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, US Provisional Application No. 63/193,511 filed on May 26, 2021, US Provisional Application No. 63/234,934 filed on August 19, 2021, and US Provisional Application No. 63/291,224 filed on December 17, 2021, each of which is incorporated herein by reference in its entirety.

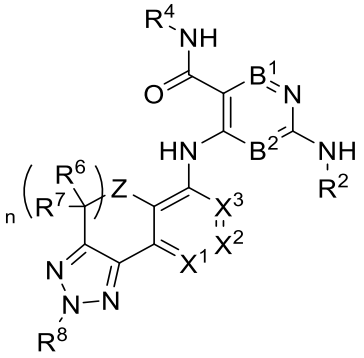
BACKGROUND OF THE INVENTION

[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, JAKl, 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-11, 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, STAT3, STAT4, and STAT6.

SUMMARY

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



Formula (XIV)

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

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 $-SO_2N(R^{16})_2$;

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^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;

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;

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; and

q is 1, 2, 3, or 4;

wherein the compound is not 6-(cyclopropanecarboxamido)-4-((2,5-dimethyl-4,5-dihydro-2H-[1,2,3]triazolo[4,5-c]quinolin-6-yl)amino)-N-methylnicotinamide.

[0003b] 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.

[0003c] In a further 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.

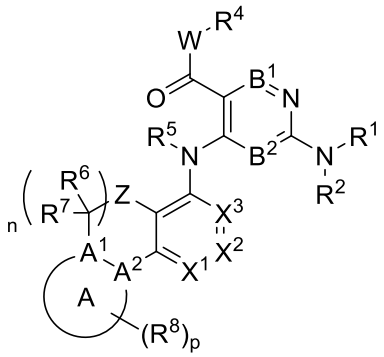
[0003d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, in the

manufacture of a medicament for treating a disease or condition in a patient in need thereof, 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.

[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 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 examples, a compound of the present disclosure may be an allosteric modulator or noncompetitive inhibitor of TYK2. In additional examples, a

compound described herein may be useful in the treatment of TYK2 mediated diseases or disorders.

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



Formula (I)

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

Ring A is an unsubstituted or substituted triazole 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 $-SO_2N(R^{16})_2$;

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

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 1; and

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

and wherein the compound is not 6-(cyclopropanecarboxamido)-4-((2,5-dimethyl-4,5-dihydro-2H-[1,2,3]triazolo[4,5-c]quinolin-6-yl)amino)-N-methylnicotinamide.

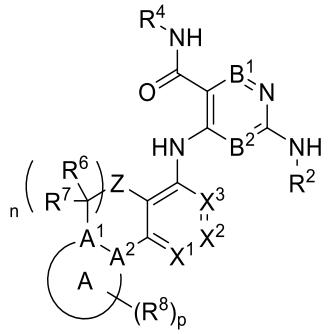
[0006] In some examples, R^1 is hydrogen or C_1-C_4 alkyl.

[0007] In some examples, R^5 is hydrogen or C_1-C_4 alkyl. In some examples, R^5 is hydrogen.

[0008] In some examples, W is -NR^3-. In some examples, R^3 is hydrogen, C_1-C_4 alkyl, or C_1-C_4 deuteroalkyl. In some examples, R^3 is hydrogen.

[0009] In some examples, R^4 is hydrogen, C_1-C_4 alkyl, or C_1-C_4 deuteroalkyl.

[0010] In some examples, the compound has a structure of Formula (II):

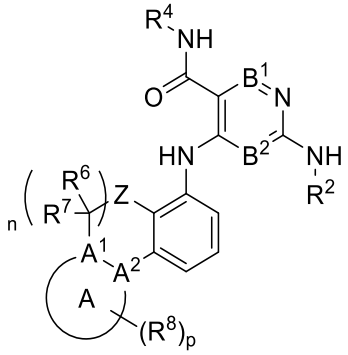


Formula (II)

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

[0011] In some examples, 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}. In some examples, 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}. In some examples, X^1 is CR^{11}, X^2 is CR^{11}, and X^3 is CR^{11}. In some examples, each R^{11} is independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, -CN, -OH, -OR^{17}, or -$N(R^{16})_2$. In some examples, each R^{11} is independently hydrogen or fluoro.

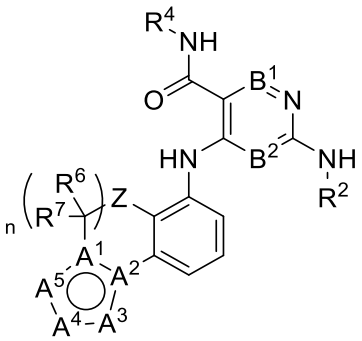
[0012] In some examples, the compound has a structure of Formula (IV):



Formula (IV)

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

[0013] In some examples, the compound has a structure of Formula (VI):

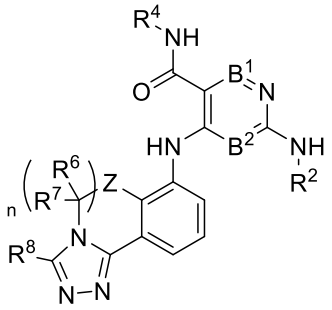


Formula (VI)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein: A^1 and A^2 are each independently N or C; and A^3, A^4, and A^5 are each independently N, NR^8, or CR^8; wherein three ring atoms selected from A^1, A^2, A^3, A^4, and A^5 are N or NR^8; and the remaining atoms are C or CR^8.

[0014] In some examples, the compound has a structure of A^1 is N; A^2 is C; A^3 is N; A^4 is N; and A^5 is CR^8; or A^1 is C; A^2 is N; A^3 is N; A^4 is CR^8; and A^5 is N; or A^1 is C; A^2 is C; A^3 is N; A^4 is NR^8; and A^5 is N; or A^1 is C; A^2 is N; A^3 is N; A^4 is N; and A^5 is CR^8.

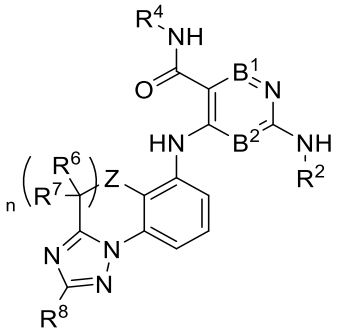
[0015] In some examples, the compound has a structure of Formula (VIb-1):



Formula (VIb-1)

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

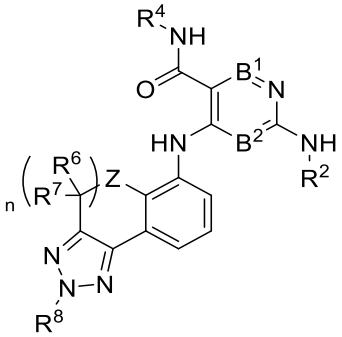
[0016] In some examples, the compound has a structure of Formula (VId-1):



Formula (VId-1)

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

[0017] In some examples, the compound has a structure of Formula (VIg-1):



Formula (VIg-1)

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

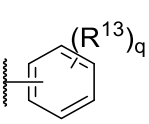
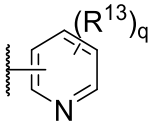
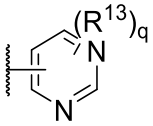
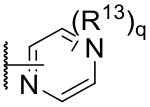
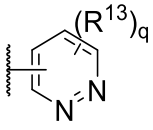
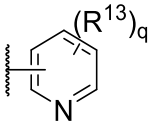
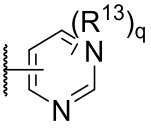
[0018] In some examples, each R^8 is independently hydrogen, halogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 deuteroalkyl, unsubstituted or substituted C_1-C_6 fluoroalkyl, unsubstituted or substituted carbocycle, unsubstituted or substituted heterocycle, -CN, -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 -$C(=O)N(R^{16})_2$. In some examples, 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. In some examples, 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.

[0019] In some examples, each R^6 and R^7 is independently hydrogen, deuterium, halogen, C_1-C_4 alkyl, or C_1-C_4 deuteroalkyl. In some examples, each R^6 and R^7 is independently hydrogen, deuterium, F, or methyl.

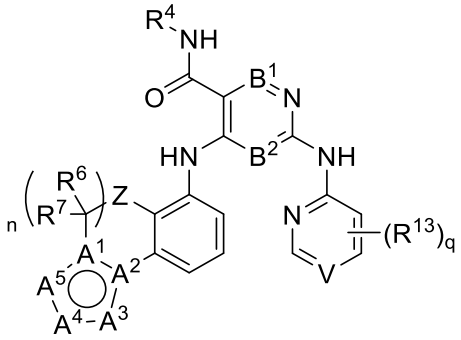
[0020] In some examples, Z is -NR^{10}-, -O-, or -SO_2-. In some examples, Z is -NR^{10}- or -O-. In some examples, Z is -NR^{10}-. In some examples, R^{10} is hydrogen, C_1-C_4 alkyl, C_1-C_4 deuteroalkyl, or cyclopropyl. In some examples, Z is -O-.

[0021] In some examples, 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}. In some examples, 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}. In some examples, 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}. In some examples, 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}. In some examples, 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}. In some examples, 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}. In some examples, 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}.

[0022] In some examples, R^2 is , , , , or ; and q is 0, 1, 2, 3, or 4. In some examples, Ring B is  or ; and q is 0, 1, 2, 3, or 4.

[0023] In some examples, the compound has a structure of Formula (VIII):



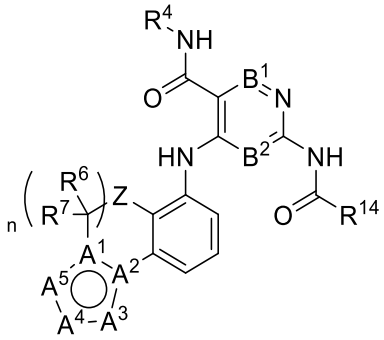
Formula (VIII)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein: V is N, CH, or CR^{13}; q is 1, 2, or 3; A^1 and A^2 are each independently N or C; and A^3, A^4, and A^5 are each independently N, NR^8, or CR^8; wherein three ring atoms selected from A^1, A^2, A^3, A^4, and A^5 are N or NR^8; and the remaining atoms are C or CR^8.

[0024] In some examples, V is N. In some examples, V is CH or CR^{13}. In some examples, 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 $-SO_2N(R^{16})_2$. In some examples, each R^{13} is independently -F, -Cl, $-CH_3$, or $-CF_3$.

[0025] In some examples, R^2 is $-C(=O)R^{14}$, $-C(=O)NR^{14}R^{15}$, or $-C(=O)OR^{14}$. In some examples, R^2 is $-C(=O)R^{14}$.

[0026] In some examples, the compound has a structure of Formula (IX):



Formula (IX)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein: A^1 and A^2 are each independently N or C; and A^3, A^4, and A^5 are each independently N, NR^8, or CR^8; wherein three ring atoms selected from A^1, A^2, A^3, A^4, and A^5 are N or NR^8; and the remaining atoms are C or CR^8.

[0027] In some examples, R^{14} is unsubstituted or substituted C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, 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 $-OCF_3$.

[0028] In some examples, 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. In some examples, B^1 is CR^{12a}; and B^2 is CR^{12b};

[0029] or B^1 is N; and B^2 is CR^{12b}. In some examples, R^{12a} and R^{12b} are each independently hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, or -CN. In some examples, R^{12a} and R^{12b} are each hydrogen.

[0030] 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.

[0031] 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 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 examples, the pharmaceutical composition is formulated for administration to a mammal by oral administration. In some 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 examples, the pharmaceutical composition is in the form of a tablet, a pill, or a capsule. In some 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 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).

[0032] 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 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 examples, the disease is selected from psoriasis, psoriatic arthritis, vitiligo, atopic dermatitis, alopecia, and hidradenitis suppurativa. In some examples, the disease is selected from interferonopathies such as, by way of example, Alcardi-Goutieres syndrome.

[0033] In any of the aforementioned examples are further 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.

[0034] In any of the aforementioned examples are further examples comprising single administrations of the effective amount of the compound, including further 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 examples, the compound is administered on a continuous dosing schedule. In some examples, the compound is administered on a continuous daily dosing schedule.

[0035] In any of the examples disclosed herein, the mammal is a human.

[0036] In some examples, compounds provided herein are topically administered to a human.

[0037] 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.

[0038] 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 examples, 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

[0039] 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.

[0040] 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.

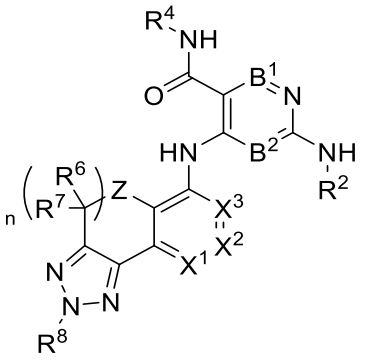
[0041] TYK2 is associated with respiratory diseases and conditions such as asthma, chronic obstructive pulmonary disease (COPD), lung cancer, and cystic fibrosis. Goblet cell hyperplasia (GCH) and mucous hypersecretion is mediated by IL-13-induced activation of the TYK2/STAT6 pathway.

[0042] 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

CLAIMS

What is claimed is:

1. A compound of Formula (XIV):



Formula (XIV)

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

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 $-SO_2N(R^{16})_2$;

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^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;

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;

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; and

q is 1, 2, 3, or 4;

wherein the compound is not 6-(cyclopropanecarboxamido)-4-((2,5-dimethyl-4,5-dihydro-2H-[1,2,3]triazolo[4,5-c]quinolin-6-yl)amino)-N-methylnicotinamide.

2. The compound of claim 1, 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};

each R^{11} is independently hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, or -CN; and

B^1 is CH or CF, and B^2 is CH or CF;

or B^1 is N, and B^2 is CH or CF.

3. The compound of claim 1, 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;

each R^{11} is hydrogen; and

B^1 is CH, and B^2 is CH;

or B^1 is N, and B^2 is CH.

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

R^4 is C_1-C_4 alkyl or C_1-C_4 deuteroalkyl.

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

R^4 is C_1-C_4 deuteroalkyl.

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

R^8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, $-C(=O)R^{16}$, $-CO_2R^{16}$, or $-C(=O)N(R^{16})_2$;

each R^{16} is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 heteroalkyl, C_3-C_7 cycloalkyl, or monocyclic 3- to 8-membered heterocycloalkyl; or two R^{16} on the same N atom are taken together with the N atom to which they are attached to form a 4- to 6-membered N-containing heterocycloalkyl; and

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

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

R^8 is hydrogen, methyl, ethyl, isopropyl, $-CD_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, oxetanyl, azetidinyl, $-CO_2H$, or $-CO_2CH_3$.

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

Z is $-NR^{10}-$;

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

n is 1; and

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

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

Z is $-N(CH_3)-$ or $-N(CD_3)-$;

n is 1; and

R^6 and R^7 are each independently hydrogen, deuterium, -F, or methyl.

10. The compound of claim 1, 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}; 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 $-SO_2N(R^{16})_2$.

11. The compound of claim 1, 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, 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 $-N(R^{18})_2$.

12. The compound of claim 11, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^{14} is unsubstituted or substituted C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, 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.

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

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})$_2$;

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

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

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

each R^{11} is independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, -CN, -OH, -OR^{17}, -N(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, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, or -CN;

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};

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})$_2$;

or R^2 is -C(=O)R^{14};

R^{14} is unsubstituted or substituted C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, 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;

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

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, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 heteroalkyl, C_3-C_7 cycloalkyl, or monocyclic 3- to 8-membered heterocycloalkyl;

or two R^{16} on the same N atom are taken together with the N atom to which they are attached to form a 4- to 6-membered N-containing heterocycloalkyl; and

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

14. The compound of claim 13, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

Z is -NR^{10}-;

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

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;

each R^{11} is hydrogen;

B^1 is CH, and B^2 is CH;

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

R^4 is C_1-C_4 alkyl or C_1-C_4 deuteroalkyl;

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

R^8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 deuteroalkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocycloalkyl, -$C(=O)R^{16}$, -CO_2R^{16}, or -$C(=O)N(R^{16})_2$;

each R^{16} is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 heteroalkyl, C_3-C_7 cycloalkyl, or monocyclic 3- to 8-membered heterocycloalkyl; or two R^{16} on the same N atom are taken together with the N atom to which they are attached to form a 4- to 6-membered N-containing heterocycloalkyl;

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

n is 1.

15. The compound of claim 13, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

Z is -$N(CH_3)$- or -$N(CD_3)$-;

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;

each R^{11} is hydrogen;

B^1 is CH, and B^2 is CH;

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

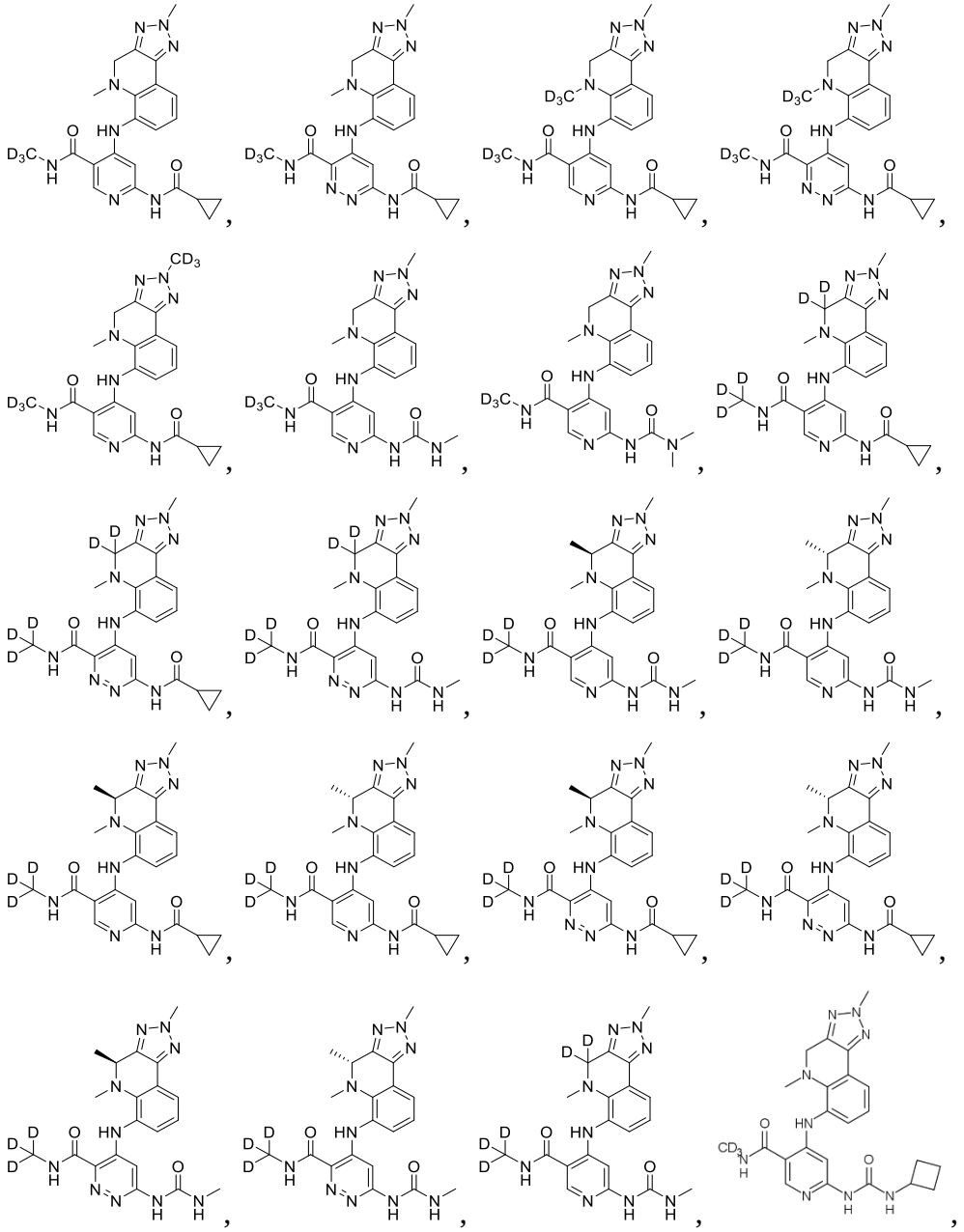
R^4 is C_1-C_4 deuteroalkyl;

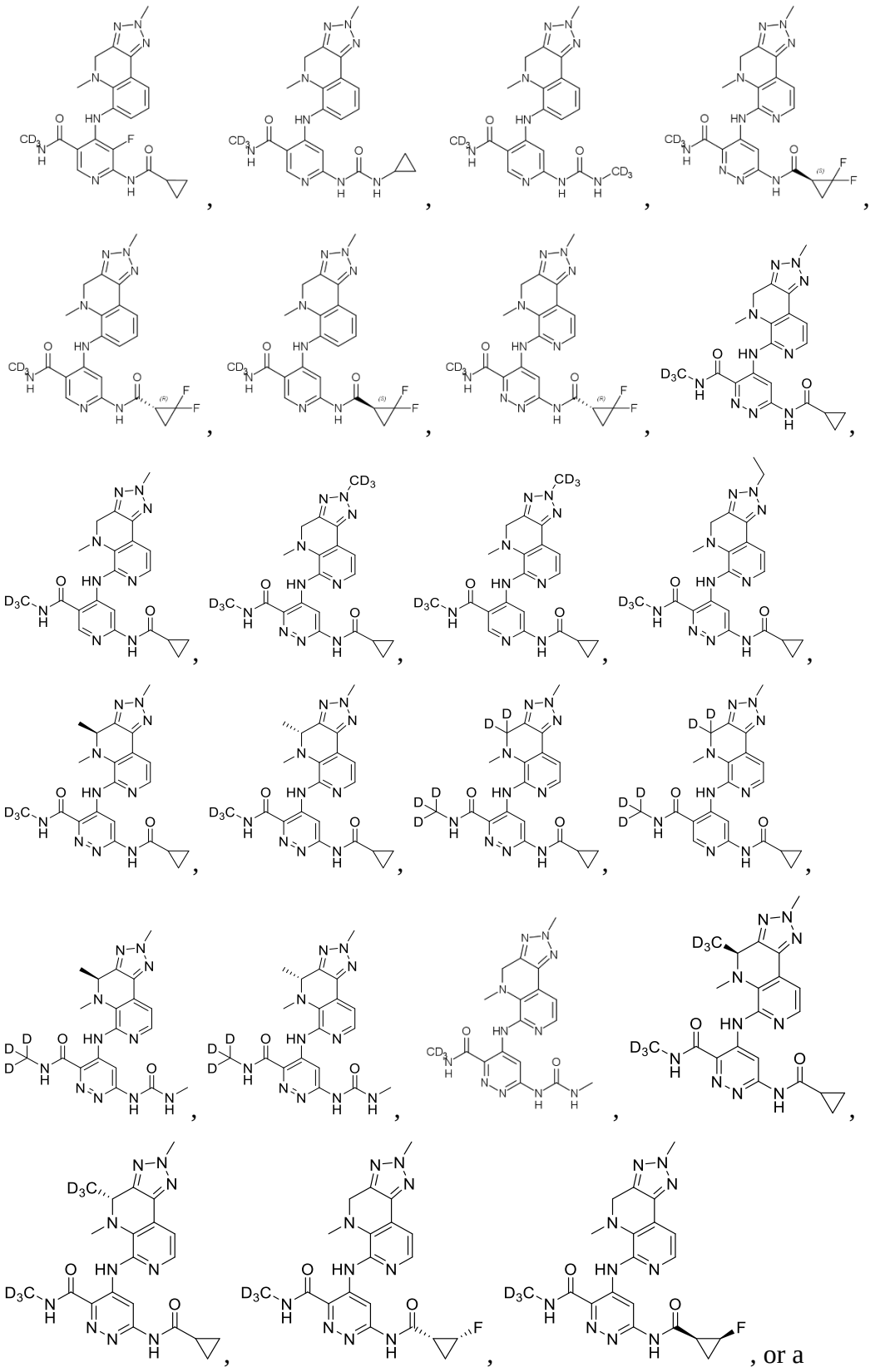
R^6 and R^7 are each independently hydrogen, deuterium, -F, or methyl;

R^8 is hydrogen, methyl, ethyl, isopropyl, $-CD_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, oxetanyl, azetidinyl, $-CO_2H$, or $-CO_2CH_3$; and

n is 1.

16. The compound of claim 1, wherein the compound is:





pharmaceutically acceptable salt, tautomer, or solvate thereof.

17. A pharmaceutical composition comprising the compound of claim 1, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, and a pharmaceutically acceptable excipient.

18. The pharmaceutical composition of claim 17, wherein the pharmaceutical composition is formulated for administration to a mammal by oral administration.

19. The pharmaceutical composition of claim 18, wherein the pharmaceutical composition is in the form of a tablet, a pill, or a capsule.

20. A compound of claim 1, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, for use in therapy.

21. Use of a compound of claim 1, or a pharmaceutically acceptable salt, tautomer, or solvate thereof, in the manufacture of a medicament for treating a disease or condition in a patient in need thereof, 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.