TYK2 PSEUDOKINASE LIGANDS

CROSS-REFERENCE

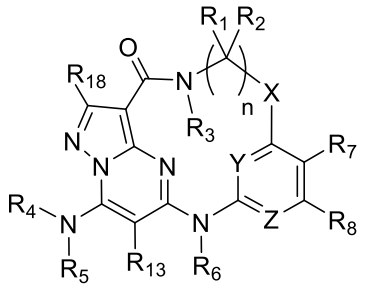
[0001] This application claims benefit of U.S. Provisional Application No. 62/824,144, filed on March 26, 2019, which is herein incorporated by reference in its entirety.

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 ~~OF THE INVENTION~~

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



Formula (III);

wherein:

X is -O- or -C(R_9)(R_{10})-;

Y is =N- or =C(R_{15})-;

Z is =N- or =C(R_{16})-;

each R_1 is independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

each R_2 is independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

R_3 is hydrogen or C_1-C_6alkyl;

R_4 is 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 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_{13} is hydrogen, deuterium, C_1-C_6alkyl, or C_1-C_6deuteroalkyl; or R_5 and R_{13} together with the atoms to which they are attached are combined to form a 5- or 6-membered heterocycloalkyl ring or a 5- or 6-membered heteroaryl ring, wherein the 5- or 6-membered heterocycloalkyl ring or 5- or 6-membered heteroaryl ring is optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and C_1-C_6haloalkoxy;

R_6 is hydrogen or C_1-C_6alkyl;

R_7 and R_8 are independently selected from hydrogen, deuterium, halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, -C_1-C_6alkyl-OH, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, C_6-C_{10}aryl, -OR_{11}, -$N(R_{11})_2$, -CN, -$C(=O)R_{12}$, -$C(=O)OR_{11}$, -$C(=O)N(R_{11})_2$, -$NR_{11}C(=O)R_{12}$, -$NR_{11}S(=O)_2R_{12}$, -$S(=O)_2R_{12}$, and -$S(=O)_2N(R_{11})_2$, wherein C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, or C_6-C_{10}aryl are optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and C_1-C_6haloalkoxy;

R_9 and R_{10} are independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

each R_{11} 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_{14}, -$N(R_{14})_2$, -$C(=O)OR_{14}$, and -$C(=O)N(R_{14})_2$;

each R_{12} is independently selected from C_1-C_6alkyl and C_1-C_6heteroalkyl;

each R_{14} is independently selected from hydrogen, C_1-C_6alkyl, and C_1-C_6haloalkyl;

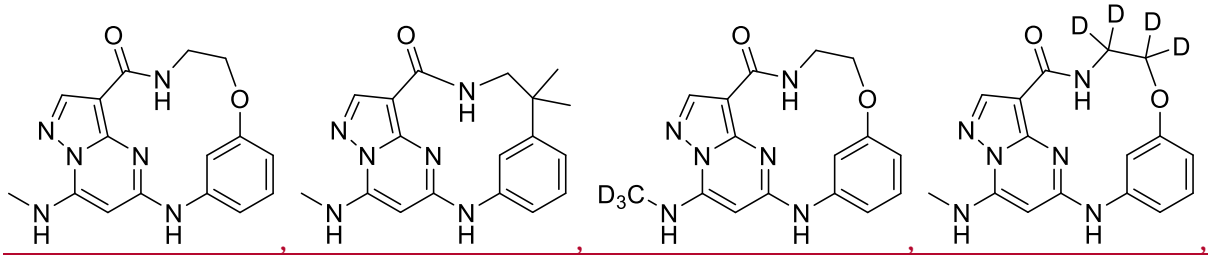
R_{15} and R_{16} are independently selected from hydrogen, deuterium, halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6heteroalkyl, -OR_{11}, -$N(R_{11})_2$, -CN, -$C(=O)R_{12}$, -$C(=O)OR_{11}$, -$C(=O)N(R_{11})_2$, -$NR_{11}C(=O)R_{12}$, -$NR_{11}S(=O)_2R_{12}$, -$S(=O)_2R_{12}$, and -$S(=O)_2N(R_{11})_2$;

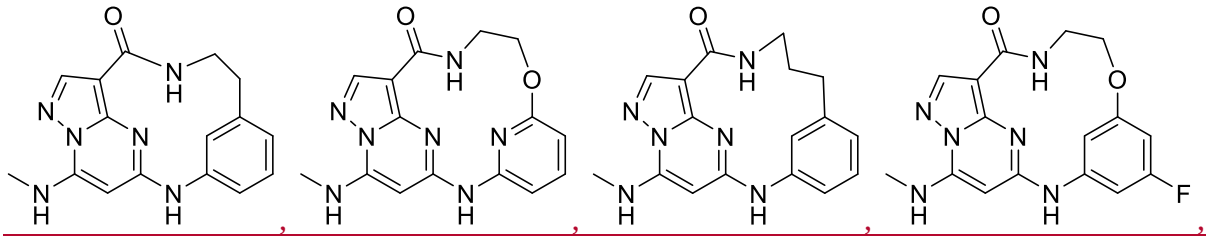
R_{18} is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6deuteroalkyl; and

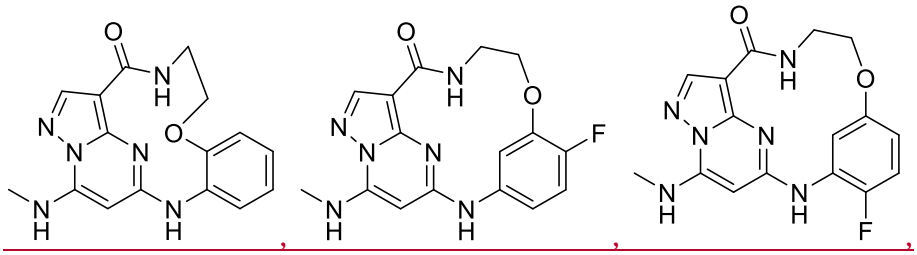
n is 1, 2, 3, or 4;

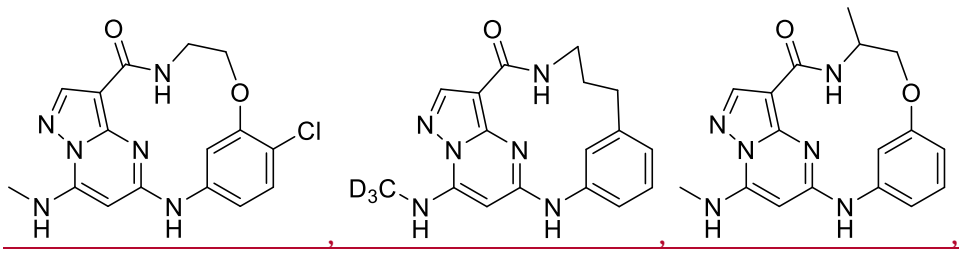
or a pharmaceutically acceptable salt or solvate thereof.

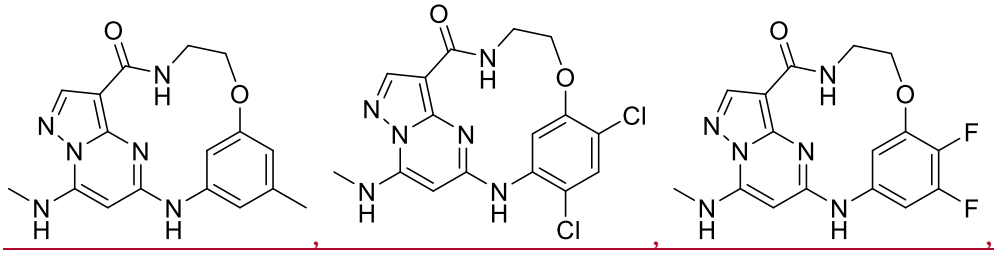
[0002b] In another aspect of the present disclosure, there is provided a compound selected from:

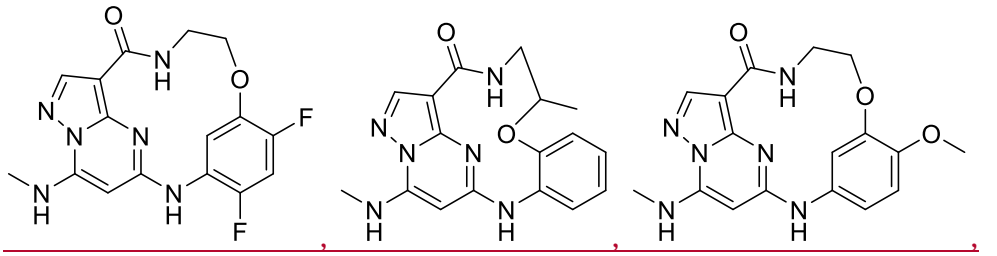


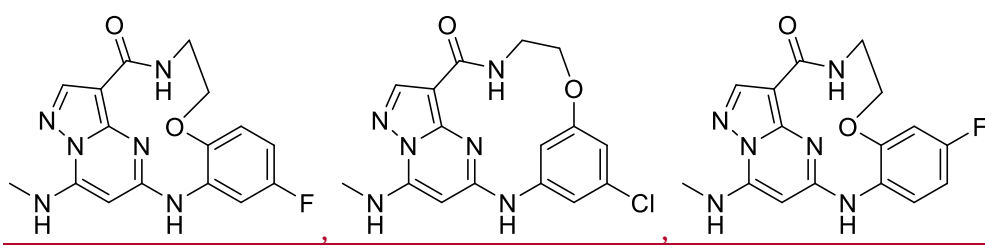




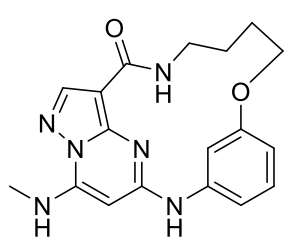
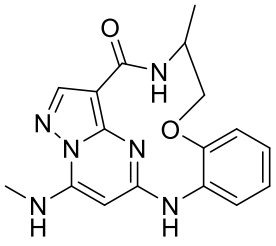
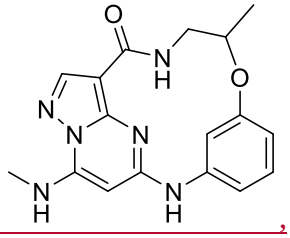


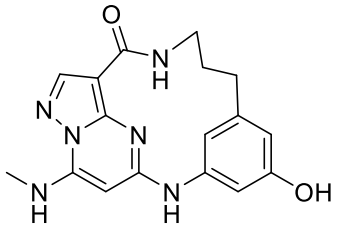
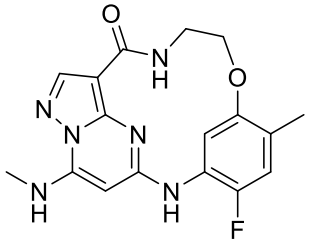
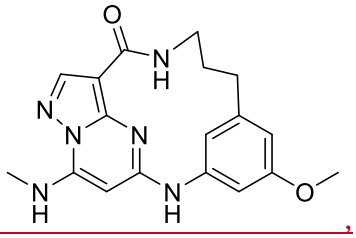


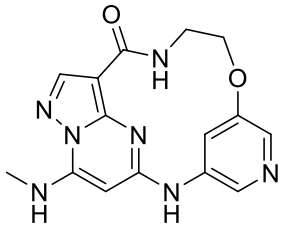
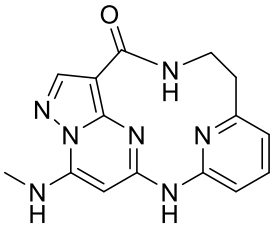
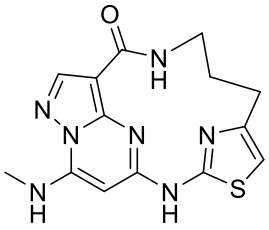
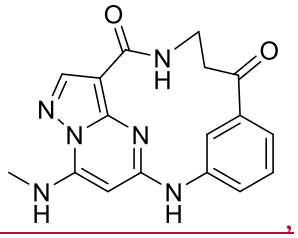


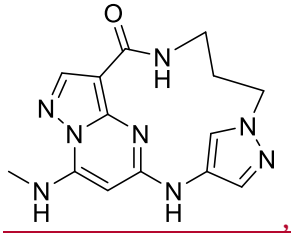
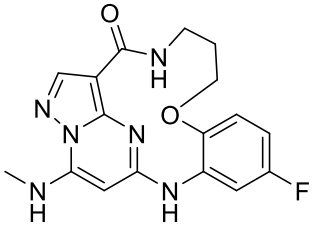
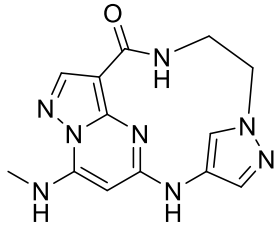


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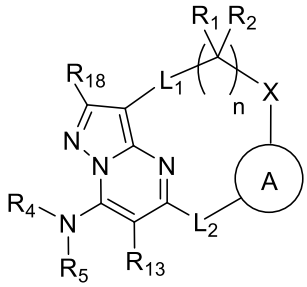
, , and ; or a pharmaceutically acceptable salt or solvate thereof.

[0002c] In a further 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.

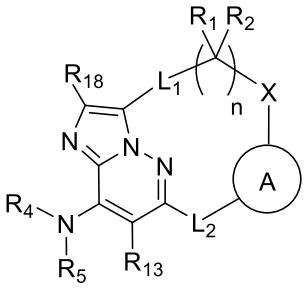
[0002d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating an inflammatory or autoimmune disease in a patient in need thereof.

[0002e] In a further 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 ~~aspect~~example, provided herein are compounds of Formula (I) or Formula (II):



Formula (I);



Formula (II);

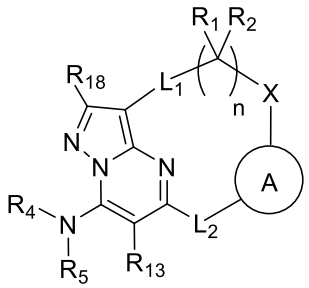
wherein:

A is C_3-C_6cycloalkyl, C_6-C_{10}aryl, C_2-C_9heterocycloalkyl, or C_2-C_9heteroaryl, wherein C_3-C_6cycloalkyl, C_6-C_{10}aryl, C_2-C_9heterocycloalkyl, or C_2-C_9heteroaryl is optionally substituted with 1, 2, 3, or 4 R_7;

n is 1, 2, 3, or 4;

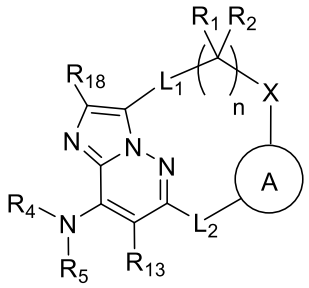
or a pharmaceutically acceptable salt or solvate thereof.

[0004] In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I).

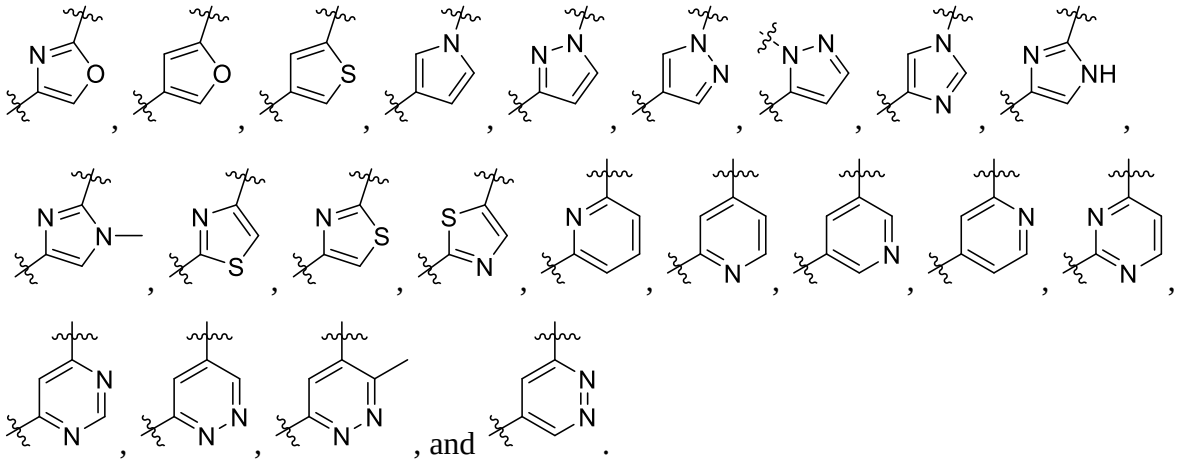
[0005] In some ~~embodiment~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



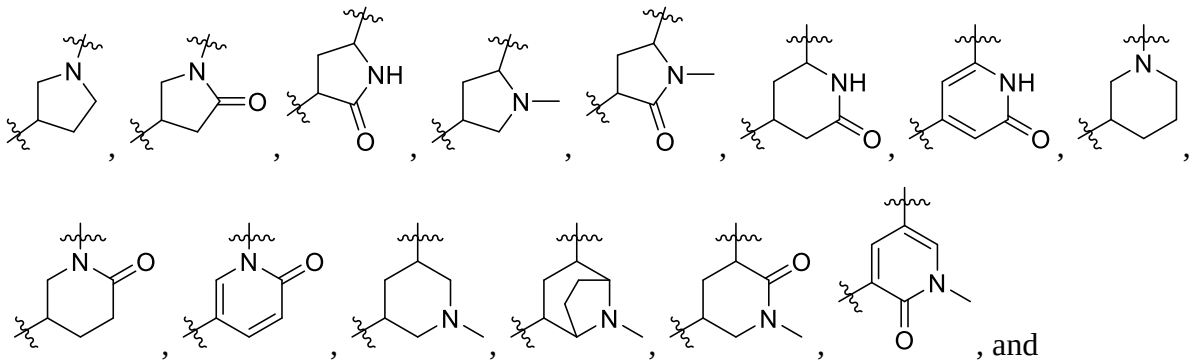
Formula (II).

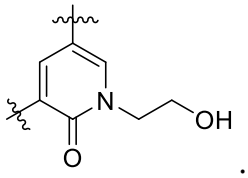
[0006] In some ~~embodiment~~examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein  is C_6-C_{10}aryl optionally substituted with 1, 2, or 3 R_7. In some ~~embodiment~~examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein  is phenyl optionally substituted with 1, 2, or 3 R_7. In some ~~embodiment~~examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein  is C_2-C_9heteroaryl optionally substituted with 1, 2, or 3 R_7. In some ~~embodiment~~examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein  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 ~~embodiment~~examples is a compound of Formula (I) or (II), or a

pharmaceutically acceptable salt or solvate thereof, wherein R_7 is selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and -CN. In some ~~embodiment~~examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein  is C_2-C_9heteroaryl selected from:



[0007] In some ~~embodiment~~examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein  is C_2-C_9heterocycloalkyl optionally substituted with 1, 2, or 3 R_7. In some ~~embodiment~~examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein  is C_3-C_6cycloalkyl optionally substituted with 1, 2, 3, or 4 R_7. In some ~~embodiment~~examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and oxo. In some ~~embodiment~~examples is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein  is C_2-C_9heterocycloalkyl selected from:

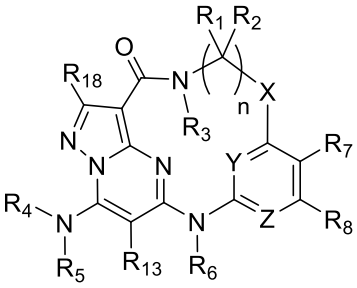




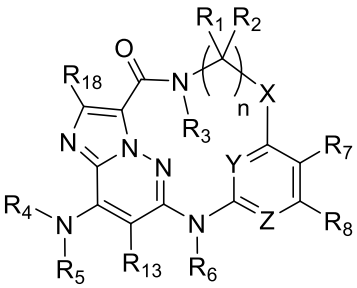
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[0008] In some ~~embodiment~~example is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein L_1 is -C(O)N(R_3)-. In some ~~embodiment~~example is a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or solvate thereof, wherein L_2 is -N(R_6)-.

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



Formula (III);



Formula (IV);

wherein:

X is -O- or -C(R_9)(R_{10})-;

Y is =N- or =C(R_{15})-;

Z is =N- or =C(R_{16})-;

each R_1 is independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

each R_2 is independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

R_3 is hydrogen or C_1-C_6alkyl;

R_4 is 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 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_{13} is hydrogen, deuterium, C_1-C_6alkyl, or C_1-C_6deuteroalkyl; or R_5 and R_{13} together with the atoms to which they are attached are combined to form a 5- or 6-membered heterocycloalkyl ring or a 5- or 6-membered heteroaryl ring, wherein the 5- or 6-membered heterocycloalkyl ring or 5- or 6-membered heteroaryl ring is optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and C_1-C_6haloalkoxy;

R_6 is hydrogen or C_1-C_6alkyl;

R_7 and R_8 are independently selected from hydrogen, deuterium, halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, -C_1-C_6alkyl-OH, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, C_6-C_{10}aryl, -OR_{11}, -$N(R_{11})_2$, -CN, -$C(=O)R_{12}$, -$C(=O)OR_{11}$, -$C(=O)N(R_{11})_2$, -$NR_{11}C(=O)R_{12}$, -$NR_{11}S(=O)_2R_{12}$, -$S(=O)_2R_{12}$, and -$S(=O)_2N(R_{11})_2$, wherein C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, or C_6-C_{10}aryl are optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and C_1-C_6haloalkoxy;

R_9 and R_{10} are independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

each R_{11} 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_{14}, -$N(R_{14})_2$, -$C(=O)OR_{14}$, and -$C(=O)N(R_{14})_2$;

each R_{12} is independently selected from C_1-C_6alkyl and C_1-C_6heteroalkyl;

each R_{14} is independently selected from hydrogen, C_1-C_6alkyl, and C_1-C_6haloalkyl;

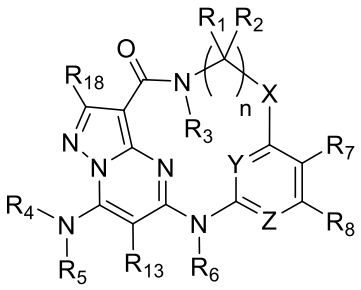
R_{15} and R_{16} are independently selected from hydrogen, deuterium, halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6heteroalkyl, -OR_{11}, -$N(R_{11})_2$, -CN, -$C(=O)R_{12}$, -$C(=O)OR_{11}$, -$C(=O)N(R_{11})_2$, -$NR_{11}C(=O)R_{12}$, -$NR_{11}S(=O)_2R_{12}$, -$S(=O)_2R_{12}$, and -$S(=O)_2N(R_{11})_2$;

R_{18} is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6deuteroalkyl; and

n is 1, 2, 3, or 4;

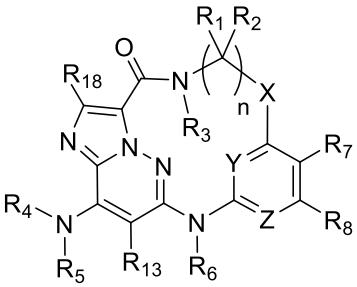
or a pharmaceutically acceptable salt or solvate thereof.

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



Formula (III).

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



Formula (IV).

[0012] In some ~~embodiment~~examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is $=C(R_{15})-$ and Z is $=C(R_{16})-$. In some ~~embodiment~~examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is =N- and Z is $=C(R_{16})-$. In some ~~embodiment~~examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{16} is selected from hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and -CN. In some ~~embodiment~~examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{16} is selected from hydrogen, halogen, or C_1-C_6alkyl. In some ~~embodiment~~examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is $=C(R_{15})-$ and Z is =N-. In some ~~embodiment~~examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{15} is selected from hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and -CN. In some ~~embodiment~~examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{15} is selected from hydrogen, halogen, or C_1-C_6alkyl. In some ~~embodiment~~examples is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein Y is =N- and Z is =N-.

[0013] In some ~~embodiment~~examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein X is -O-. In some ~~embodiment~~examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein X is $-C(R_9)(R_{10})-$. In some ~~embodiment~~examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_9 and R_{10} are hydrogen. In some ~~embodiment~~examples is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are independently selected from hydrogen, halogen, C_1-C_6alkyl, - C_1-C_6haloalkyl, C_1-C_6alkoxy, C_2-C_9heteroaryl, $-OR_{11}$, $-N(R_{11})_2$, -CN, $-C(=O)OR_{11}$, $-C(=O)N(R_{11})_2$, $-NR_{11}C(=O)R_{12}$, $-NR_{11}S(=O)_2R_{12}$, $-S(=O)_2R_{12}$, and $-S(=O)_2N(R_{11})_2$, wherein C_2-C_9heteroaryl is optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-

C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and C_1-C_6haloalkoxy. In some ~~embodiment~~example is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are independently selected from hydrogen, halogen, C_1-C_6alkyl, - C_1-C_6haloalkyl, C_2-C_9heteroaryl, -OR_{11}, -CN, -$C(=O)N(R_{11})_2$, -$NR_{11}S(=O)_2R_{12}$, wherein C_2-C_9heteroaryl is optionally substituted with 1 or 2 groups selected from halogen or C_1-C_6alkyl. In some ~~embodiment~~example is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are independently selected from hydrogen, halogen, and C_1-C_6alkyl. In some ~~embodiment~~example is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 and R_5 are independently selected from hydrogen and C_1-C_6alkyl. In some ~~embodiment~~example is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 is hydrogen and R_5 is C_1-C_6alkyl. In some ~~embodiment~~example is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_3 is hydrogen. In some ~~embodiment~~example 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 ~~embodiment~~example is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some ~~embodiment~~example is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some ~~embodiment~~example is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 3. In some ~~embodiment~~example is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is hydrogen. In some ~~embodiment~~example 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 ~~embodiment~~example is a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{18} is hydrogen.

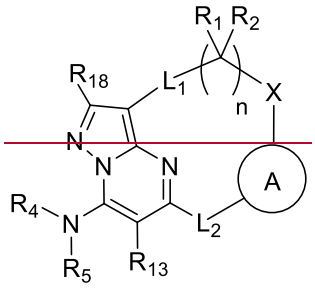
[0014] In another ~~aspect~~example described herein is a pharmaceutical composition comprising a compound of Formula (I), (II), (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0015] In another ~~aspect~~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), (II), (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof. In some ~~embodiment~~example 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), (II), (III) or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease is selected from rheumatoid

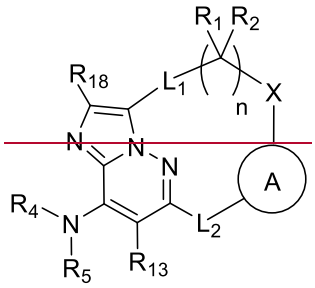
CLAIMS

WHAT IS CLAIMED IS:

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



Formula (I);



Formula (II);

wherein:

A is C_3-C_6cycloalkyl, C_6-C_{10}aryl, C_2-C_9heterocycloalkyl, or C_2-C_9heteroaryl, wherein C_3-C_6cycloalkyl, C_6-C_{10}aryl, C_2-C_9heterocycloalkyl, or C_2-C_9heteroaryl is optionally substituted with 1, 2, 3, or 4 R_7;

X is -O-, $-C(R_9)(R_{10})$-, $-C(R_9)(R_{10})$-O-, -O-$C(R_9)(R_{10})$-, -C(O)-, -C(O)$N(R_3)$-, $-N(R_3)C(O)$-, or $-N(R_{17})$-;

L_1 is $-C(O)N(R_3)$-, $-N(R_3)C(O)$-, $-C(R_9)(R_{10})$-O-, or -O-$C(R_9)(R_{10})$-;

L_2 is $-N(R_6)$-, $-N(R_6)CH_2$-, or $-CH_2N(R_6)$-;

each R_1 is independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

each R_2 is independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl; or R_1 and R_2 are combined to form a 3-, 4-, 5-, or 6-membered cycloalkyl ring or a 4-, 5-, or 6-membered heterocycloalkyl ring;

each R_3 is independently hydrogen or C_1-C_6alkyl; or R_2 and R_3 together with the atoms to which they are attached are combined to form a 5- or 6-membered heterocycloalkyl ring optionally substituted 1, 2, or 3 with groups selected from halogen, -OH, C_1-C_6alkyl, and -C_1-C_6alkyl-OH;

R_4 is 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 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_{13} is hydrogen, deuterium, C_1-C_6alkyl, or C_1-C_6deuteroalkyl; or R_5 and R_{13} together with the atoms to which they are attached are combined to form a 5- or 6-membered heterocycloalkyl ring or a 5- or 6-membered heteroaryl ring, wherein the 5- or 6-membered heterocycloalkyl ring or 5- or 6-membered heteroaryl ring is optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and C_1-C_6haloalkoxy;

R_6 is hydrogen or C_1-C_6alkyl;

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_6heteroalkyl, oxo, $-OR_{11}$, $-N(R_{11})_2$, $-CN$, $-C(=O)R_{12}$, $-C(=O)OR_{11}$, $-C(=O)N(R_{11})_2$, $-NR_{11}C(=O)R_{12}$, $-NR_{11}S(=O)_2R_{12}$, $-S(=O)_2R_{12}$, and $-S(=O)_2N(R_{11})_2$;

each R_9 and each R_{10} are independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

each R_{11} 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, $-OR_{14}$, $-N(R_{14})_2$, $-C(=O)OR_{14}$, and $-C(=O)N(R_{14})_2$;

each R_{12} is independently selected from C_1-C_6alkyl and C_1-C_6heteroalkyl;

each R_{14} is independently selected from hydrogen, C_1-C_6alkyl, and C_1-C_6haloalkyl;

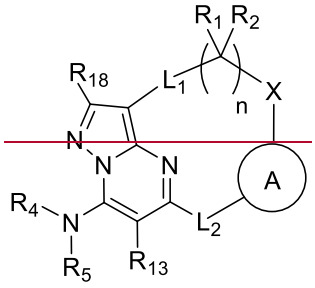
R_{17} is hydrogen or C_1-C_6alkyl;

R_{18} is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6deuteroalkyl; and

n is 1, 2, 3, or 4;

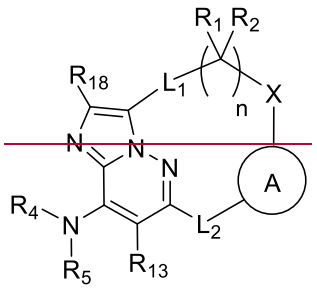
or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (I):



Formula (I).

3. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (II):



Formula (II).

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein  is C_6-C_{10}aryl optionally substituted with 1, 2, or 3 R_7.

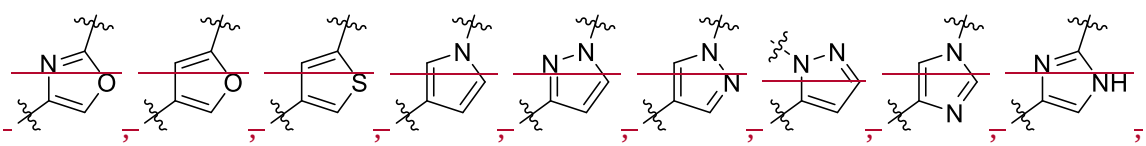
5. The compound of claim 4, or a pharmaceutically acceptable salt or solvate thereof, wherein  is phenyl optionally substituted with 1, 2, or 3 R_7.

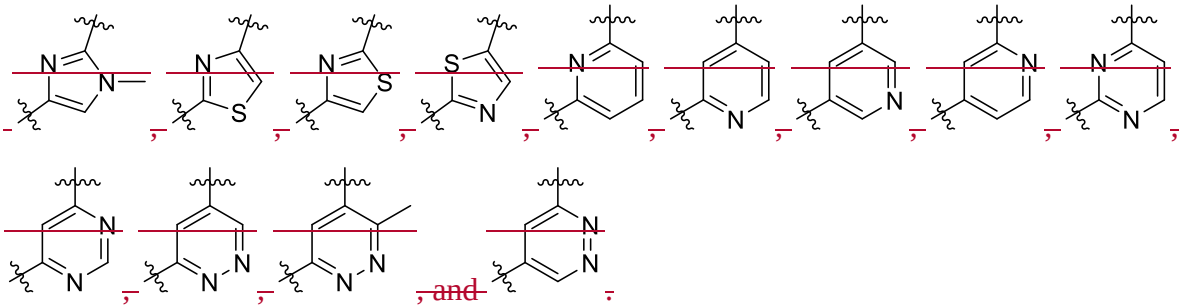
6. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein  is C_2-C_9heteroaryl optionally substituted with 1, 2, or 3 R_7.

7. The compound of claim 6, or a pharmaceutically acceptable salt or solvate thereof, wherein  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.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and -CN.

9. The compound of claim 7, or a pharmaceutically acceptable salt or solvate thereof, wherein  is C_2-C_9heteroaryl selected from:





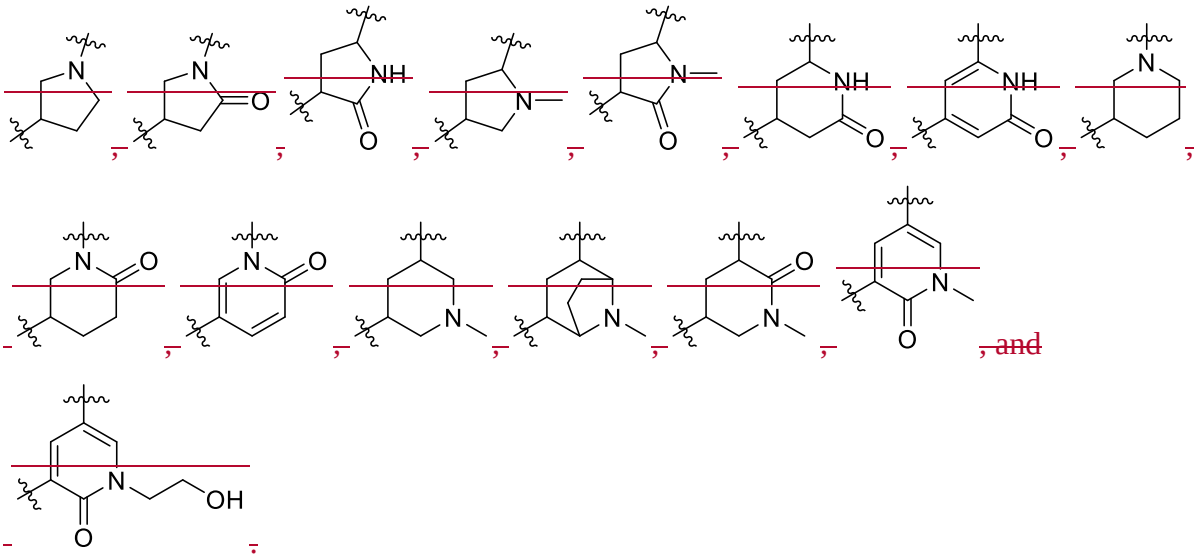
, and .

10. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein  is C_2-C_9heterocycloalkyl optionally substituted with 1, 2, or 3 R_7.

11. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein  is C_3-C_6cycloalkyl optionally substituted with 1, 2, 3, or 4 R_7.

12. The compound of claim 10 or claim 11, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 is selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and oxo.

13. The compound of claim 10, or a pharmaceutically acceptable salt or solvate thereof, wherein  is C_2-C_9heterocycloalkyl selected from:



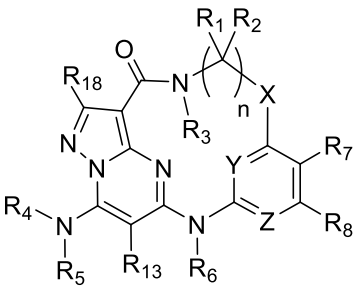
, and

.

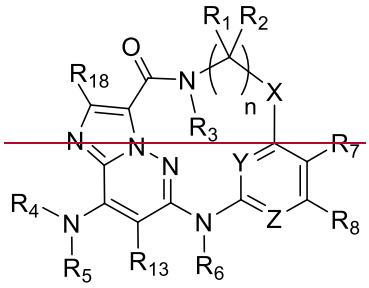
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt or solvate thereof, wherein L_1 is -C(O)N(R_3) .

15. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt or solvate thereof, wherein L_2 is -N(R_6).

16.1. A compound having the structure of Formula (III) or Formula (IV):



Formula (III);



~~Formula (IV);~~

wherein:

X is -O- or -C(R_9)(R_{10})-;

Y is =N- or =C(R_{15})-;

Z is =N- or =C(R_{16})-;

each R_1 is independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

each R_2 is independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

R_3 is hydrogen or C_1-C_6alkyl;

R_4 is 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 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_{13} is hydrogen, deuterium, C_1-C_6alkyl, or C_1-C_6deuteroalkyl; or R_5 and R_{13} together with the atoms to which they are attached are combined to form a 5- or 6-membered heterocycloalkyl ring or a 5- or 6-membered heteroaryl ring, wherein the 5- or 6-membered heterocycloalkyl ring or 5- or 6-membered heteroaryl ring is optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and C_1-C_6haloalkoxy;

R_6 is hydrogen or C_1-C_6alkyl;

R_7 and R_8 are independently selected from hydrogen, deuterium, halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, -C_1-C_6alkyl-OH, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_2-C_9heteroaryl, C_6-C_{10}aryl, -OR_{11}, -$N(R_{11})_2$, -CN, -$C(=O)R_{12}$, -$C(=O)OR_{11}$, -

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

R_9 and R_{10} are independently selected from hydrogen, deuterium, C_1-C_6alkyl, and C_1-C_6deuteroalkyl;

each R_{11} 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, $-OR_{14}$, $-N(R_{14})_2$, $-C(=O)OR_{14}$, and $-C(=O)N(R_{14})_2$;

each R_{12} is independently selected from C_1-C_6alkyl and C_1-C_6heteroalkyl;

each R_{14} is independently selected from hydrogen, C_1-C_6alkyl, and C_1-C_6haloalkyl;

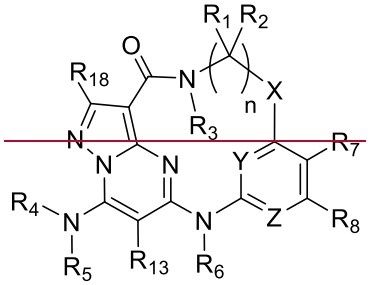
R_{15} and R_{16} are independently selected from hydrogen, deuterium, halogen, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6heteroalkyl, $-OR_{11}$, $-N(R_{11})_2$, $-CN$, $-C(=O)R_{12}$, $-C(=O)OR_{11}$, $-C(=O)N(R_{11})_2$, $-NR_{11}C(=O)R_{12}$, $-NR_{11}S(=O)_2R_{12}$, $-S(=O)_2R_{12}$, and $-S(=O)_2N(R_{11})_2$;

R_{18} is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6deuteroalkyl; and

n is 1, 2, 3, or 4;

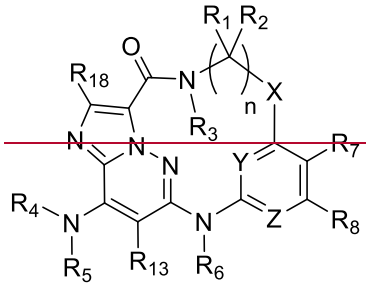
or a pharmaceutically acceptable salt or solvate thereof.

~~17. The compound of claim 16, or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (III):~~



~~Formula (III).~~

~~18. The compound of claim 16, or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (IV):~~



~~Formula (IV).~~

~~19.~~2. The compound of ~~any one of claims 16-18~~claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is =C(R_{15})-; and

Z is =C(R_{16})-.

~~20. The compound of any one of claims 16-18, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is =N- and Z is =C(R_{16})-.~~

~~21. The compound of any one of claims 16-20, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{16} is selected from hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and -CN.~~

~~22.~~3. The compound of ~~any one of claims 16-21~~claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_{16} is selected from hydrogen, halogen, or C_1-C_6alkyl.

~~23. The compound of any one of claims 16-18, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is =C(R_{15})- and Z is =N-.~~

~~24. The compound of any one of claims 16-23, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{15} is selected from hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and -CN.~~

~~25.~~4. The compound of any one of claims ~~16-24~~1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_{15} is selected from hydrogen, halogen, or C_1-C_6alkyl.

~~26. The compound of any one of claims 16-18, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is =N- and Z is =N-.~~

~~27. The compound of any one of claims 16-26, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are independently selected from hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_2-C_9heteroaryl, $-OR_{11}$, $-N(R_{11})_2$, -CN, $-C(=O)OR_{11}$, $-C(=O)N(R_{11})_2$, $-NR_{11}C(=O)R_{12}$, $-NR_{11}S(=O)_2R_{12}$, $-S(=O)_2R_{12}$, and $-S(=O)_2N(R_{11})_2$, wherein C_2-C_9heteroaryl is optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and C_1-C_6haloalkoxy.~~

~~28. The compound of any one of claims 16-27, or a pharmaceutically acceptable salt or solvate thereof, wherein R_7 and R_8 are independently selected from hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_9heteroaryl, $-OR_{11}$, -CN, $-C(=O)N(R_{11})_2$, and $-NR_{11}S(=O)_2R_{12}$, wherein C_2-C_9heteroaryl is optionally substituted with 1 or 2 groups selected from halogen or C_1-C_6alkyl.~~

~~29.~~5. The compound of any one of claims ~~16-28~~1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_7 and R_8 are independently selected from hydrogen, halogen, and C_1-C_6alkyl.

~~30.~~6. The compound of any one of claims 1-~~29~~5, or a pharmaceutically acceptable salt or solvate thereof, wherein:

X is -O-.

~~31.~~7. The compound of any one of claims 1-~~29~~5, or a pharmaceutically acceptable salt or solvate thereof, wherein:

X is -C(R_9)(R_{10})-.

~~32.~~8. The compound of claim ~~31~~7, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_9 and R_{10} are hydrogen.

~~33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt or solvate thereof, wherein R_4 and R_5 are independently selected from hydrogen and C_1-C_6alkyl.~~

~~34.~~9. The compound of any one of claims 1-~~33~~8, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_4 is hydrogen; and

R_5 is C_1-C_6alkyl.

~~35.~~10. The compound of any one of claims 1-~~34~~9, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_3 is hydrogen; and

R_6 is hydrogen.

~~36. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is hydrogen.~~

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

~~38. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2.~~

~~39. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 3.~~

~~40.~~11. The compound of any one of claims 1-~~39~~10, or a pharmaceutically acceptable salt or solvate thereof, wherein:

each R_1 is hydrogen;

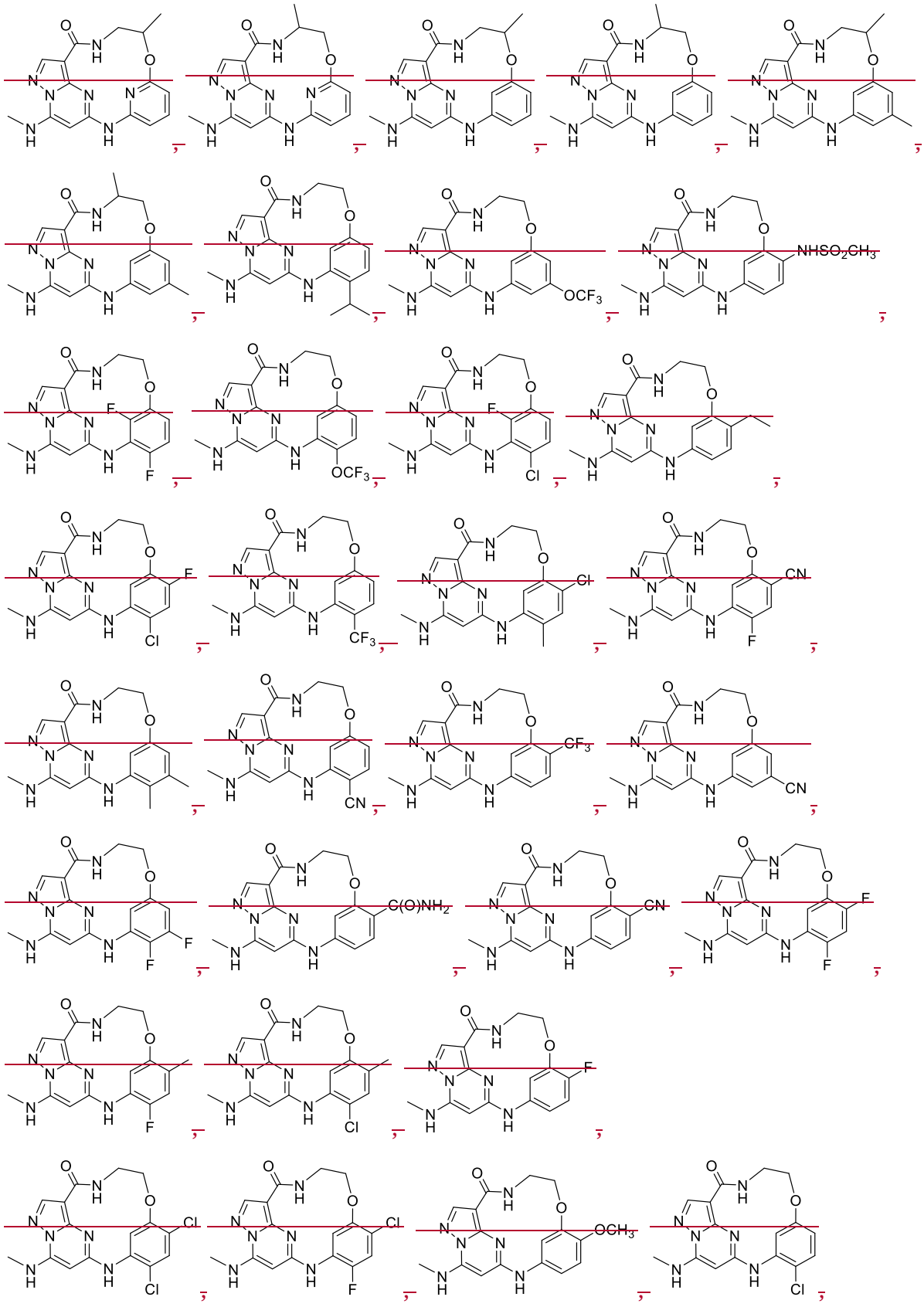
each R_2 is hydrogen; and

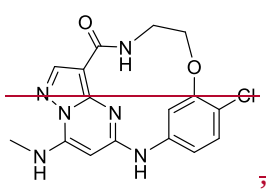
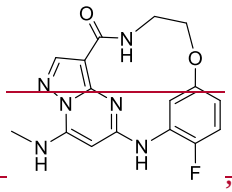
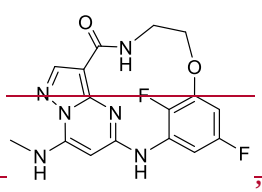
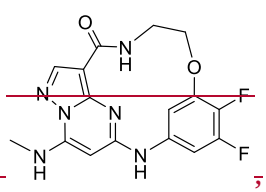
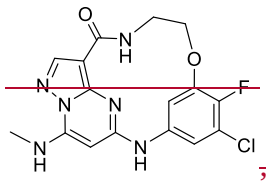
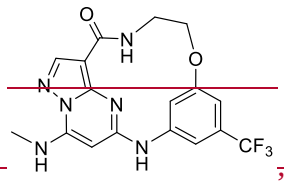
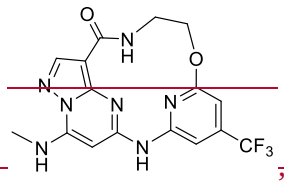
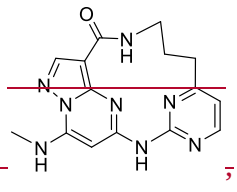
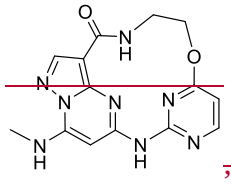
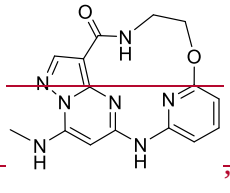
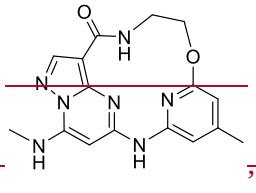
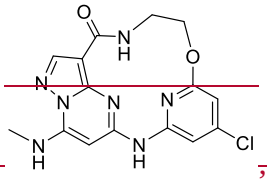
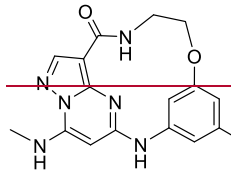
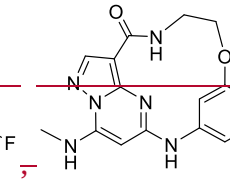
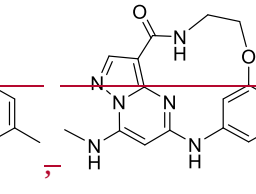
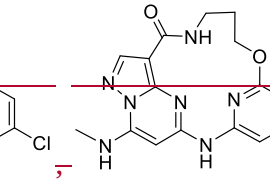
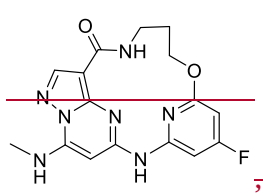
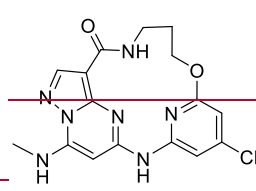
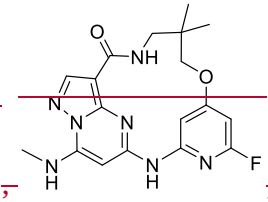
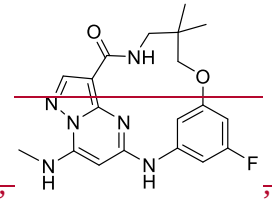
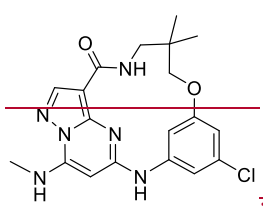
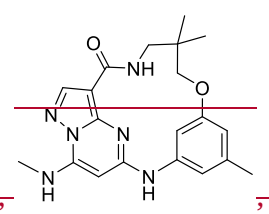
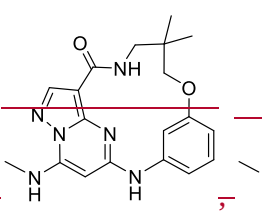
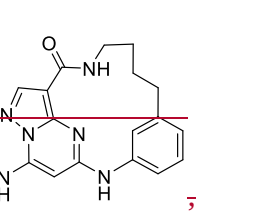
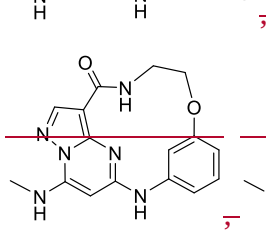
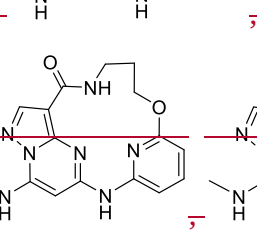
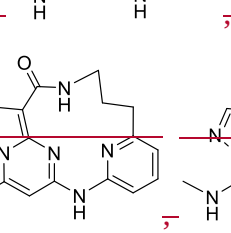
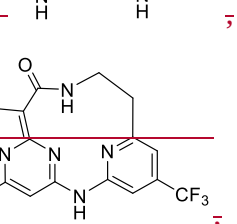
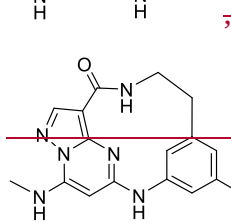
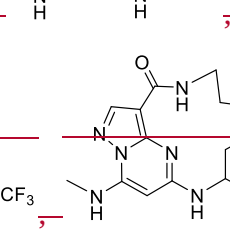
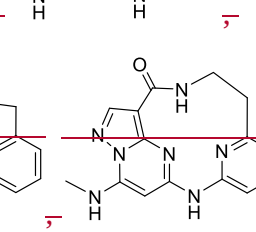
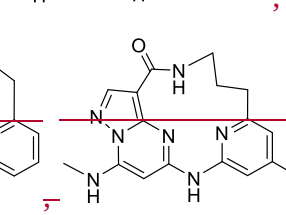
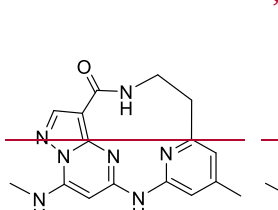
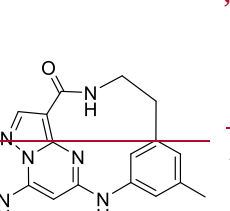
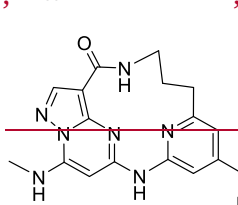
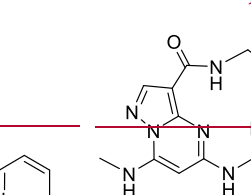
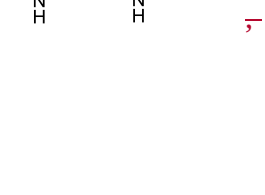
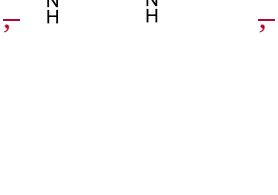
R_{18} is hydrogen.

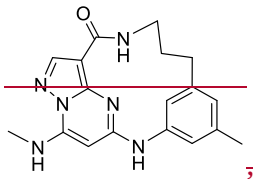
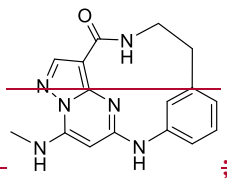
~~41. The compound of any one of claims 1-40, or a pharmaceutically acceptable salt or solvate thereof, wherein each R_2 is hydrogen.~~

42. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{18} is hydrogen.

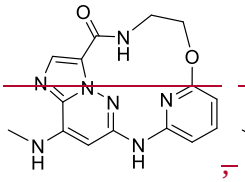
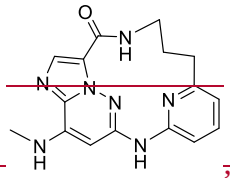
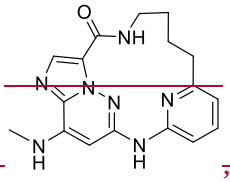
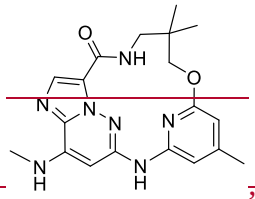
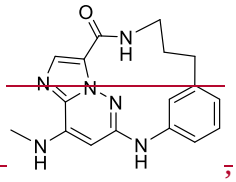
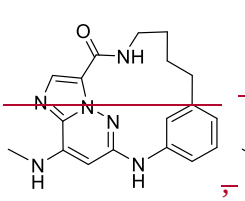
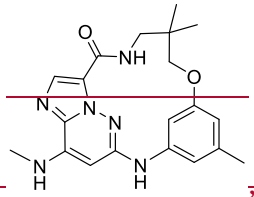
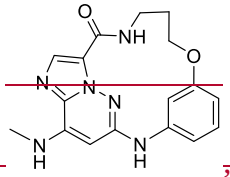
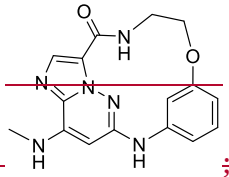
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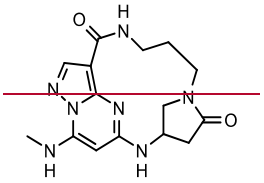
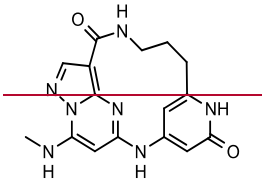
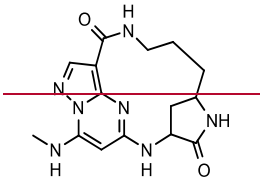
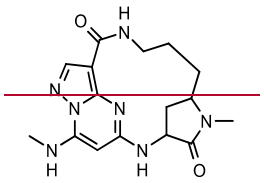
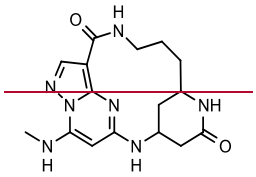
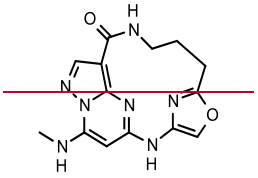
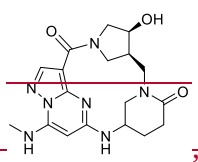
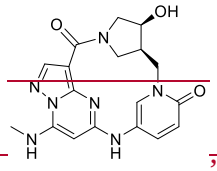
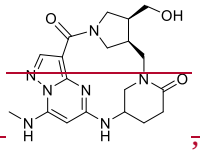
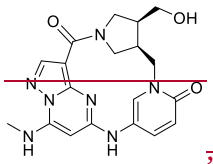
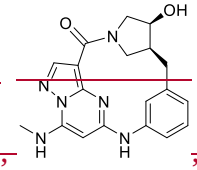
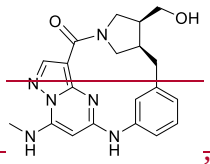
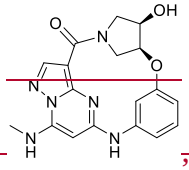
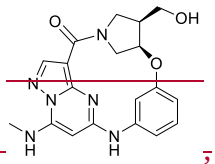
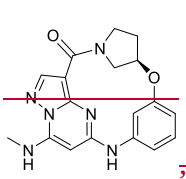
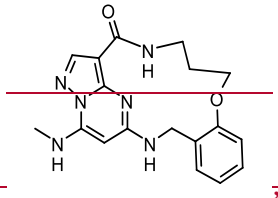
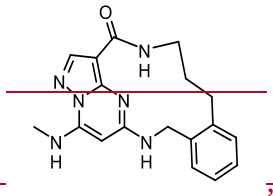
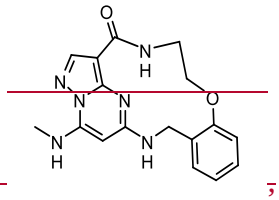
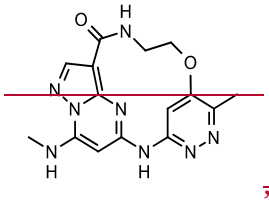
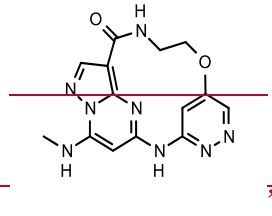
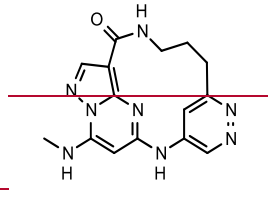
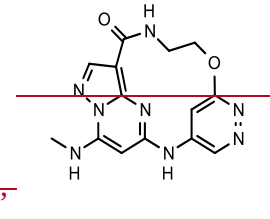







































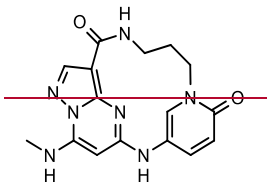
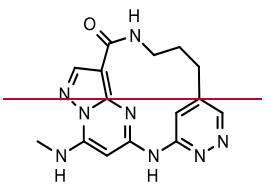
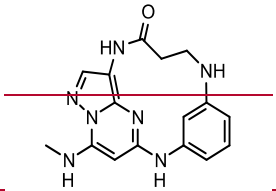
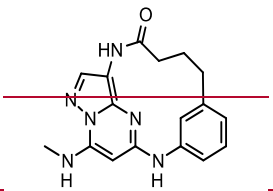
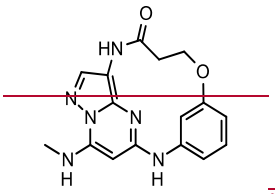
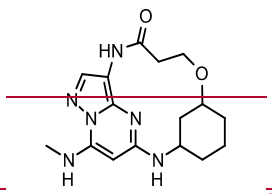
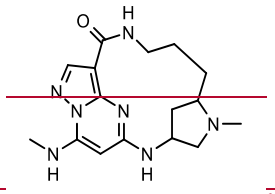
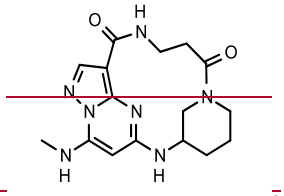
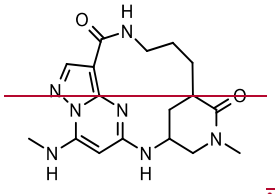
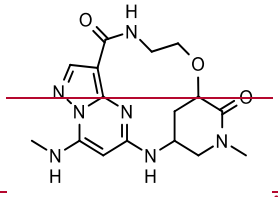
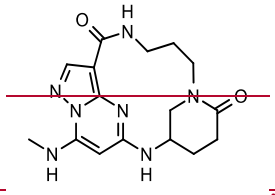
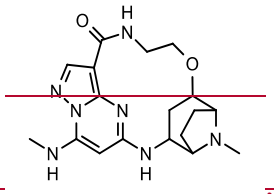
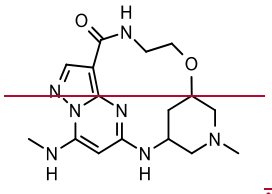
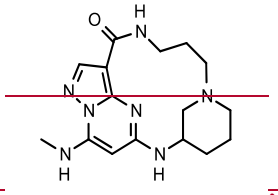
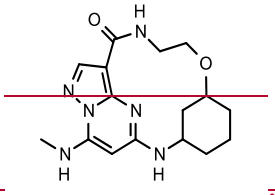
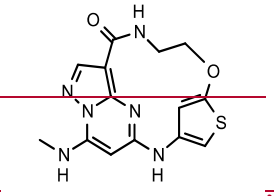
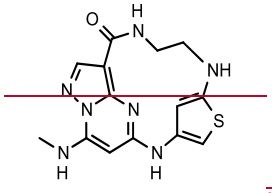
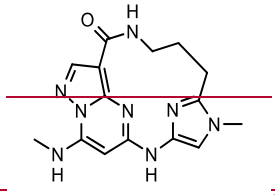
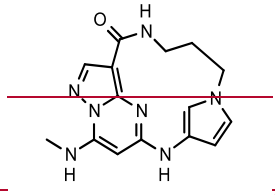
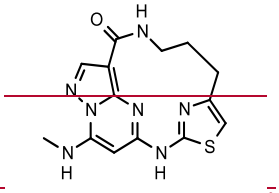


, and ; or a pharmaceutically acceptable salt or solvate thereof.

44. A compound selected from:

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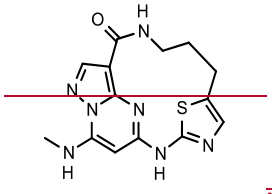
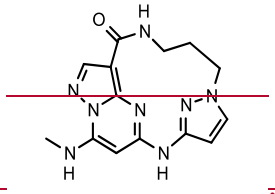
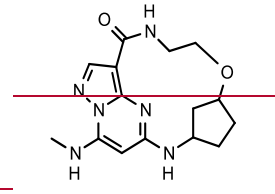
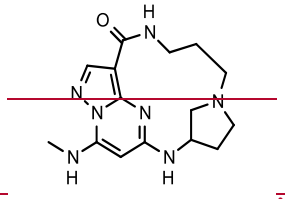
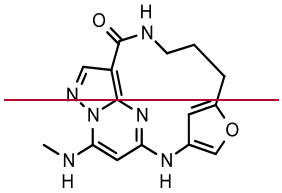
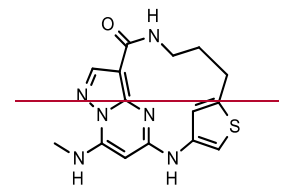
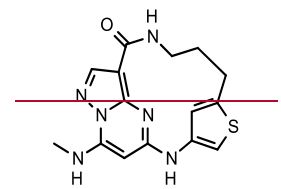
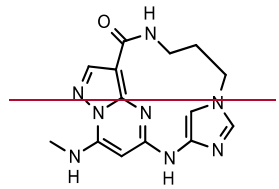
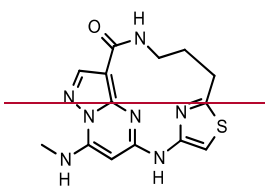
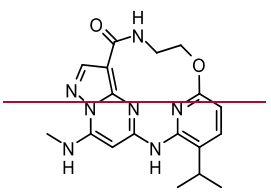
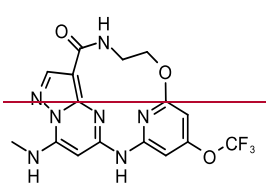
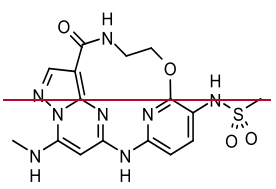
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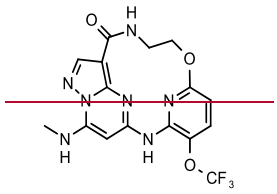
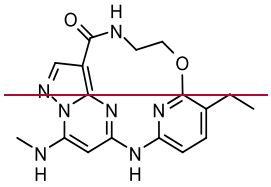
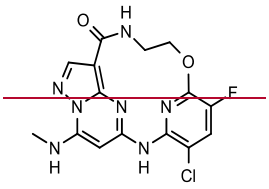
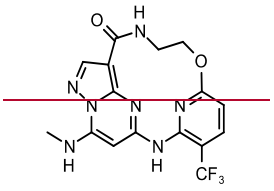
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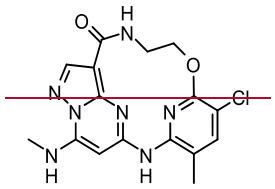
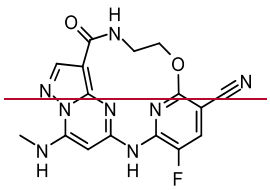
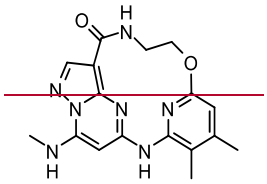
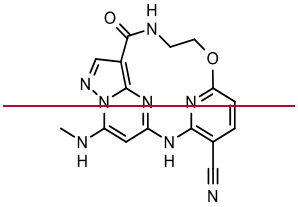
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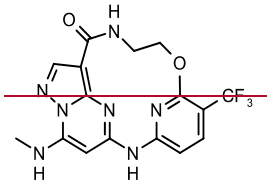
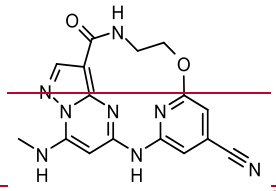
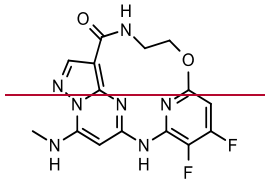
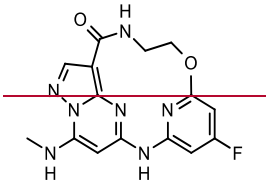
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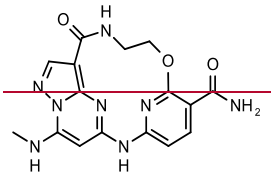
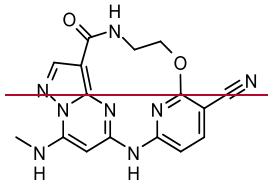
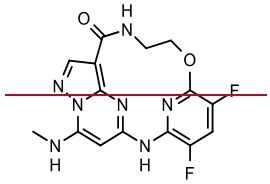
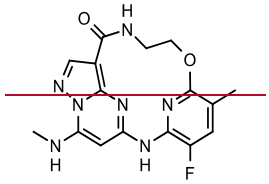
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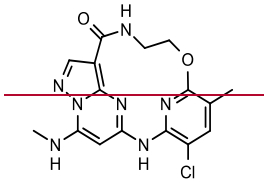
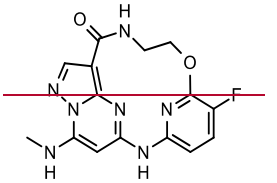
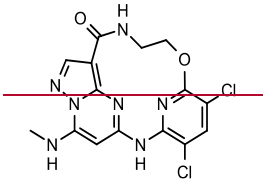
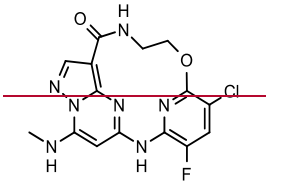
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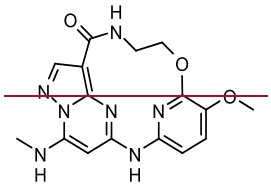
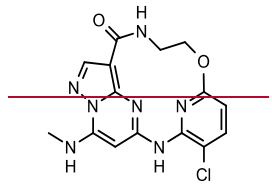
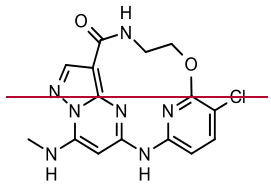
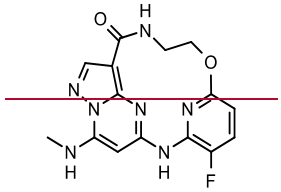
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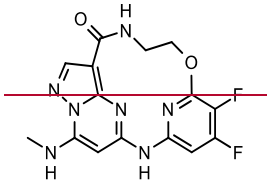
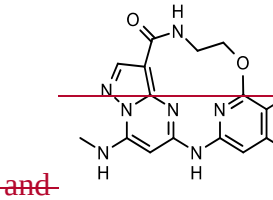
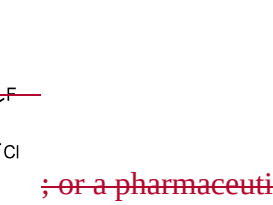
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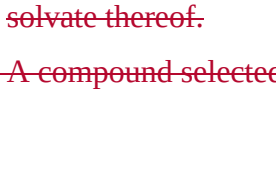
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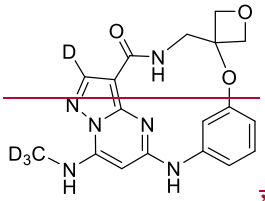
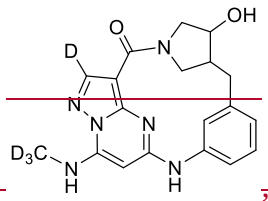
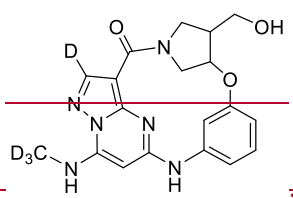
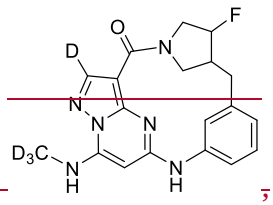
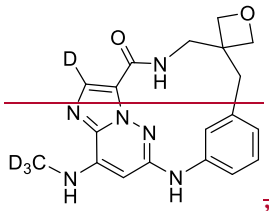
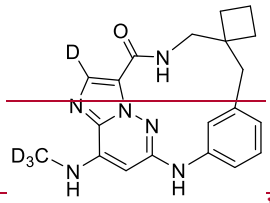
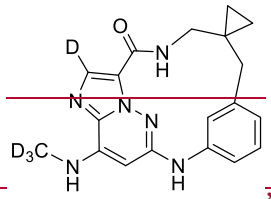
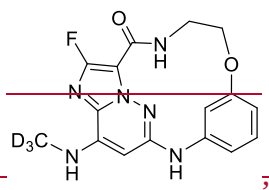
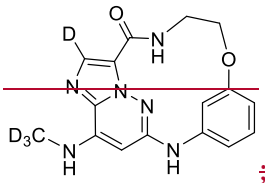
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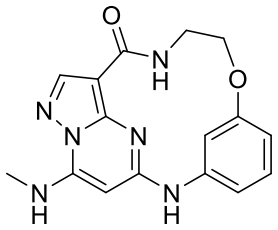
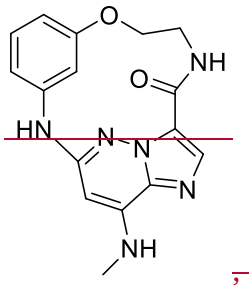
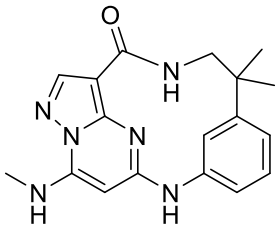
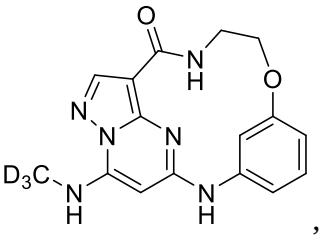
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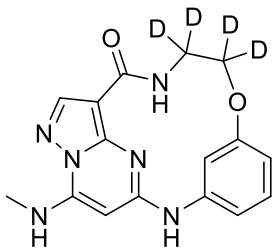
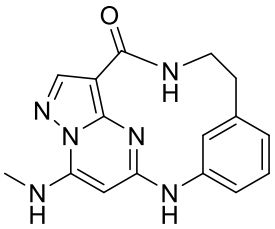
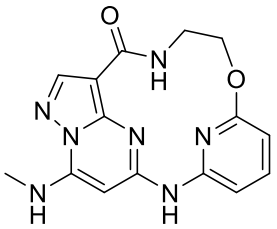
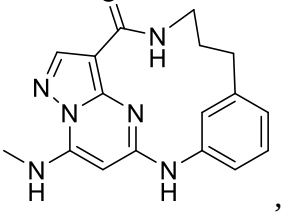
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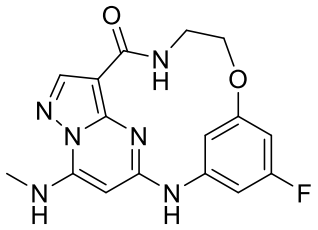
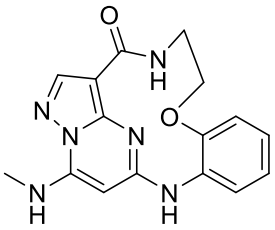
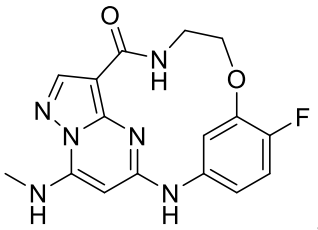
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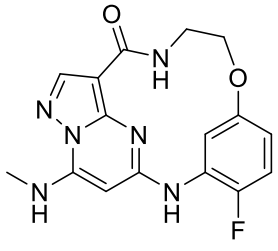
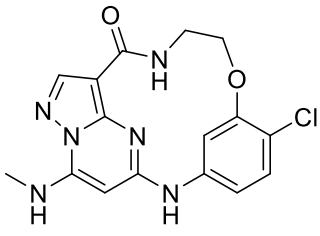
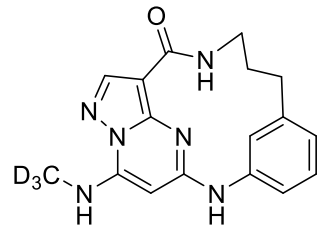
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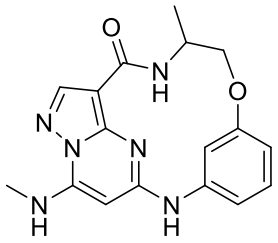
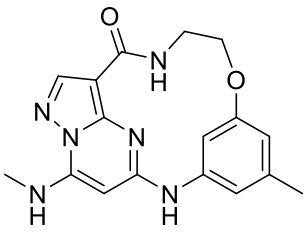
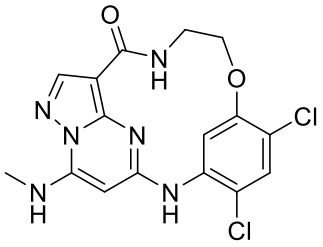
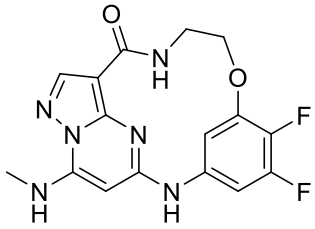
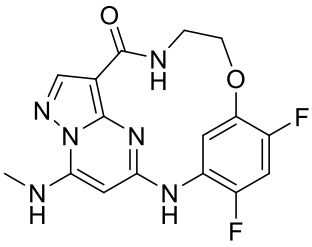
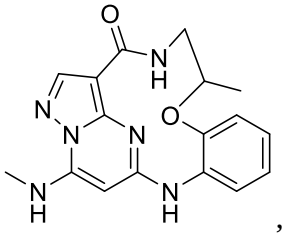
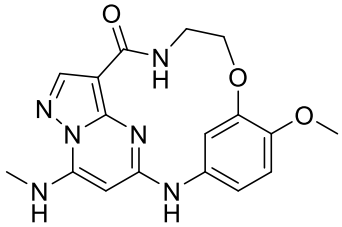
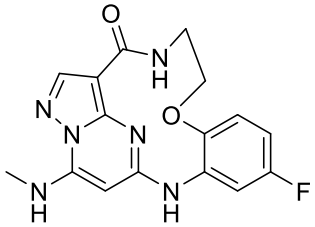
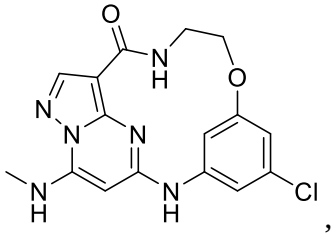
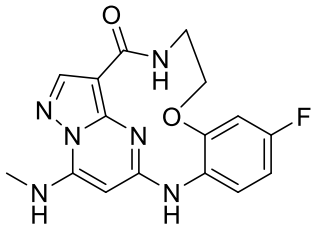
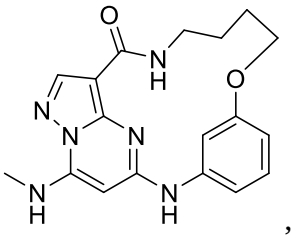
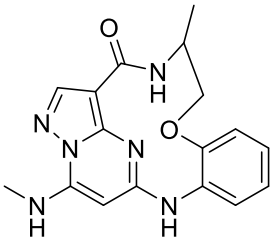
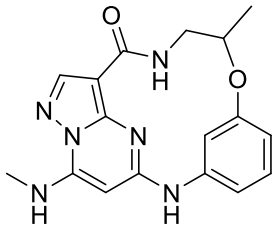
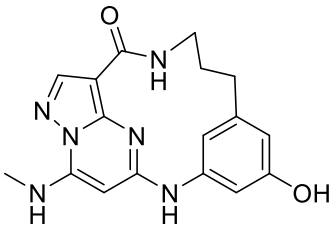
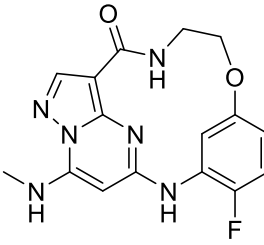
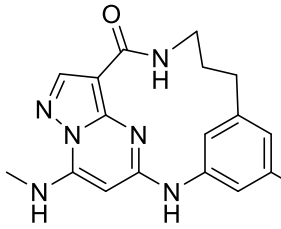
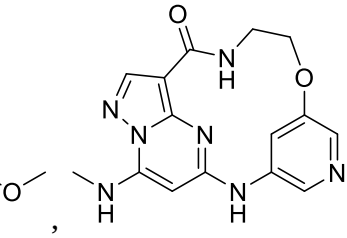
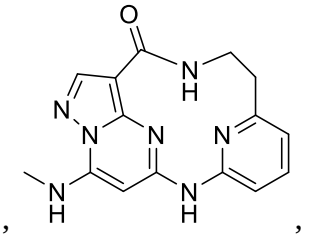
47.12. A compound selected from:

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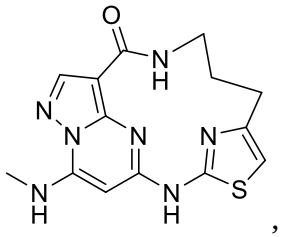
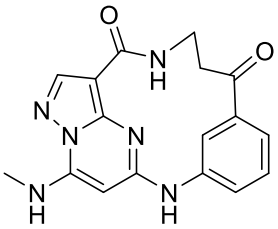
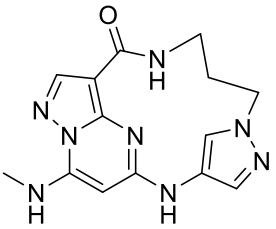
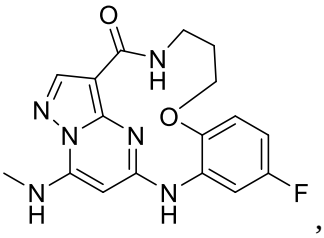
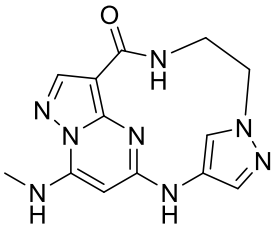
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~~48.~~13. A pharmaceutical composition comprising a compound of any one of claims 1-~~47~~12, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

~~49.~~14. Use~~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 any one of claims 1-12~~47~~, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating an inflammatory or autoimmune disease in a patient in need thereof.

~~50.~~15. The use according to ~~method of~~ claim 14~~49~~, 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.

16. A compound of any one of claims 1-12, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.