -NH_2, -OH, -$NH(CH_3)$, -$N(CH_3)_2$, -CH_3, -CH_2CH_3, -CHF_2, -CF_3, -OCH_3, -$OCHF_2$, and -OCF_3.~~

~~56.~~15. The compound of any one of claims 1-14~~55~~, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

B^1 is CR^{12a}; and B^2 is CR^{12b};

or B^1 is N; and B^2 is CR^{12b};

or B^1 is CR^{12a}; and B^2 is N;

or B^1 is N; and B^2 is N; and

R^{12a} and R^{12b} are each independently hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, or -CN.

~~57.~~16. The compound of any one of claims 1-15~~56~~, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

B^1 is CH~~C~~R^{12a}; and B^2 is CH~~C~~R^{12b};

or B^1 is N; and B^2 is ~~C~~R^{12b}CH.

~~58. The compound of any one of claims 1-57, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein R^{12a} and R^{12b} are each independently hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, or -CN.~~

~~59. The compound of any one of claims 1-58, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein R^{12a} and R^{12b} are each hydrogen.~~

~~60.~~17. A compound selected from:

1: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)pyridazine-3-carboxamide;

2: 6-((5-fluoropyridin-2-yl)amino)-N-(methyl-d3)-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)pyridazine-3-carboxamide; and

3: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)nicotinamide;

4: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrimido[5,4-c]quinolin-7-yl)amino)nicotinamide;

5: 6-(cyclopropanecarboxamido)-4-((3-fluoro-6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)-N-(methyl-d3)nicotinamide;

6: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrimido[5,4-c]quinolin-7-yl)amino)pyridazine-3-carboxamide;

7: 6-(cyclopropanecarboxamido)-4-((3-fluoro-6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

8: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrazino[2,3-c]quinolin-7-yl)amino)nicotinamide;

9: 6-(cyclopropanecarboxamido)-4-((2,6-dimethyl-1-oxo-1,2,5,6-tetrahydrobenzo[c][2,6]naphthyridin-7-yl)amino)-N-(methyl-d3)nicotinamide;

10: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrazino[2,3-c]quinolin-7-yl)amino)pyridazine-3-carboxamide;

11: 6-(cyclopropanecarboxamido)-4-((2,6-dimethyl-1-oxo-1,2,5,6-tetrahydrobenzo[c][2,6]naphthyridin-7-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

12: 4-((3-cyano-6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)-6-(cyclopropanecarboxamido)-N-(methyl-d3)nicotinamide;

13: 4-((3-cyano-6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)-6-(cyclopropanecarboxamido)-N-(methyl-d3)pyridazine-3-carboxamide;

14: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrazino[2,3-c][1,7]naphthyridin-7-yl)amino)nicotinamide;

15: 6-(cyclopropanecarboxamido)-N-methyl-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)nicotinamide;

16: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrazino[2,3-c]quinolin-7-yl)amino)pyridazine-3-carboxamide;

17: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-(methyl-d3)-5,6-dihydropyrazino[2,3-c]quinolin-7-yl)amino)nicotinamide;

1**8:** 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-(methyl-d3)-5,6-dihydropyrazino[2,3-c]quinolin-7-yl)amino)pyridazine-3-carboxamide;

19: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydropyrido[3,4-h][1,6]naphthyridin-7-yl)amino)nicotinamide;

20: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)nicotinamide;

21: 6-(cyclopropanecarboxamido)-4-((3-fluoro-6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

22: 6-(cyclopropanecarboxamido)-4-((3-fluoro-6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)-N-(methyl-d3)nicotinamide;

23: 6-(cyclopropanecarboxamido)-4-((2,6-dimethyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

24: 6-(cyclopropanecarboxamido)-4-((2,6-dimethyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)-N-(methyl-d3)nicotinamide;

25: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-2-(trifluoromethyl)-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)nicotinamide;

26: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-2-(trifluoromethyl)-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl-5,5-d2)amino)pyridazine-3-carboxamide;

27: 6-(cyclopropanecarboxamido)-4-((2,6-dimethyl-1-oxo-1,2,5,6-tetrahydropyridazino[4,5-c]quinolin-7-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

28: 6-(cyclopropanecarboxamido)-4-((2,6-dimethyl-1-oxo-1,2,5,6-tetrahydropyridazino[4,5-c]quinolin-7-yl)amino)-N-(methyl-d3)nicotinamide;

29: 6-(cyclopropanecarboxamido)-N-methyl-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)pyridazine-3-carboxamide;

30: 6-(cyclopropanecarboxamido)-N-methyl-4-((6-methyl-5,6-dihydropyrazino[2,3-c]quinolin-7-yl)amino)nicotinamide;

31: 6-(cyclopropanecarboxamido)-4-((10-fluoro-5-methyl-5,6-dihydrophenanthridin-4-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

32: (R)-6-(cyclopropanecarboxamido)-4-((5,6-dimethyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide; and

33: (S)-6-(cyclopropanecarboxamido)-4-((5,6-dimethyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide;

or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

18. A compound selected from:

3: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)nicotinamide;

15: 6-(cyclopropanecarboxamido)-N-methyl-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)nicotinamide;

34: 6-(cyclopropanecarboxamido)-4-((2,5-dimethyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinolin-6-yl)amino)-N-methylpyridazine-3-carboxamide;

35: 4-((2,5-dimethyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinolin-6-yl)amino)-6-((5-fluoropyridin-2-yl)amino)-N-methylnicotinamide;

36: 4-((2,5-dimethyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinolin-6-yl)amino)-6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methylnicotinamide;

37: 6-(cyclopropanecarboxamido)-4-((2,5-dimethyl-4,5-dihydro-2H-[1,2,3]triazolo[4,5-c]quinolin-6-yl)amino)-N-methylnicotinamide; and

38: 6-(cyclopropanecarboxamido)-4-((2,5-dimethyl-4,5-dihydropyrazolo[1,5-a]quinoxalin-6-yl)amino)-N-methylpyridazine-3-carboxamide;

or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

~~61.~~19. A pharmaceutical composition comprising the compound of any one of claims 1-~~60~~18, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, and a pharmaceutically acceptable excipient.

~~62.~~20. Use of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, in the manufacture of a medicament for ~~A method of~~ treating a TYK2-mediated disease or condition in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-60, or a pharmaceutically acceptable salt, tautomer, or solvate thereof~~.

~~63.~~21. Use of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, in the manfacture of a medicament for ~~A method of~~ treating an inflammatory disease or condition or autoimmune disease or condition in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-60, or a pharmaceutically acceptable salt, tautomer, or solvate thereof~~.

~~64.~~22. The ~~method~~ use of claim ~~62~~ 18 or claim ~~63~~19, wherein the disease or condition is selected from rheumatoid arthritis, multiple sclerosis, psoriasis, psoriatic arthritis, lupus, systemic lupus erythematosus, Sjögren's syndrome, ankylosing spondylitis, vitiligo, atopic dermatitis, scleroderma, alopecia, hidradenitis suppurativa, uveitis, dry eye, intestinal bowel disease, Crohn's disease, ulcerative colitis, celiac disease, Bechet's disease, type 1 diabetes, systemic sclerosis, and idiopathic pulmonary fibrosis.

23. Use of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, in the manufacture of a medicament for treating a disease or condition of the eye in a patient in need thereof.

24. The use of claim 23, wherein the disease or condition of the eye is selected from Sjögren's syndrome, uveitis, and dry eye, or a combination thereof.

25. A compound of any one of claims 1-18, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, for use in therapy.

~~65. The method of any one of claims 62-64, wherein the compound is administered topically.~~

~~66. The method of claim 65, wherein the compound is provided in a gel, cream, ointment, liquid, or transdermal patch.~~

67. The method of any one of claims 62-64, wherein the compound is administered by ophthalmic administration.

68. The method of claim 67, wherein the compound is provided in a liquid solution, suspension, gel, depot, or other preparation that can be administered to the eye or surrounding tissue (e.g., eye drops).

69. A compound selected from:

3: 6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)nicotinamide;

15: 6-(cyclopropanecarboxamido)-N-methyl-4-((6-methyl-5,6-dihydrobenzo[h][1,6]naphthyridin-7-yl)amino)nicotinamide;

34: 6-(cyclopropanecarboxamido)-4-((2,5-dimethyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinolin-6-yl)amino)-N-methylpyridazine-3-carboxamide;

35: 4-((2,5-dimethyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinolin-6-yl)amino)-6-((5-fluoropyridin-2-yl)amino)-N-methylnicotinamide;

36: 4-((2,5-dimethyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinolin-6-yl)amino)-6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methylnicotinamide;

37: 6-(cyclopropanecarboxamido)-4-((2,5-dimethyl-4,5-dihydro-2H-[1,2,3]triazolo[4,5-c]quinolin-6-yl)amino)-N-methylnicotinamide; and

38: 6-(cyclopropanecarboxamido)-4-((2,5-dimethyl-4,5-dihydropyrazolo[1,5-a]quinoxalin-6-yl)amino)-N-methylpyridazine-3-carboxamide;

or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

70. A pharmaceutical composition comprising the compound of claim 69, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, and a pharmaceutically acceptable excipient.

71. A method of treating a TYK2-mediated disease or condition in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of claim 69, or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

72. A method of treating an inflammatory disease or condition or autoimmune disease or condition in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of claim 69, or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

73. The method of claim 71 or claim 72, wherein the disease or condition is selected from rheumatoid arthritis, multiple sclerosis, psoriasis, psoriatic arthritis, lupus, systemic lupus erythematosus, Sjögren's syndrome, ankylosing spondylitis, vitiligo, atopic

~~dermatitis, scleroderma, alopecia, hidradenitis suppurativa, uveitis, dry eye, intestinal bowel disease, Crohn's disease, ulcerative colitis, celiac disease, Bechet's disease, type 1 diabetes, systemic sclerosis, and idiopathic pulmonary fibrosis.~~

~~74. The method of any one of claims 71-73, wherein the compound is administered topically.~~

~~75. The method of claim 74, wherein the compound is provided in a gel, cream, ointment, liquid, or transdermal patch.~~

~~76. The method of any one of claims 71-73, wherein the compound is administered by ophthalmic administration.~~

~~77. The method of claim 76, wherein the compound is provided in a liquid solution, suspension, gel, depot, or other preparation that can be administered to the eye or surrounding tissue (e.g., eye drops).~~