TYK2 PSEUDOKINASE LIGANDS

CROSS-REFERENCE

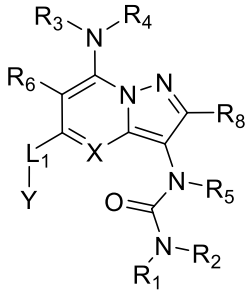
[0001] This application claims benefit of U.S. Provisional Application No. 62/933,179, filed on November 8, 2019, and U.S. Provisional Application No. 63/046,514, filed on June 30, 2020, both of which are herein incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Janus kinase (JAK) is a family of intracellular, non-receptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-STAT pathway. The four JAK family members are Janus kinase 1 (JAK1), Janus kinase 2 (JAK2), Janus kinase 3 (JAK3), and Tyrosine kinase 2 (TYK2) and have been shown to be key components of cytokine-mediated effects. Unlike JAK1 deficient mice, TYK2 deficient mice are viable and the TYK2 deficiency has been shown to be protective in various models of autoimmunity.

SUMMARY

[0002a] In an aspect of the present disclosure, there is provided a compound having the structure of Formula (I'):

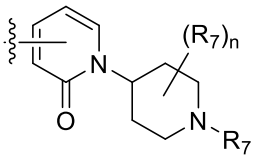


Formula (I');

wherein:

X is N or C(R_6);

Y is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl, or



, wherein C_1-C_6alkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, or C_2-C_9heteroaryl are optionally substituted by 1, 2, 3, or 4 R_7;

L_1 is a bond, -O-, -C(O)-, -N(R_9)-, -N(R_9)CH_2-, or -CH_2N(R_9)-;

R_1 is C_3-C_6cycloalkyl substituted by 1, 2, or 3 R_{13};

R_2, R_3, and R_4 are independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

R_5 is hydrogen or C_1-C_6alkyl;

each R_6 is independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

each R_7 is independently selected from deuterium, halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl, oxo, -OR_{10}, -$N(R_{10})_2$, -CN, -$C(=O)R_{11}$, -$C(=O)OR_{10}$, -$C(=O)N(R_{10})_2$, -$NR_{10}C(=O)R_{11}$, -$NR_{10}S(=O)_2R_{11}$, -$S(=O)_2R_{11}$, and -$S(=O)_2N(R_{10})_2$, wherein C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl are optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, -OR_{12}, -$N(R_{12})_2$, -$C(=O)OR_{12}$, and -$C(=O)N(R_{12})_2$; or two R_7 are combined to form a 5-, 6-, or 7-membered heterocycloalkyl ring or a 4-, 5-, or 6-membered cycloalkyl ring;

R_8 is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6deuteroalkyl;

R_9 is hydrogen or C_1-C_6alkyl;

each R_{10} is independently selected from hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, and phenyl, wherein phenyl is optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, -OR_{12}, -$N(R_{12})_2$, -$C(=O)OR_{12}$, and -$C(=O)N(R_{12})_2$;

each R_{11} is independently selected from C_1-C_6alkyl and C_1-C_6heteroalkyl;

each R_{12} is independently selected from hydrogen, C_1-C_6alkyl, and C_1-C_6haloalkyl;

each R_{13} is independently selected from halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl, oxo, -OR_{10}, -$N(R_{10})_2$, -CN, -$C(=O)R_{11}$, -$C(=O)OR_{10}$, -$C(=O)N(R_{10})_2$, -$NR_{10}C(=O)R_{11}$, -$NR_{10}S(=O)_2R_{11}$, -$S(=O)_2R_{11}$, and -$S(=O)_2N(R_{10})_2$, wherein C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl are optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, -OR_{12}, -$N(R_{12})_2$, -$C(=O)OR_{12}$, and -$C(=O)N(R_{12})_2$; and

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

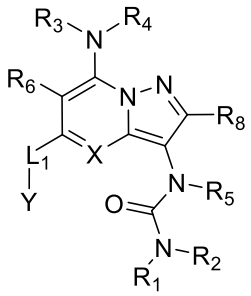
or a pharmaceutically acceptable salt or solvate thereof.

[0002b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0002c] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating an inflammatory or autoimmune disease in a patient.

[0002d] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

[0003] In one example, provided herein are compounds of Formula (I'):

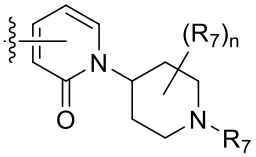


Formula (I');

wherein:

X is N or C(R_6);

Y is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl, or



, wherein C_1-C_6alkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, or C_2-C_9heteroaryl are optionally substituted by 1, 2, 3, or 4 R_7;

L_1 is a bond, -O-, -C(O)-, -N(R_9)-, -N(R_9)CH_2-, or -CH_2N(R_9)-;

R_1 is C_3-C_6cycloalkyl substituted by 1, 2, or 3 R_{13};

R_2, R_3, and R_4 are independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

R_5 is hydrogen or C_1-C_6alkyl;

each R_6 is independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

each R_7 is independently selected from deuterium, halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl, oxo, $-OR_{10}$, $-N(R_{10})_2$, -CN, $-C(=O)R_{11}$, $-C(=O)OR_{10}$, $-C(=O)N(R_{10})_2$, $-NR_{10}C(=O)R_{11}$, $-NR_{10}S(=O)_2R_{11}$, $-S(=O)_2R_{11}$, and $-S(=O)_2N(R_{10})_2$, wherein C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl are optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, $-OR_{12}$, $-N(R_{12})_2$, $-C(=O)OR_{12}$, and $-C(=O)N(R_{12})_2$; or two R_7 are combined to form a 5-, 6-, or 7-membered heterocycloalkyl ring or a 4-, 5-, or 6-membered cycloalkyl ring;

R_8 is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6deuteroalkyl;

R_9 is hydrogen or C_1-C_6alkyl;

each R_{10} is independently selected from hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, and phenyl, wherein phenyl is optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, $-OR_{12}$, $-N(R_{12})_2$, $-C(=O)OR_{12}$, and $-C(=O)N(R_{12})_2$;

each R_{11} is independently selected from C_1-C_6alkyl and C_1-C_6heteroalkyl;

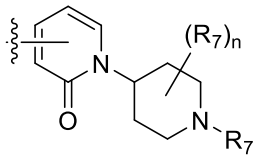
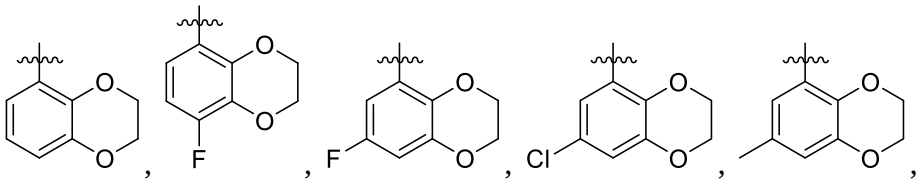
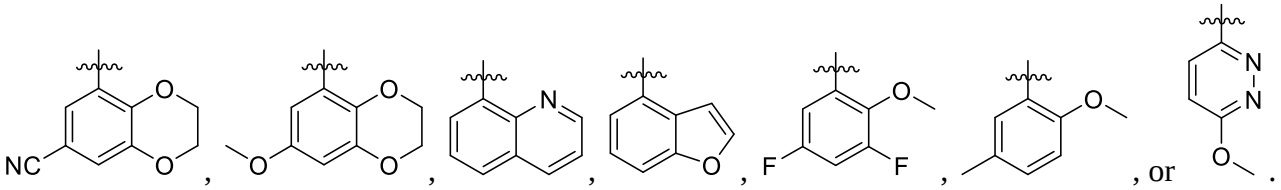
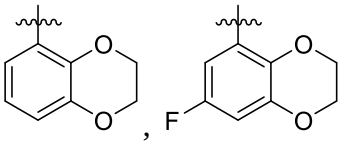
each R_{12} is independently selected from hydrogen, C_1-C_6alkyl, and C_1-C_6haloalkyl;

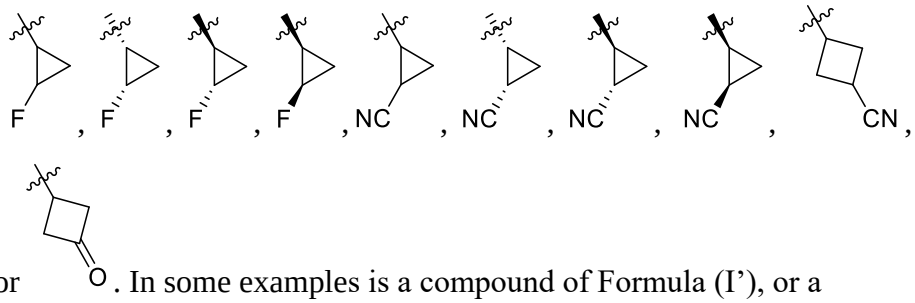
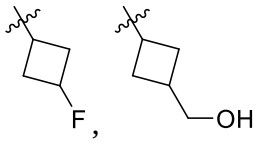
each R_{13} is independently selected from halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl, oxo, $-OR_{10}$, $-N(R_{10})_2$, -CN, $-C(=O)R_{11}$, $-C(=O)OR_{10}$, $-C(=O)N(R_{10})_2$, $-NR_{10}C(=O)R_{11}$, $-NR_{10}S(=O)_2R_{11}$, $-S(=O)_2R_{11}$, and $-S(=O)_2N(R_{10})_2$, wherein C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl are optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, $-OR_{12}$, $-N(R_{12})_2$, $-C(=O)OR_{12}$, and $-C(=O)N(R_{12})_2$; and

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

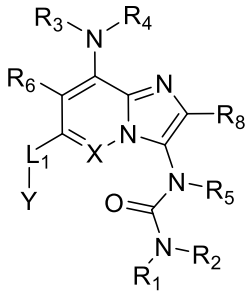
or a pharmaceutically acceptable salt or solvate thereof.

[0004] In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is C_6-C_{10}aryl optionally substituted with 1, 2, or 3 R_7. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is phenyl optionally substituted with 1, 2, or 3 R_7. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is C_2-C_9heteroaryl optionally substituted with 1, 2, or 3 R_7. In some examples is a compound of

Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is C_2-C_9heteroaryl selected from oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl, wherein oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl are optionally substituted with 1, 2, or 3 R_7. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is . In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0, 1, or 2. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_7 is independently selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_1-C_6alkoxy. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is , . In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is . In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_{13} is independently selected from halogen, -OH, -CN, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and oxo. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_{13} is independently selected from halogen, -OH, and -CN. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is cyclopropyl substituted by 1 R_{13}. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is cyclobutyl optionally substituted by 1 or 2 R_{13}. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate

thereof, wherein R_1 is , , or . In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L_1 is a bond. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein L_1 is -N(H)-. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 and R_4 are independently selected from hydrogen and C_1-C_6alkyl. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen and R_4 is C_1-C_6alkyl. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen and R_4 is C_1-C_6deuteroalkyl. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is hydrogen. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_8 is hydrogen. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein X is N. In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein X is C(R_6). In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, wherein X is C(H).

[0005] In another example, provided herein are compounds of Formula (I) or Formula (II):



Formula (I);

each R_{10} is independently selected from hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, and phenyl, wherein phenyl is optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, $-OR_{12}$, $-N(R_{12})_2$, $-C(=O)OR_{12}$, and $-C(=O)N(R_{12})_2$;

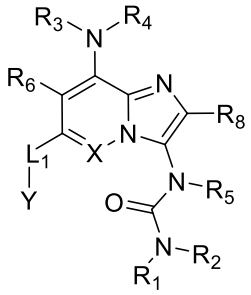
each R_{11} is independently selected from C_1-C_6alkyl and C_1-C_6heteroalkyl;

each R_{12} is independently selected from hydrogen, C_1-C_6alkyl, and C_1-C_6haloalkyl; and

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

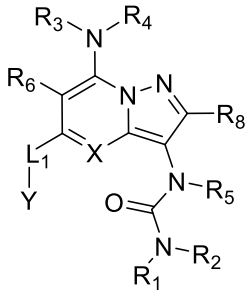
or a pharmaceutically acceptable salt or solvate thereof.

[0006] In some examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



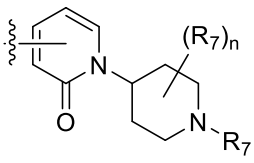
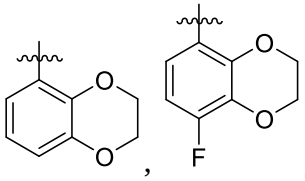
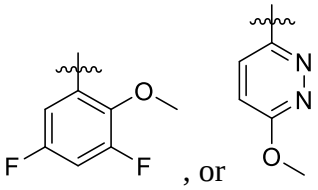
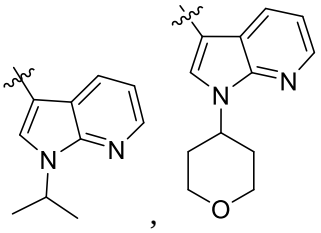
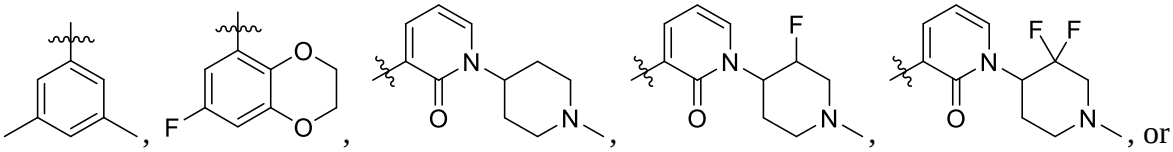
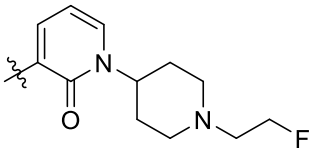
Formula (I).

[0007] In some examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



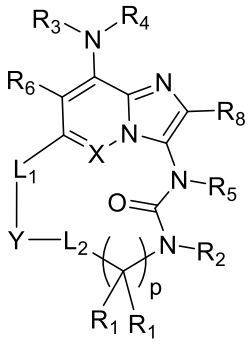
Formula (II).

[0008] In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is C_6-C_{10}aryl optionally substituted with 1, 2, or 3 R_7. In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is phenyl optionally substituted with 1, 2, or 3 R_7. In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is C_2-C_9heteroaryl optionally substituted with 1, 2, or 3 R_7. In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is C_2-C_9heteroaryl selected from oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl,

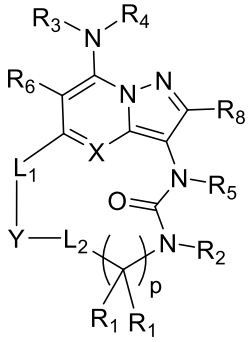
wherein oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl are optionally substituted with 1, 2, or 3 R_7. In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is . In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0, 1, or 2. In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_7 is independently selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_1-C_6alkoxy. In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is , , or . In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is , , or . In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is hydrogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_3-C_6cycloalkyl, -C_1-C_6alkyl-C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, and C_2-C_9heteroaryl, wherein C_1-C_6alkyl, C_3-C_6cycloalkyl, -C_1-C_6alkyl-C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, or C_2-C_9heteroaryl are optionally substituted by 1, 2, or 3 R_7. In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is hydrogen. In some examples is a compound of Formula (I) or (II), or a

pharmaceutically acceptable salt or solvate thereof, wherein R_1 is C_1-C_6alkyl optionally substituted by 1, 2, or 3 R_7. In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is unsubstituted C_1-C_6alkyl. In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is C_3-C_6cycloalkyl optionally substituted by 1, 2, or 3 R_7. In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is unsubstituted C_3-C_6cycloalkyl. In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is C_2-C_9heterocycloalkyl optionally substituted by 1, 2, or 3 R_7. In some examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is C_2-C_9heteroaryl optionally substituted by 1, 2, or 3 R_7.

[0009] In another example, provided herein are compounds of Formula (III) or Formula (IV):



Formula (III);



Formula (IV);

wherein:

X is N or C(R_6);

Y is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, or C_2-C_9heteroaryl, wherein C_1-C_6alkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, or C_2-C_9heteroaryl are optionally substituted by 1, 2, 3, or 4 R_7;

L_1 is a bond, -O-, -C(O)-, -N(R_9)-, -N(R_9)CH_2-, or -CH_2N(R_9)-;

L_2 is a bond, -N(R_9)-, -O-, C_1-C_6alkyl, or C_3-C_6cycloalkyl;

each R_1 is independently selected from deuterium, halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, oxo, $-OR_{10}$, $-N(R_{10})_2$, -CN, $-C(=O)R_{11}$, $-C(=O)OR_{10}$, $-C(=O)N(R_{10})_2$, $-NR_{10}C(=O)R_{11}$, $-NR_{10}S(=O)_2R_{11}$, $-S(=O)_2R_{11}$, and $-S(=O)_2N(R_{10})_2$; or two R_1 are combined to form a 3-, 4-, 5-, or 6-membered cycloalkyl ring or a 3-, 4-, 5-, or 6-membered heterocycloalkyl ring;

R_2, R_3, and R_4 are independently selected from hydrogen, deuterium, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, and C_2-C_9heterocycloalkyl;

R_5 is hydrogen or C_1-C_6alkyl;

each R_6 is independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

each R_7 is independently selected from deuterium, halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl, oxo, $-OR_{10}$, $-N(R_{10})_2$, -CN, $-C(=O)R_{11}$, $-C(=O)OR_{10}$, $-C(=O)N(R_{10})_2$, $-NR_{10}C(=O)R_{11}$, $-NR_{10}S(=O)_2R_{11}$, $-S(=O)_2R_{11}$, and $-S(=O)_2N(R_{10})_2$, wherein C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl are optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, $-OR_{12}$, $-N(R_{12})_2$, $-C(=O)OR_{12}$, and $-C(=O)N(R_{12})_2$; or two R_7 are combined to form a 5-, 6-, or 7-membered heterocycloalkyl ring or a 4-, 5-, or 6-membered cycloalkyl ring;

R_8 is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6deuteroalkyl;

R_9 is hydrogen or C_1-C_6alkyl;

each R_{10} is independently selected from hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, and phenyl, wherein phenyl is optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, $-OR_{12}$, $-N(R_{12})_2$, $-C(=O)OR_{12}$, and $-C(=O)N(R_{12})_2$;

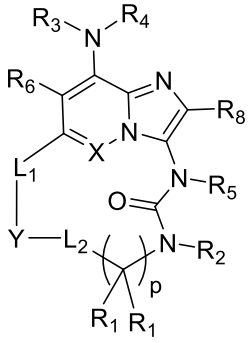
each R_{11} is independently selected from C_1-C_6alkyl and C_1-C_6heteroalkyl;

each R_{12} is independently selected from hydrogen, C_1-C_6alkyl, and C_1-C_6haloalkyl; and

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

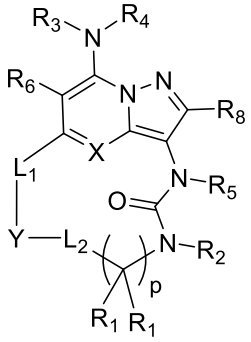
or a pharmaceutically acceptable salt or solvate thereof.

[0010] In some examples is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof:

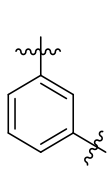
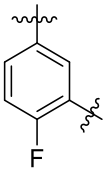
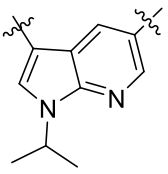


Formula (III).

[0011] In some examples is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV).

[0012] In some examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is C_6-C_{10}aryl optionally substituted with 1, 2, or 3 R_7. In some examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is phenyl optionally substituted with 1, 2, or 3 R_7. In some examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is C_2-C_9heteroaryl optionally substituted with 1, 2, or 3 R_7. In some examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_1-C_6alkoxy. In some examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is selected from , , and . In some examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_1 is hydrogen. In some examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein p is 1. In some examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein p is 2. In some examples is a compound of Formula (III) or (IV), or a

pharmaceutically acceptable salt or solvate thereof, wherein p is 0. In some examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein L_2 is a bond. In some examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein L_2 is -O-. In some examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein L_2 is C_1-C_6alkyl. In some examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein L_2 is C_3-C_6cycloalkyl.

[0013] In some examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein L_1 is a bond. In some examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein L_1 is -N(H)-. In some examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 and R_4 are independently selected from hydrogen and C_1-C_6alkyl. In some examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen and R_4 is C_1-C_6alkyl. In some examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen and R_4 is C_1-C_6deuteroalkyl. In some examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is hydrogen. In some examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_8 is hydrogen. In some examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen. In some examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen. In some examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein X is N. In some examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein X is C(R_6). In some examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein X is C(H).

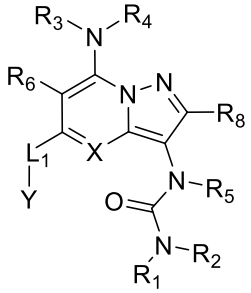
[0014] In another example described herein is a pharmaceutical composition comprising a compound of Formula (I'), (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0015] In another example described herein is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I'), (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof. In some examples is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a

CLAIMS

WHAT IS CLAIMED IS:

1. A compound having the structure of Formula (I'):

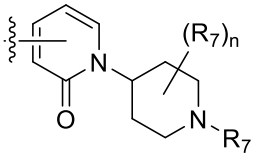


Formula (I');

wherein:

X is N or C(R_6);

Y is C_1-C_6alkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl, or



, wherein C_1-C_6alkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, or C_2-C_9heteroaryl are optionally substituted by 1, 2, 3, or 4 R_7;

L_1 is a bond, -O-, -C(O)-, -N(R_9)-, -N(R_9)CH_2-, or -CH_2N(R_9)-;

R_1 is C_3-C_6cycloalkyl substituted by 1, 2, or 3 R_{13};

R_2, R_3, and R_4 are independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

R_5 is hydrogen or C_1-C_6alkyl;

each R_6 is independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

each R_7 is independently selected from deuterium, halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl, oxo, -OR_{10}, -N(R_{10})$_2$, -CN, -C(=O)R_{11}, -C(=O)OR_{10}, -C(=O)N(R_{10})$_2$, -NR_{10}C(=O)R_{11}, -NR_{10}S(=O)$_2R_{11}$, -S(=O)$_2R_{11}$, and -S(=O)$_2$N(R_{10})$_2$, wherein C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl are optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, -OR_{12}, -N(R_{12})$_2$, -C(=O)OR_{12}, and -C(=O)N(R_{12})$_2$; or two R_7 are combined to form a 5-, 6-, or 7-membered heterocycloalkyl ring or a 4-, 5-, or 6-membered cycloalkyl ring;

R_8 is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6deuteroalkyl;

R_9 is hydrogen or C_1-C_6alkyl;

each R_{10} is independently selected from hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, and phenyl, wherein phenyl is optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, $-OR_{12}$, $-N(R_{12})_2$, $-C(=O)OR_{12}$, and $-C(=O)N(R_{12})_2$;

each R_{11} is independently selected from C_1-C_6alkyl and C_1-C_6heteroalkyl;

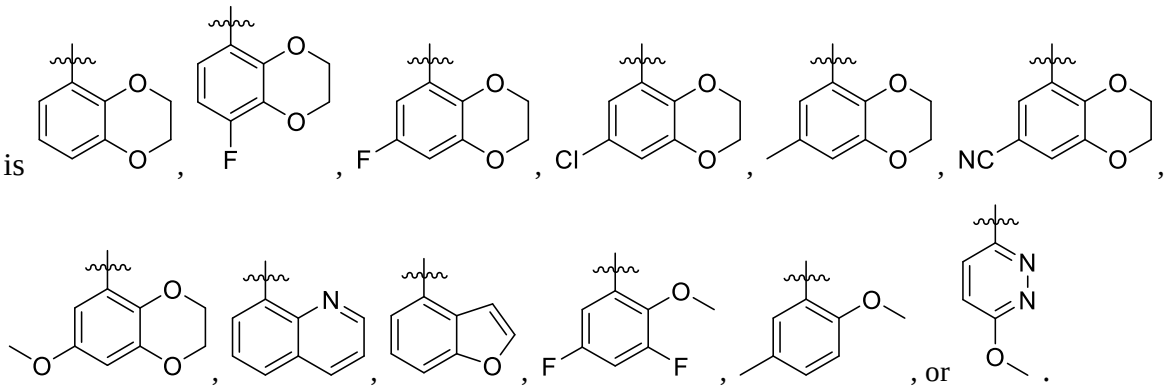
each R_{12} is independently selected from hydrogen, C_1-C_6alkyl, and C_1-C_6haloalkyl;

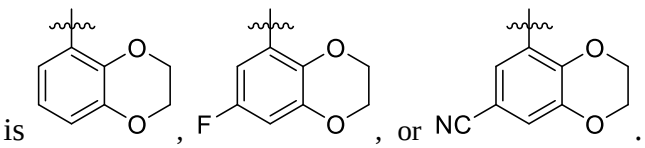
each R_{13} is independently selected from halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl, oxo, $-OR_{10}$, $-N(R_{10})_2$, -CN, $-C(=O)R_{11}$, $-C(=O)OR_{10}$, $-C(=O)N(R_{10})_2$, $-NR_{10}C(=O)R_{11}$, $-NR_{10}S(=O)_2R_{11}$, $-S(=O)_2R_{11}$, and $-S(=O)_2N(R_{10})_2$, wherein C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl are optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, $-OR_{12}$, $-N(R_{12})_2$, $-C(=O)OR_{12}$, and $-C(=O)N(R_{12})_2$; and

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

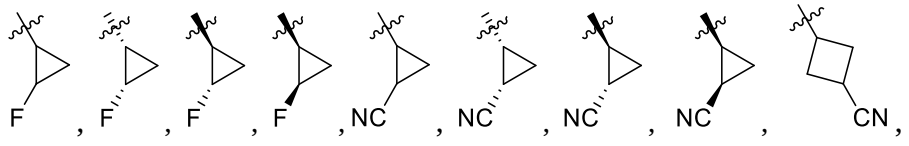
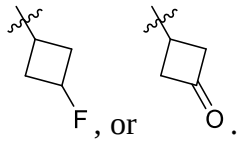
or a pharmaceutically acceptable salt or solvate thereof.

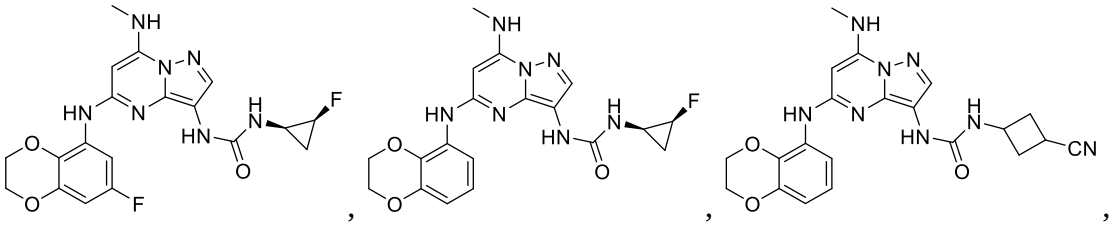
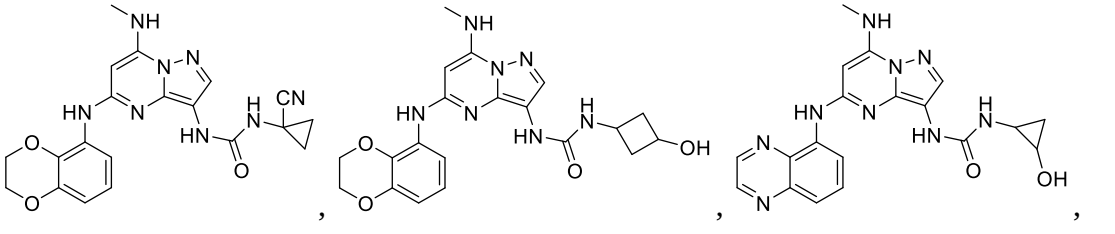
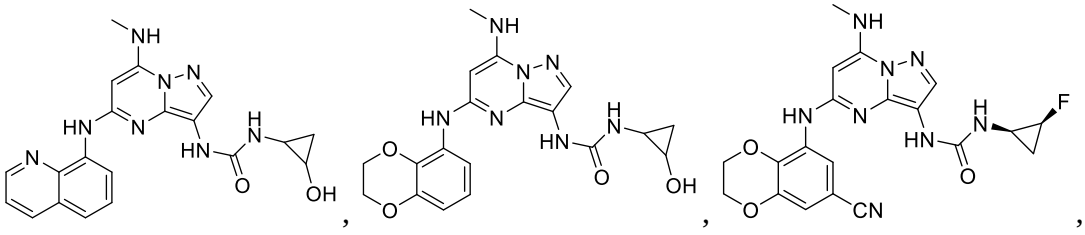
2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is phenyl optionally substituted with 1, 2, or 3 R_7.

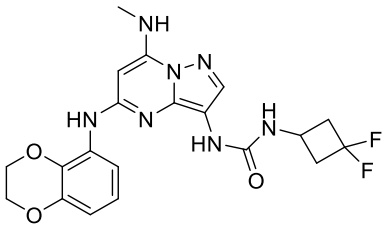
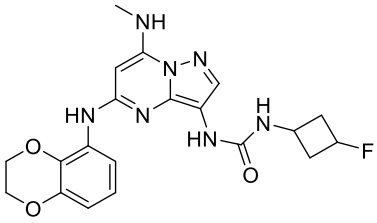
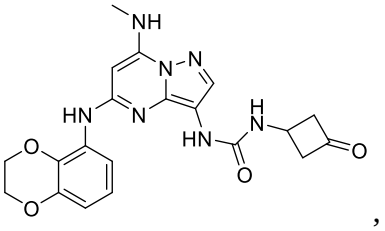
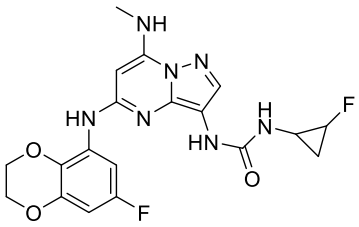
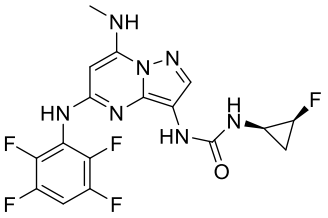
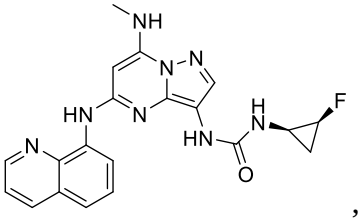
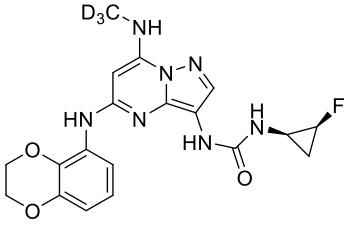
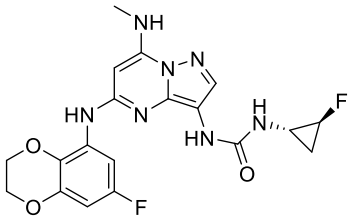
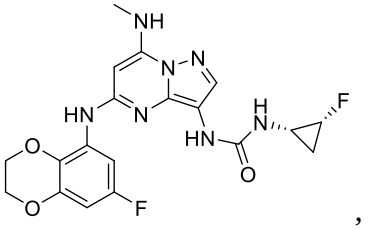
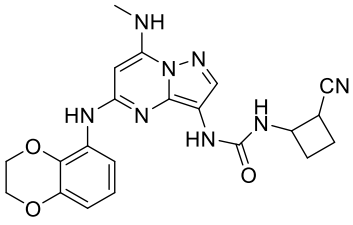
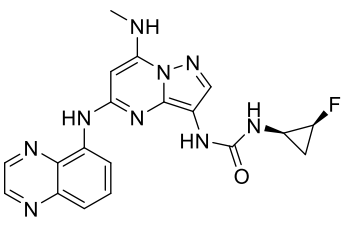
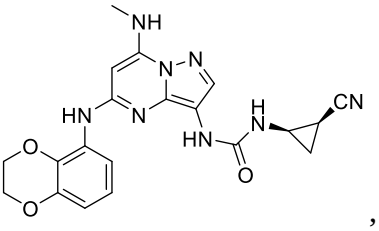
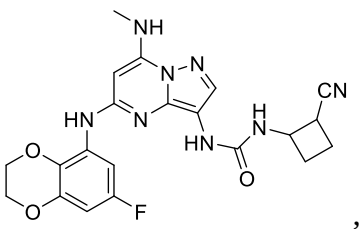
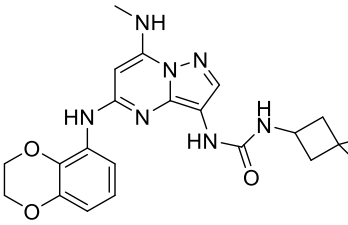
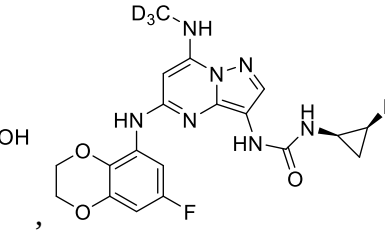
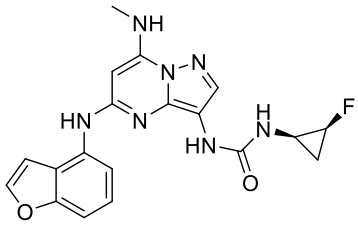
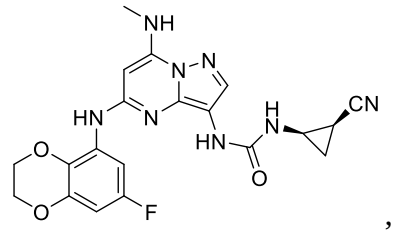
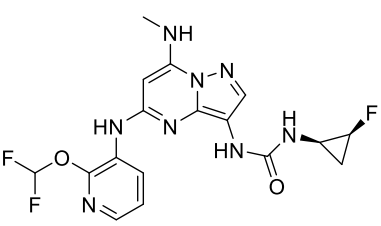
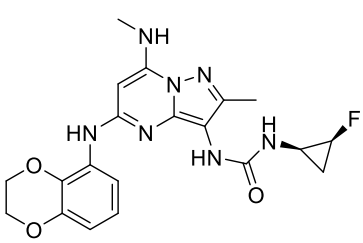
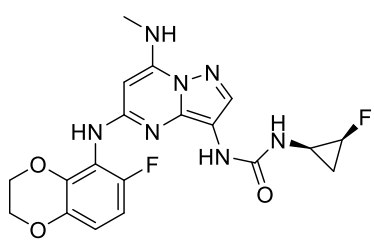
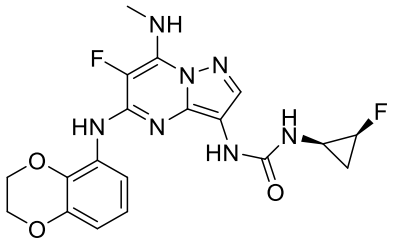
3. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is .

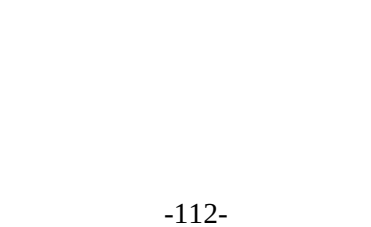
4. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is .

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein each R_{13} is independently selected from halogen, -OH, -CN, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, and oxo.

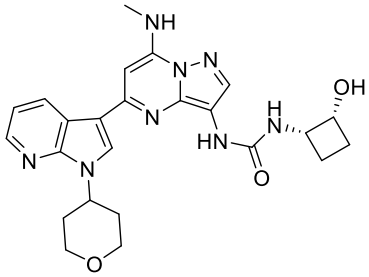
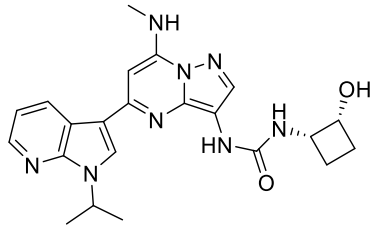
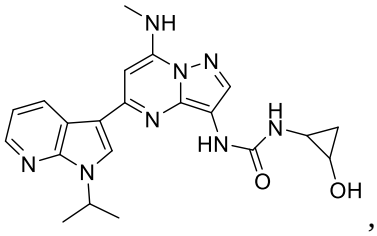
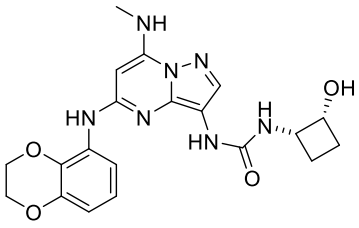
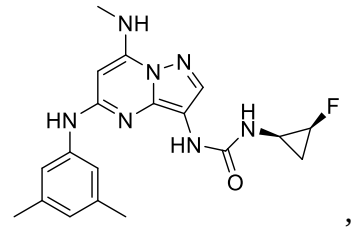
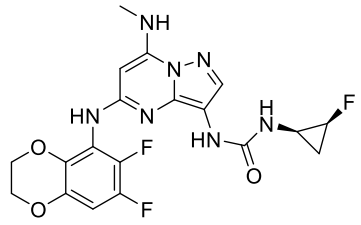
6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt or solvate thereof, wherein each R_{13} is independently selected from halogen, -OH, and -CN.
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is cyclopropyl substituted by 1 R_{13}.
8. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is , .
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein L_1 is -N(H)-.
10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 and R_4 are independently selected from hydrogen and C_1-C_6alkyl.
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen and R_4 is C_1-C_6alkyl.
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is hydrogen, R_5 is hydrogen, R_6 is hydrogen, and R_8 is hydrogen.
13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt or solvate thereof, wherein X is N.
14. The compound of claim 1, selected from:


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pharmaceutically acceptable salt or solvate thereof.

15. A pharmaceutical composition comprising a compound of any one of claims 1-14, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.
16. Use of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating an inflammatory or autoimmune disease in a patient.
17. The use of claim 16, wherein the disease is selected from rheumatoid arthritis, multiple sclerosis, psoriasis, lupus, intestinal bowel disease, Crohn's disease, ulcerative colitis, ankylosing spondylitis, vitiligo, and atopic dermatitis.
18. A compound of any one of claims 1-14, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.