and -CH_2-C_3-C_8cycloalkyl are optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, NH(C_1-C_6alkyl), or N(C_1-C_6alkyl)$_2$; or

two R^{5a} together with the atoms to which they are attached can form C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the heterocyclyl and heteroaryl contain 1-3 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

two geminal R^{5a} can form an oxo group;

each R^{5b} is independently H, D, halogen, OH, CN, –NO_2,–SR^6, –OR^6, –NHR^6, –NR^6R^7, –$S(O)_2N(R^6)_2$–, –$S(O)_2R^6$, –$C(O)R^6$, –$C(O)OR^6$, –$C(O)NR^6R^7$,–$NR^6S(O)_2R^7$, –$S(O)R^6$, –$S(O)NR^6R^7$, –$NR^6S(O)R^7$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, or C_2-C_6alkynyl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, and C_2-C_6alkynyl are optionally substituted with D, halogen, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$;

R^6 and R^7 are independently, at each occurrence H, D, C_1-C_8alkyl, C_2-C_8alkenyl, C_4-C_8cycloalkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the heterocyclyl and heteroaryl contain 1-5 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_1-C_6alkyl, C_2-C_8alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with D, halogen, C_1-C_6alkyl, -OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

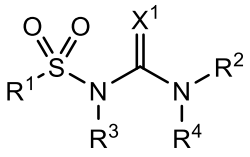
R^6 and R^7 together with the atom to which they are attached can form heterocyclyl or heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, S, P and O;

each m is independently an integer from one to 4; and

n is an integer from zero to 5;

provided that when the ring comprising A and/or A^1 is an imidazole, then at least one A^2 is N, NR^{5a}, O, S, or $S(O)_2$.

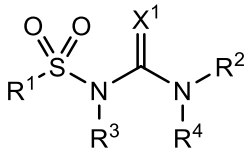
[0018] The present disclosure provides a compound of Formula Ie:



(Ie)

provided that when the ring comprising A and/or A^1 is an imidazole, then at least one A^2 is N, NR^{5a2}, O, S, or $S(O)_2$.

[0019] The present disclosure provides a compound of Formula If:



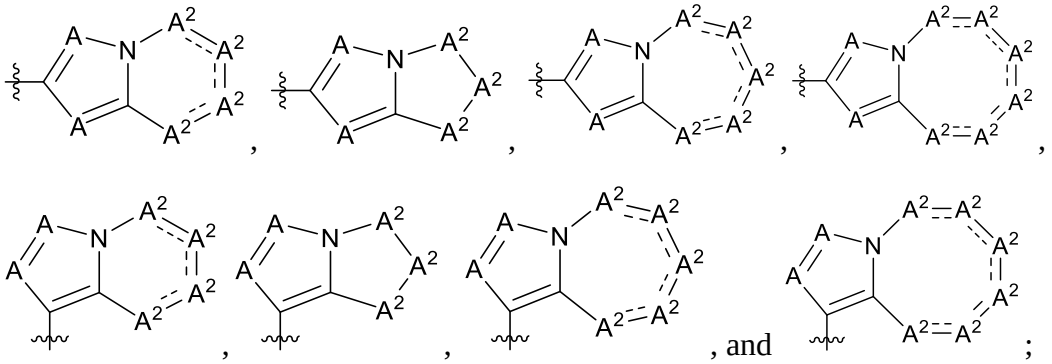
(If)

or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof,

wherein:

X^1 is O or S;

R^1 is selected from the group consisting of

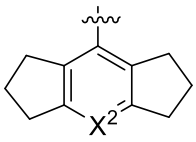
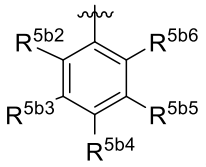


, and ;

wherein ⎓ represents a single bond or a double bond provided that the ring comprising one or more A^2 is a non-aromatic ring;

each A is independently CR^{5a1} or N;

each A^2 is independently CR^{5a2}, $C(R^{5a2})_2$, N, NR^{5a2}, O, S, or $S(O)_2$;

R^2 is  or  ;

X^2 is N or CR^{5b1};

R^3 and R^4 are H;

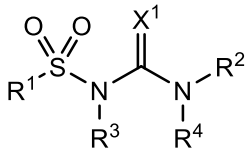
each R^{5a1} is independently H, D, halogen, OH, CN, $–NO_2$,$–SR^6$, $–OR^6$, $–NHR^6$, $–NR^6R^7$, $-NR^6C(O)R^6$, $-NR^6C(O)OR^6$, $-NR^6C(O)NR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-CH_2$-C_3-C_8cycloalkyl; wherein the

P and O; wherein the C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, C_4-C_8cycloalkenyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with D, -CN, halogen, C_1-C_6alkyl,-OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

R^6 and R^7 together with the atom to which they are attached can form heterocyclyl or heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, S, P and O;

provided that when the ring comprising A and/or A^1 is an imidazole, then at least one A^2 is N, NR^{5a2}, O, S, or $S(O)_2$.

[0020] The present disclosure provides a compound of Formula Ig:

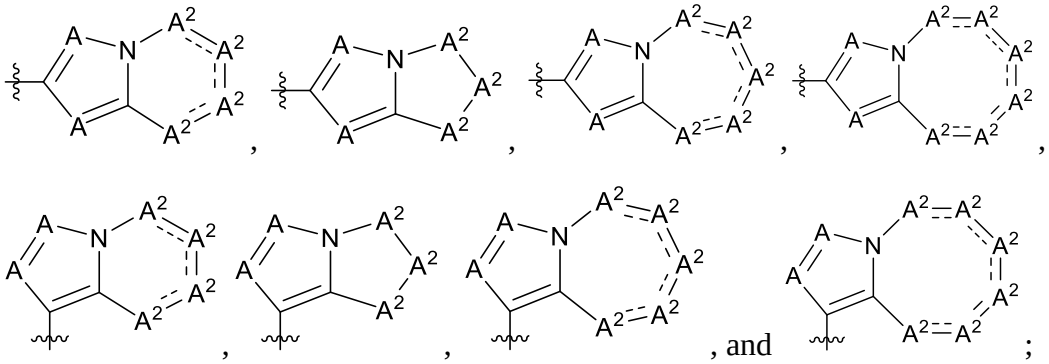

(Ig)

or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or a tautomer thereof,

wherein:

X^1 is O or S;

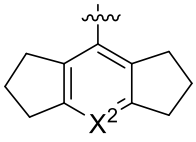
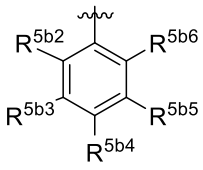
R^1 is selected from the group consisting of


, and ;

wherein ⎓ represents a single bond or a double bond provided that the ring comprising one or more A^2 is a non-aromatic ring;

each A is independently CR^{5a1} or N;

each A^2 is independently CR^{5a2}, $C(R^{5a2})_2$, N, NR^{5a2}, O, S, or $S(O)_2$;

R^2 is  or  ;

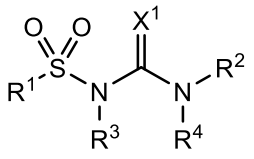
heterocyclyl, aryl, or heteroaryl are optionally substituted with halogen, -CN, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; and

R^6 and R^7 are independently, at each occurrence, H, D, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, C_4-C_8cycloalkenyl, heterocyclyl, aryl, or heteroaryl; wherein the heterocyclyl and heteroaryl contain 1-5 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, C_4-C_8cycloalkenyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with D, -CN, halogen, C_1-C_6alkyl,-OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

R^6 and R^7 together with the atom to which they are attached can form heterocyclyl or heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, S, P and O;

provided that when the ring comprising A and/or A^1 is an imidazole, then at least one A^2 is N, NR^{5a2}, O, S, or S(O)$_2$

[0021] The present disclosure provides a compound of Formula Ih:



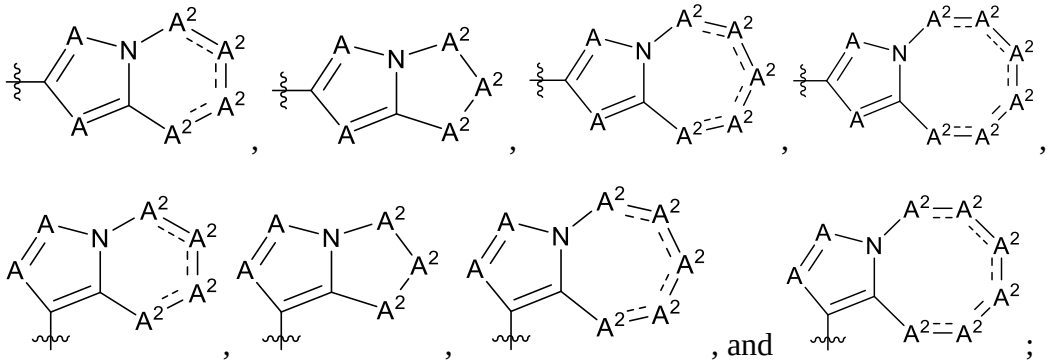
(Ih)

or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or a tautomer thereof,

wherein:

X^1 is O or S;

R^1 is selected from the group consisting of



, and ;

wherein ⎓ represents a single bond or a double bond provided that the ring comprising one or more A^2 is a non-aromatic ring;

C_2-C_6alkynyl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_3-C_8cycloalkyl, and C_2-C_6alkynyl are optionally substituted with D, halogen, -CN, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

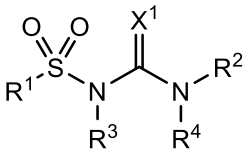
two adjacent R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} together with the atoms to which they are attached can form C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted with halogen, -CN, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; and

R^6 and R^7 are independently, at each occurrence, H, D, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, C_4-C_8cycloalkenyl, heterocyclyl, aryl, or heteroaryl; wherein the heterocyclyl and heteroaryl contain 1-5 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, C_4-C_8cycloalkenyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with D, -CN, halogen, C_1-C_6alkyl,-OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

R^6 and R^7 together with the atom to which they are attached can form heterocyclyl or heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, S, P and O;

provided that when the ring comprising A and/or A^1 is an imidazole, then at least one A^2 is N, NR^{5a2}, O, S, or S(O)$_2$.

[0021a] In one aspect, the present disclosure provides for a compound of formula Ib:

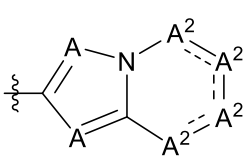
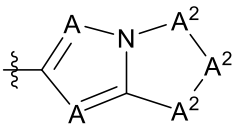
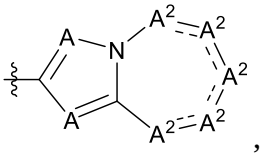
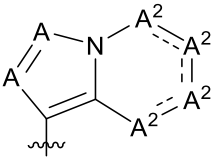
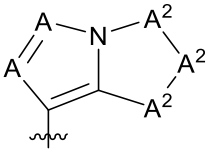
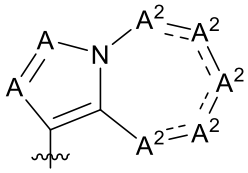

(Ib)

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

wherein:

X^1 is O or S;

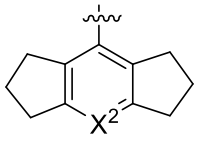
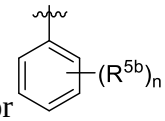
R^1 is selected from the group consisting of:


,

,

,

,

,
and

;

wherein ⁼⁼⁼ represents a single bond or a double bond provided that the ring comprising one or more A^2 is a non-aromatic ring;

each A is independently CR^{5a} or N;

each A^2 is independently CR^{5a}, $C(R^{5a})_2$, N, NR^{5a}, O, S, or $S(O)_2$;

R^2 is

or

;

X^2 is N or CR^{5b};

R^3 and R^4 are H;

each R^{5a} is independently H, D, halogen, OH, CN, $–NO_2$,$–SR^6$, $–OR^6$, $–NHR^6$, $–NR^6R^7$, $–S(O)_2N(R^6)_2–$, $–S(O)_2R^6$, $–C(O)R^6$, $–C(O)OR^6$, $–C(O)NR^6R^7$, $–NR^6S(O)_2R^7$, $–S(O)R^6$, $–S(O)NR^6R^7$, $–NR^6S(O)R^7$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-

C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or -CH_2-C_3-C_8cycloalkyl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, and -CH_2-C_3-C_8cycloalkyl are optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or two R^{5a} together with the atoms to which they are attached can form C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the heterocyclyl and heteroaryl contain 1-3 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, NH(C_1-C_6alkyl), or N(C_1-C_6alkyl)$_2$; or

two geminal R^{5a} can form an oxo group;

each R^{5b} is independently H, D, halogen, OH, CN, –NO_2,–SR^6, –OR^6, –NHR^6, –NR^6R^7, –$S(O)_2N(R^6)_2$–, –$S(O)_2R^6$, -$C(O)R^6$, -$C(O)OR^6$, –$C(O)NR^6R^7$,–$NR^6S(O)_2R^7$, –$S(O)R^6$, –$S(O)NR^6R^7$, –$NR^6S(O)R^7$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, or C_2-C_6alkynyl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, and C_2-C_6alkynyl are optionally substituted with D, halogen, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$;

R^6 and R^7 are independently, at each occurrence H, D, C_1-C_8alkyl, C_2-C_8alkenyl, C_4-C_8cycloalkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the heterocyclyl and heteroaryl contain 1-5 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_1-C_6alkyl, C_2-C_8alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with D, halogen, C_1-C_6alkyl,-OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

R^6 and R^7 together with the atom to which they are attached can form heterocyclyl or heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, S, P and O; and

n is an integer from 0 to 5;

provided that when the ring comprising A is an imidazole, then at least one A^2 is N, NR^{5a}, O, S, or $S(O)_2$.

[0021b] In another aspect, the present disclosure provides for a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0022] The present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, isomers, and tautomers thereof, and a pharmaceutically acceptable carrier, diluent and/or excipient. In one aspect, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0023] The present disclosure provides a method of treatment or prevention of a disease, disorder or condition including the step of administering an effective amount of a compound of the present disclosure, and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, isomers, and tautomers thereof to thereby treat or prevent the disease, disorder or condition in a subject in need thereof.

[0023a] In another aspect, the present disclosure provides for a compound as described herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, for use in therapy.

[0023b] In another aspect, the present disclosure provides for a use of a compound as described herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment of a disease, disorder, or condition that is of the immune system, the cardiovascular system, the endocrine system, the gastrointestinal tract, the renal system, the respiratory system, the central nervous system, that is a cancer or other malignancy, or that is caused by or associated with a pathogen.

[0023c] In another aspect, the present disclosure provides for a use of a compound as described herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment of an inflammatory or autoimmune disease, disorder, or condition.

[0023d] In another aspect, the present disclosure provides for a use of a compound as described herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment of a disease, disorder, or condition selected from the group consisting of constitutive inflammation, the cryopyrin-associated periodic syndromes (CAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), neonatal-onset multisystem inflammatory disease (NOMID), autoinflammatory diseases, familial

Mediterranean fever (FMF), TNF receptor associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), hyperimmunoglobulinemia D, periodic fever syndrome (HIDS), deficiency of interleukin 1 receptor (DIRA) antagonist, Majeed syndrome, pyogenic arthritis, pyoderma gangrenosum and acne (PAPA), haploinsufficiency of A20 (HA20), pediatric granulomatous arthritis (PGA), PLCG2-associated antibody deficiency and immune dysregulation (PLAID), PLCG2-associated autoinflammation, antibody deficiency and immune dysregulation (APLAID), sideroblastic anemia with B-cell immunodeficiency, periodic fevers, developmental delay (SIFD), Sweet's syndrome, chronic nonbacterial osteomyelitis (CNO), chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, osteitis syndrome (SAPHO), autoimmune diseases including multiple sclerosis (MS), type-1 diabetes, psoriasis, rheumatoid arthritis, Behcet's disease, Sjogren's syndrome, Schnitzler syndrome, respiratory diseases, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disorder (COPD), steroid-resistant asthma, asbestosis, silicosis, cystic fibrosis, central nervous system diseases, Parkinson's disease, Alzheimer's disease, motor neuron disease, Huntington's disease, cerebral malaria, brain injury from pneumococcal meningitis, metabolic diseases, Type 2 diabetes, atherosclerosis, obesity, gout, pseudo-gout, ocular disease, disease of the ocular epithelium, age-related macular degeneration (AMD), corneal infection, uveitis, dry eye, kidney disease, chronic kidney disease, oxalate nephropathy, diabetic nephropathy, liver disease, non-alcoholic steatohepatitis, alcoholic liver disease, inflammatory reactions in skin, contact hypersensitivity, sunburn, inflammatory reactions in the joints, osteoarthritis, systemic juvenile idiopathic arthritis, adult-onset Still's disease, relapsing polychondritis, viral infections, alpha virus infection, Chikungunya virus infection, Ross River virus infection, flavivirus infection, Dengue virus infection, Zika virus infection, flu, HIV infection, hidradenitis suppurativa (HS), cyst-causing skin diseases, cancers, lung cancer metastasis, pancreatic cancers, gastric cancers, myelodisplastic syndrome, leukemia, polymyositis, stroke, myocardial infarction, Graft versus Host Disease, hypertension, colitis, helminth infection, bacterial infection, abdominal aortic aneurism, wound healing, depression, psychological stress, pericarditis, Dressler's syndrome, ischaemia reperfusion injury, and any disease where an individual has been determined to carry a germ line or somatic non-silent mutation in NLRP3.

[0023e] In another aspect, the present disclosure provides for a use of a compound as described herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, in the

manufacture of a medicament for the treatment of a disease, disorder, or condition selected from the group consisting of cryopyrin-associated periodic syndromes (CAPS), atherosclerosis, gout, pseudo-gout, rheumatoid arthritis, systemic juvenile idiopathic arthritis, non-alcoholic steatohepatitis, myocardial infarction, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and type-1 diabetes.

[0024] The present disclosure provides a compound of the present disclosure, and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, isomers, and tautomers thereof, or the pharmaceutical composition of the present disclosure for use in the treatment or prevention of a disease, disorder or condition in a subject in need thereof.

[0025] The present disclosure provides for use of a compound of the present disclosure, and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, isomers, and tautomers thereof, for the treatment or prevention of a disease, disorder or condition in a subject in need thereof.

[0026] The present disclosure provides for use of a compound of the present disclosure, and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, isomers, and tautomers thereof, in the manufacture of a medicament for the treatment or prevention of a disease, disorder or condition.

[0027] In certain embodiments, the disease, disorder or condition is responsive to inhibition of an inflammasome.

[0028] In certain embodiments, the disease, disorder or condition is responsive to inhibition of activation of the NLRP3 inflammasome.

[0029] In certain embodiments, the disease, disorder or condition is a disease, disorder or condition of the immune system, the liver, the lung, the skin, the cardiovascular system, the renal system, the gastrointestinal tract, the respiratory system, the endocrine system, the central nervous system, or is a cancer or other malignancy, or is caused by or associated with a pathogen.

[0030] The present disclosure provides a method of modulating the activity of a biological target comprising the step of exposing the biological target to a compound of the present disclosure, and pharmaceutically acceptable salts thereof.

[0031] The biological target may be selected from the group consisting of the NLRP3 inflammasome, IL-6, IL-1β, IL-17, IL-18, IL-1α, IL-37, IL-22, IL-33 and Th17 cells.

Brief Description of the Drawings

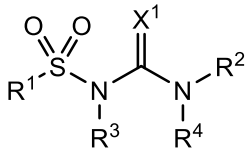
[0032] Figure 1 shows inhibition of IL-1β production in peripheral blood mononucleocytes (PBMCs) as a result of treatment with Compound 1, Compound 2, or Compound 3.

[0033] Figure 2 shows inhibition of IL-1β and IL-18 production, but not TNFα production in Kupffer cells (KCs) as a result of treatment with Compound 1, Compound 4, or Compound 5.

[0034] Figure 3 shows modulation of IL-1β in an LPS and ATP challenge model of Compound 1 and Compound 2.

CLAIMS:

1. A compound of formula Ib:



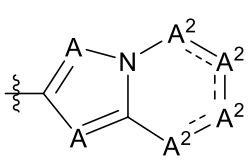
(Ib)

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

wherein:

X^1 is O or S;

R^1 is selected from the group consisting of: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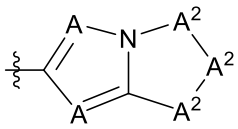
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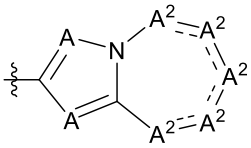
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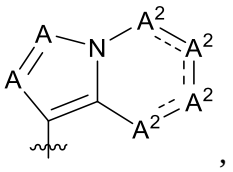
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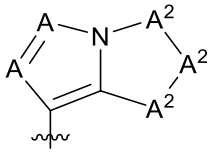
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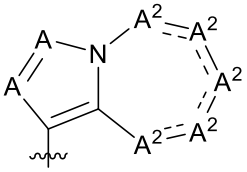
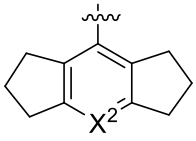
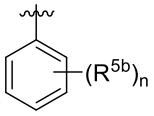

;

wherein ⎓ represents a single bond or a double bond provided that the ring comprising one or more A^2 is a non-aromatic ring;

each A is independently CR^{5a} or N;

each A^2 is independently CR^{5a}, $C(R^{5a})_2$, N, NR^{5a}, O, S, or $S(O)_2$;

R^2 is  or  ;

X^2 is N or CR^{5b};

R^3 and R^4 are H;

each R^{5a} is independently H, D, halogen, OH, CN, $–NO_2$,$–SR^6$, $–OR^6$, $–NHR^6$, $–NR^6R^7$, $–S(O)_2N(R^6)_2–$, $–S(O)_2R^6$, $–C(O)R^6$, $–C(O)OR^6$, $–C(O)NR^6R^7$, $–NR^6S(O)_2R^7$, $–S(O)R^6$, $–S(O)NR^6R^7$, $–NR^6S(O)R^7$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or -CH_2-C_3-C_8cycloalkyl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl,

and -CH_2-C_3-C_8cycloalkyl are optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

two R^{5a} together with the atoms to which they are attached can form C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the heterocyclyl and heteroaryl contain 1-3 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, NH(C_1-C_6alkyl), or N(C_1-C_6alkyl)$_2$; or

two geminal R^{5a} can form an oxo group;

each R^{5b} is independently H, D, halogen, OH, CN, –NO_2,–SR^6, –OR^6, –NHR^6, −NR^6R^7, –$S(O)_2N(R^6)_2$–, –$S(O)_2R^6$, -$C(O)R^6$, -$C(O)OR^6$, –$C(O)NR^6R^7$,–$NR^6S(O)_2R^7$, −$S(O)R^6$, −$S(O)NR^6R^7$, −$NR^6S(O)R^7$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, or C_2-C_6alkynyl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, and C_2-C_6alkynyl are optionally substituted with D, halogen, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$;

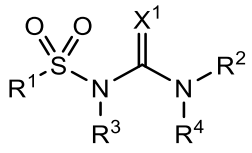
R^6 and R^7 are independently, at each occurrence H, D, C_1-C_8alkyl, C_2-C_8alkenyl, C_4-C_8cycloalkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the heterocyclyl and heteroaryl contain 1-5 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_1-C_6alkyl, C_2-C_8alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with D, halogen, C_1-C_6alkyl,-OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

R^6 and R^7 together with the atom to which they are attached can form heterocyclyl or heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, S, P and O; and

n is an integer from 0 to 5;

provided that when the ring comprising A is an imidazole, then at least one A^2 is N, NR^{5a}, O, S, or $S(O)_2$.

2. The compound of claim 1, wherein the compound is of formula (I):

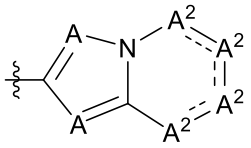
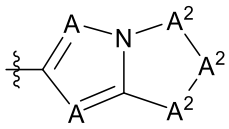
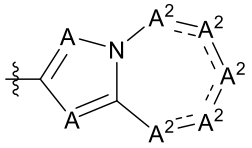


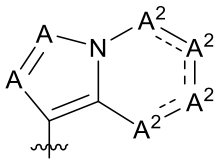
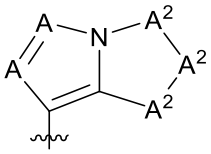
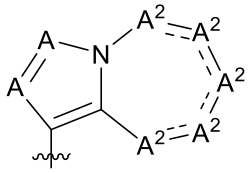
(I),

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

X^1 is O or S;

R^1 is selected from the group consisting of:

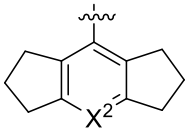
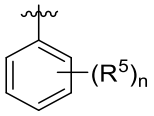
 ,  ,  ,

 ,  , and  ;

wherein ⁼⁼⁼ represents a single bond or a double bond provided that the ring comprising one or more A^2 is a non-aromatic ring;

each A is independently CR^5 or N;

each A^2 is independently CR^5, $C(R^5)_2$, N, NR_5, O, S, or $S(O)_2$;

R^2 is  or  ;

X^2 is N or CR^5;

R^3 and R^4 are H;

each R^5 is independently H, D, halogen, OH, CN, $–NO_2$, $–SR^6$, $–OR^6$, $–NHR^6$, $–NR^6R^7$, $–S(O)_2N(R^6)_2–$, $–S(O)_2R^6$, $–C(O)R^6$, $–C(O)OR^6$, $–C(O)NR^6R^7$,$–NR^6S(O)_2R^7$, $–S(O)R^6$, $–S(O)NR^6R^7$, $–NR^6S(O)R^7$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, or C_2-C_6alkynyl; or

R^6 and R^7 are independently, at each occurrence H, D, C_1-C_8alkyl, C_2-C_8alkenyl, C_4-C_8cycloalkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the heterocyclyl and heteroaryl contain 1-5 heteroatoms selected from the group consisting of N, S, P and O; or

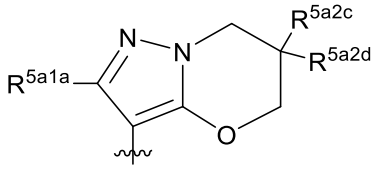
R^6 and R^7 together with the atom to which they are attached can form heterocyclyl or heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, S, P and O; and

n is an integer from 0 to 5;

provided that when the ring comprising A is an imidazole, then at least one A^2 is N, NR^5, O, S, or $S(O)_2$.

3. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein one A is CR^{5a} and the other A is N; and each A^2 is independently $C(R^{5a})_2$, NR^{5a}, or O.

4. The compound of claim 1 or 3, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein each R^{5a} is independently H, -NHR^6, -NR^6R^7, C_1-C_6alkyl, or heterocyclyl containing N, wherein the C_1-C_6alkyl is substituted with -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$, and wherein the heterocyclyl is optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$.

5. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^1 is 

, wherein:

R^{5a1a} is H, D, halogen, -OH, -CN, -NO_2, -SR^6, -OR^6, -NHR^6, -NR^6R^7, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or -CH_2-C_3-C_8cycloalkyl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, and -CH_2-C_3-C_8cycloalkyl are optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$;

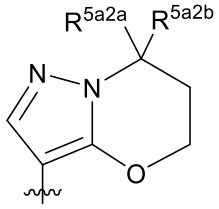
R^{5a2c} and R^{5a2d} are each independently H, D, halogen, -OH, -CN, -NO_2, -SR^6, -OR^6, -NHR^6, -NR^6R^7, -$C(O)R^6$, -$S(O)_2R^6$, -$C(O)OR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or -CH_2-C_3-C_8cycloalkyl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, and -CH_2-C_3-C_8cycloalkyl are optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

R^{5a2c} and R^{5a2d} together with the atoms to which they are attached can form C_3-C_8cycloalkyl or heterocyclyl; wherein the heterocyclyl contains 1-3 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_3-C_8cycloalkyl and heterocyclyl are optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

R^{5a2c} and R^{5a2d} can form an oxo group.

6. The compound of claim 5, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein each R^{5a2c} and R^{5a2d} is independently H, halogen, -OH, –OR^6, -NR^6R^7, C_1-C_6alkyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or -CH_2-C_3-C_8cycloalkyl.

7. The compound of claim 5, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^{5a2c} and R^{5a2d} together with the atoms to which they are attached form C_3-C_8cycloalkyl or heterocyclyl.

8. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^1 is 

, wherein:

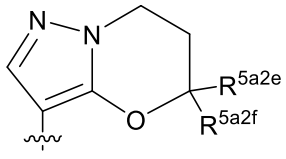
R^{5a2a} and R^{5a2b} are each independently H, D, halogen, -OH, -CN, -NO_2, -SR^6, -OR^6, -NHR^6, -NR^6R^7, -$C(O)R^6$, -$S(O)_2R^6$, -$C(O)OR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or -CH_2-C_3-C_8cycloalkyl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, and -CH_2-C_3-C_8cycloalkyl are optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

R^{5a2a} and R^{5a2b} together with the atoms to which they are attached can form C_3-C_8cycloalkyl or heterocyclyl; wherein the heterocyclyl contains 1-3 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_3-C_8cycloalkyl and heterocyclyl are optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

R^{5a2a} and R^{5a2b} can form an oxo group.

9. The compound of claim 8, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein each R^{5a2a} and R^{5a2b} is independently H, halogen, -OH, –OR^6, -NR^6R^7, C_1-C_6alkyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or -CH_2-C_3-C_8cycloalkyl.

10. The compound of claim 8, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^{5a2a} and R^{5a2b} together with the atoms to which they are attached form C_3-C_8cycloalkyl or heterocyclyl.

11. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^1 is 

, wherein:

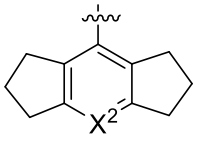
R^{5a2e} and R^{5a2f} are each independently H, D, halogen, -OH, -CN, $-NO_2$, $-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-CH_2$-C_3-C_8cycloalkyl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, and $-CH_2$-C_3-C_8cycloalkyl are optionally substituted with D, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), or $-N(C_1$-C_6alkyl)$_2$; or

R^{5a2e} and R^{5a2f} together with the atoms to which they are attached can form C_3-C_8cycloalkyl or heterocyclyl; wherein the heterocyclyl contains 1-3 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_3-C_8cycloalkyl and heterocyclyl are optionally substituted with D, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), or $-N(C_1$-C_6alkyl)$_2$; or

R^{5a2e} and R^{5a2f} can form an oxo group.

12. The compound of claim 11, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein each R^{5a2e} and R^{5a2f} is independently H, halogen, -OH, $–OR^6$, $-NR^6R^7$, C_1-C_6alkyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-CH_2$-C_3-C_8cycloalkyl.

13. The compound of claim 12, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^{5a2e} and R^{5a2f} together with the atoms to which they are attached form C_3-C_8cycloalkyl or heterocyclyl.

14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^2 is 

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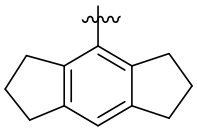
15. The compound of claim 14, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein X^2 is CR^{5b} and R^{5b} is H, fluoro, chloro, or methyl.

16. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^2 is 
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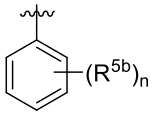
17. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^2 is 

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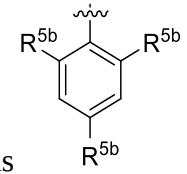
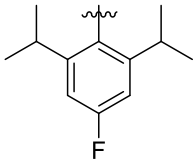
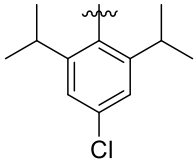
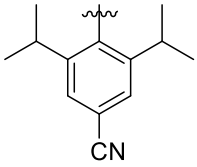
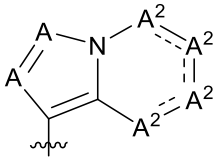
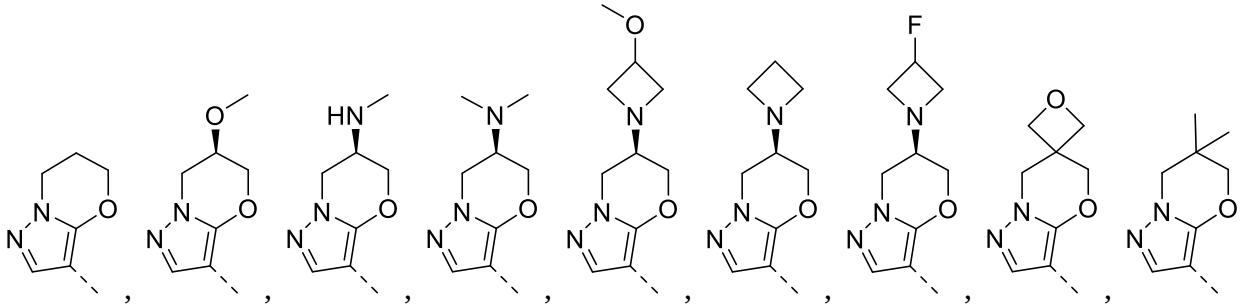
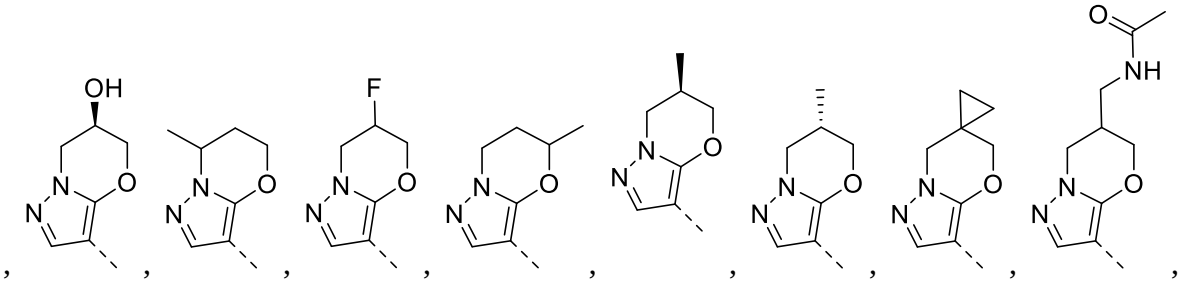
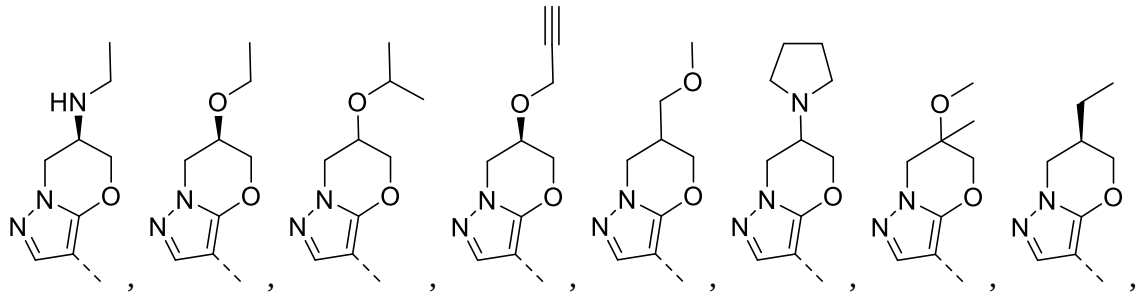
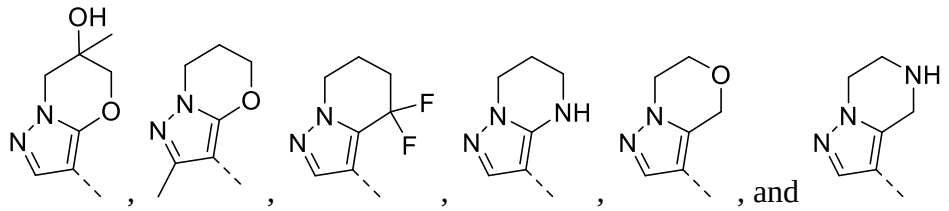
18. The compound of claim 17, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^2 is  .

19. The compound of claim 1, 17 or 18, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein each R^{5b} is independently selected from the group consisting of H, halogen, -OH, -CN, $–NO_2$, $–OR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, and C_4-C_8cycloalkenyl.

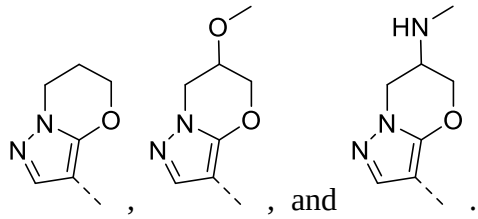
20. The compound of claim 18, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^2 is selected from the group consisting of  ,  , and  .

21. The compound of any one of claims 1 to 4 or 14 to 20, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein X^1 is O and R^1 is  .

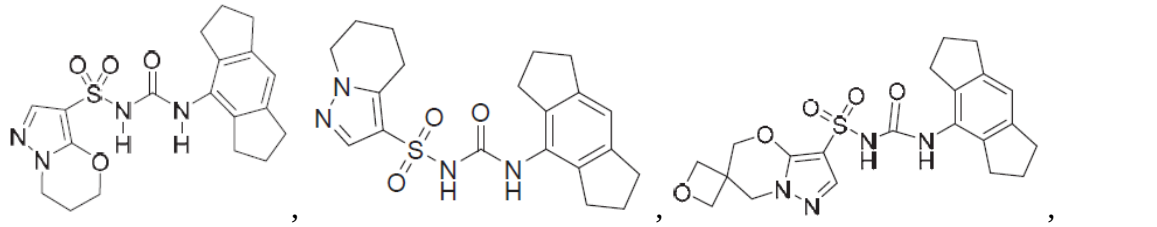
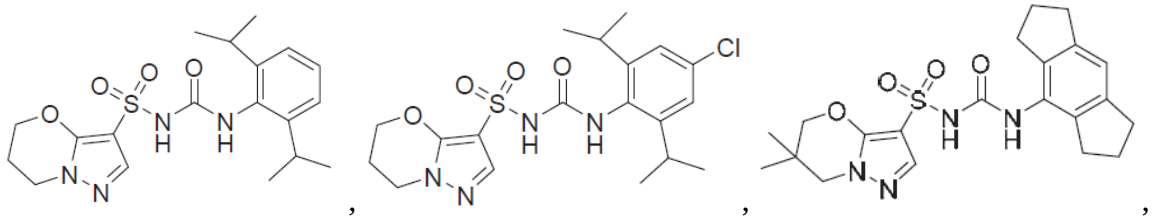
22. The compound of any one of claims 1 or 14 to 21, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^1 is selected from the group consisting of  .

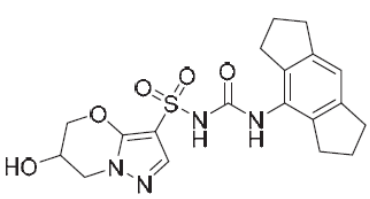
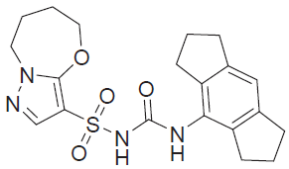
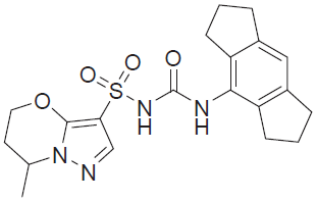




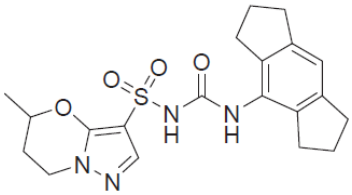
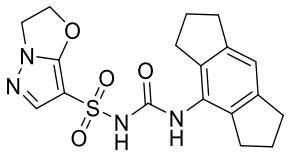
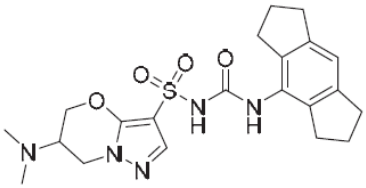
23. The compound of any one of claims 1 or 14 to 21, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^1 is selected from the group consisting of

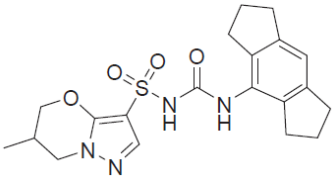
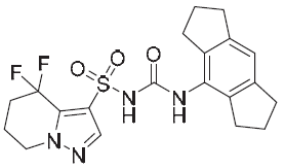
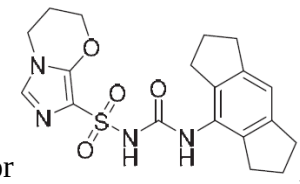


24. The compound of claim 1, wherein the compound is:

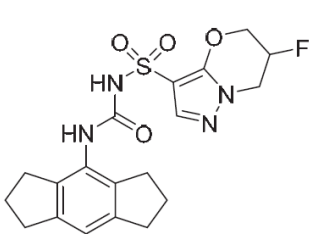
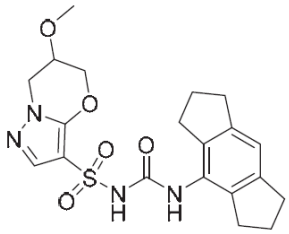
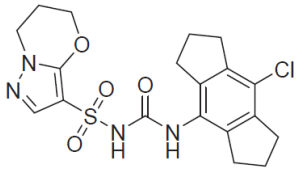
 ,  ,  ,

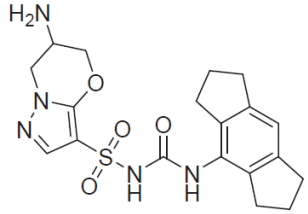
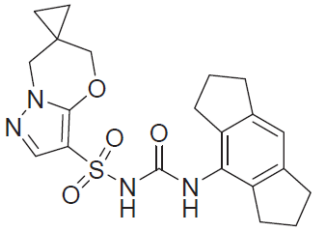
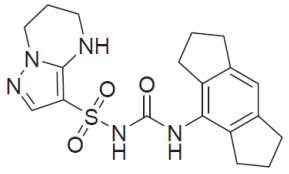
 ,  ,  ,

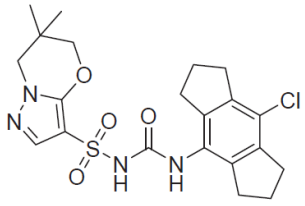
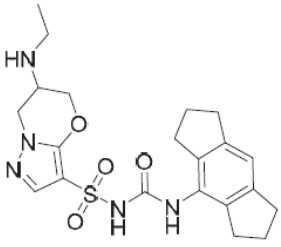
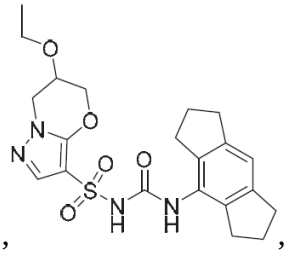
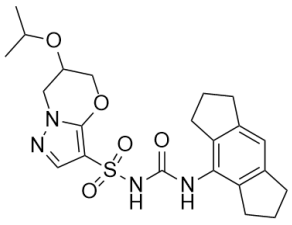
 ,  , or  ,

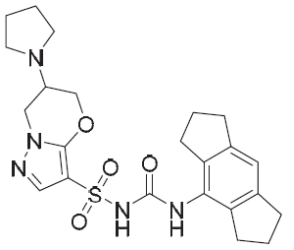
or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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

 ,  ,  ,

 ,  ,  ,

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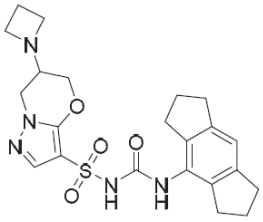
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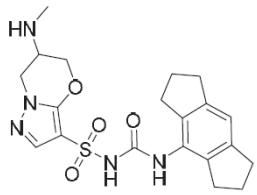
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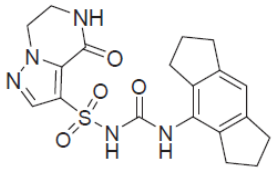
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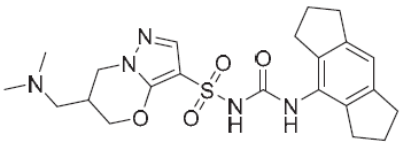
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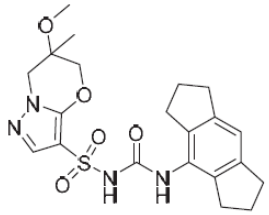
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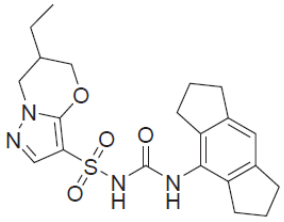
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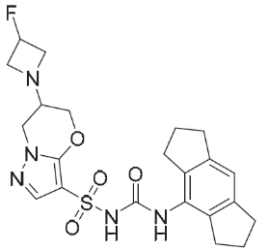
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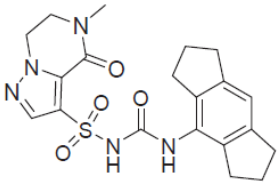
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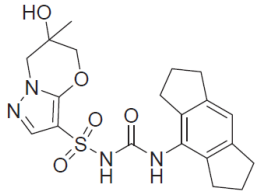
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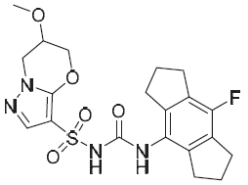
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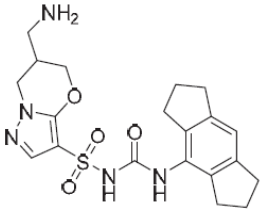
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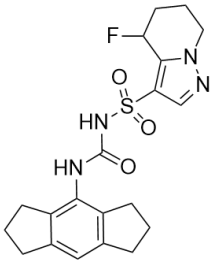
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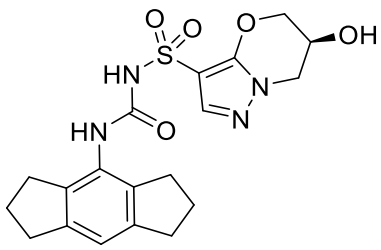
or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

26. The compound of claim 1, wherein the compound is: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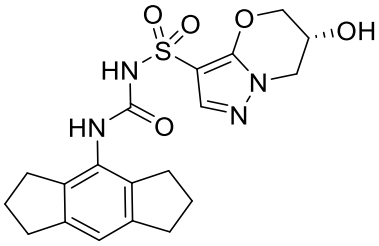
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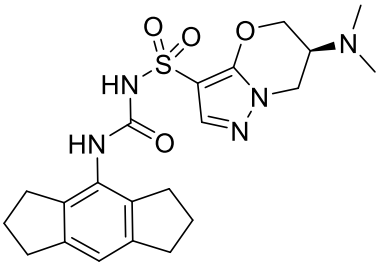
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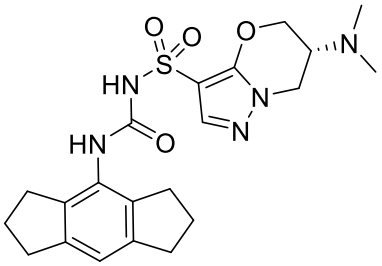
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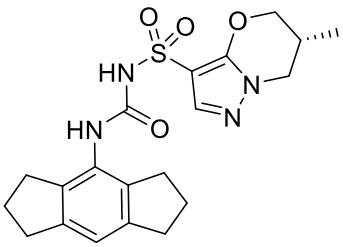
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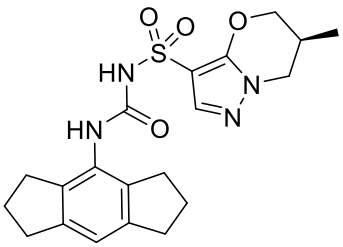
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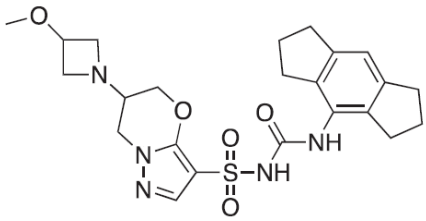
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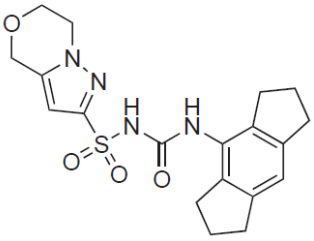
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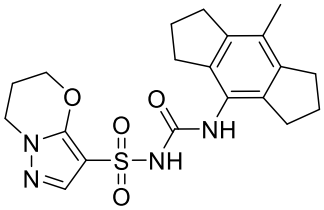
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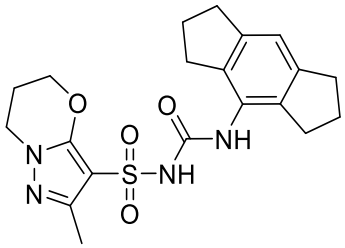
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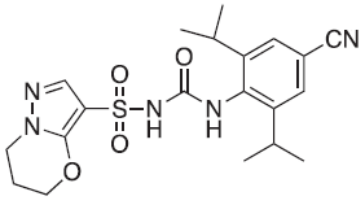
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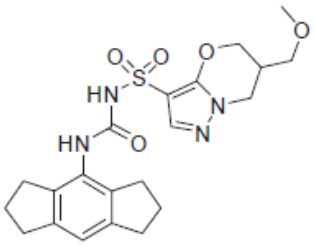
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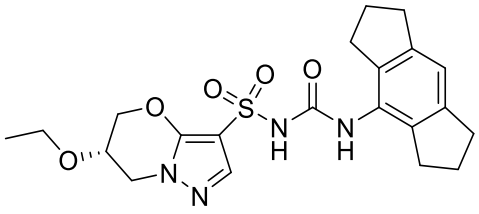
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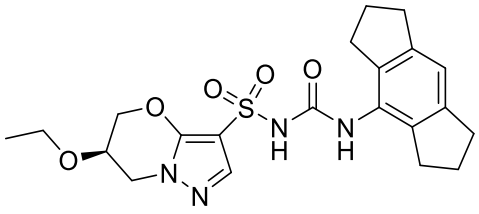
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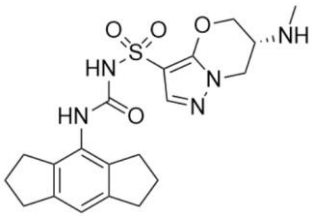
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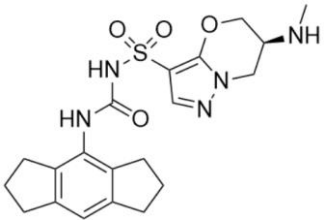
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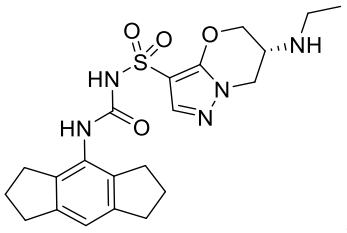
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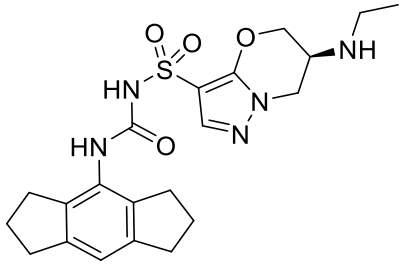
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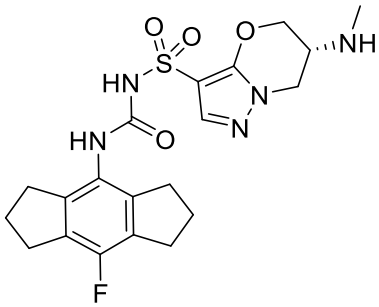
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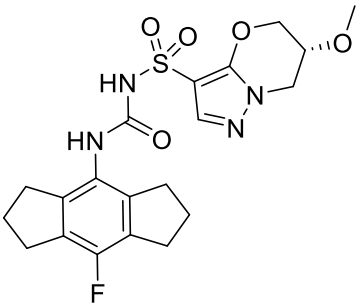
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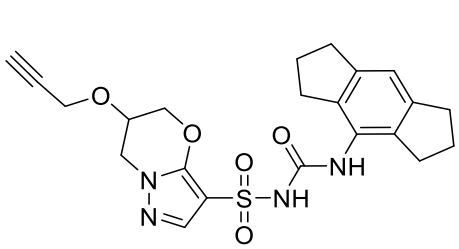
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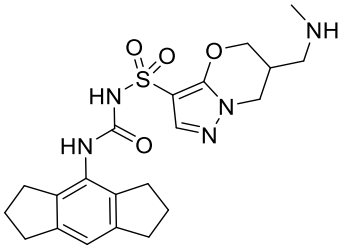
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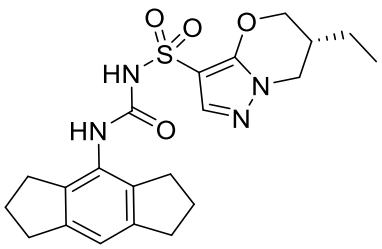
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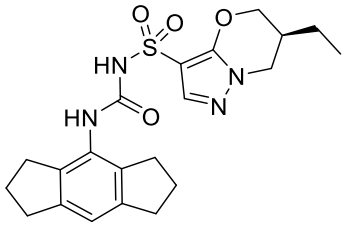
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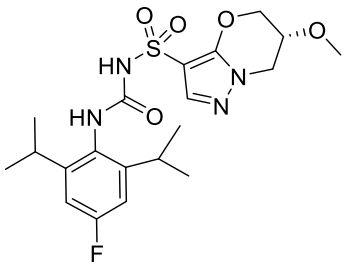
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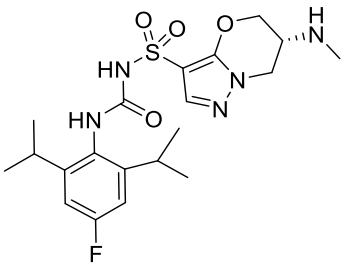
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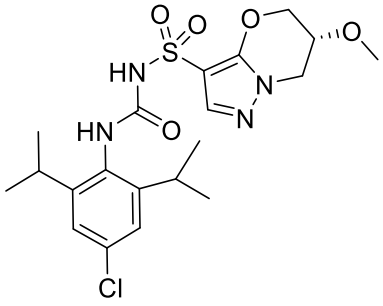
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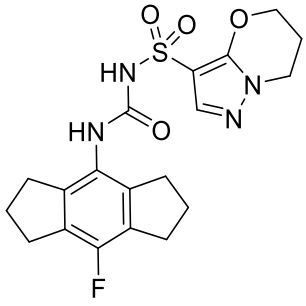
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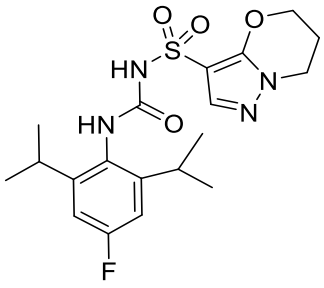
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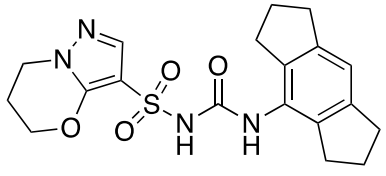
or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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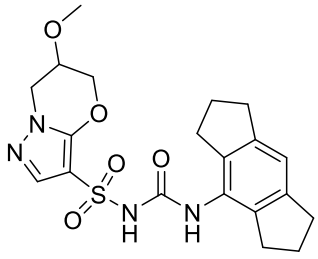
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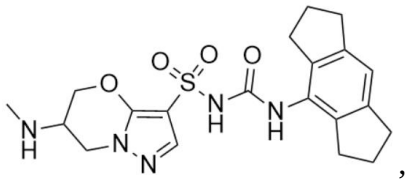
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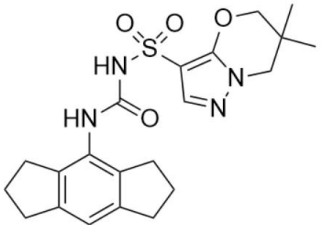
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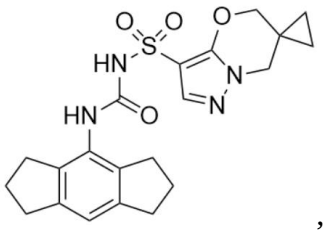
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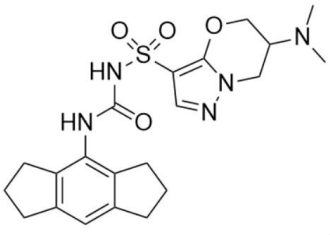
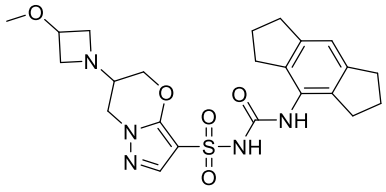

, or a

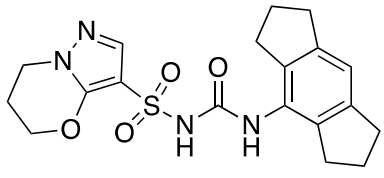
pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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



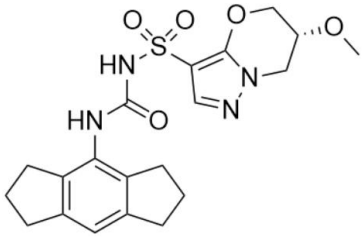
, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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



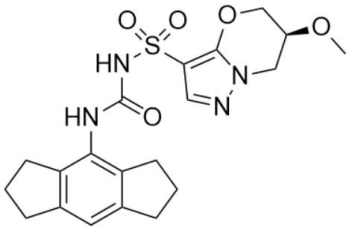
, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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



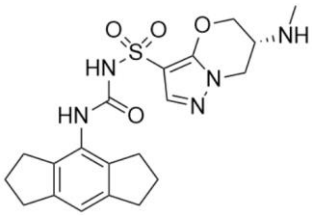
, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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



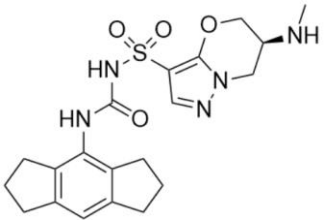
, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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



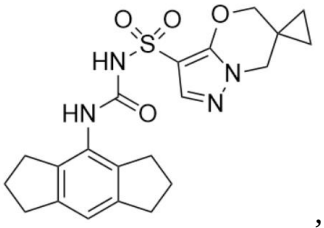
, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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



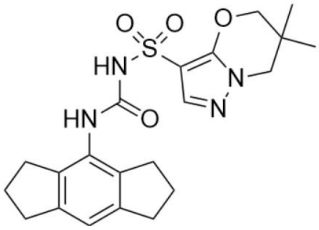
, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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



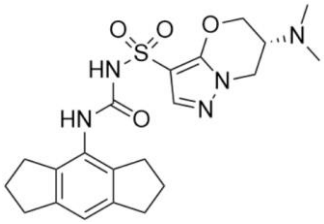
, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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



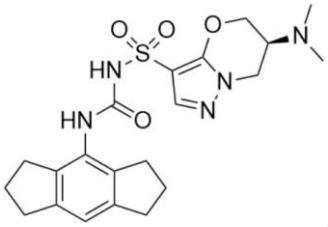
, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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



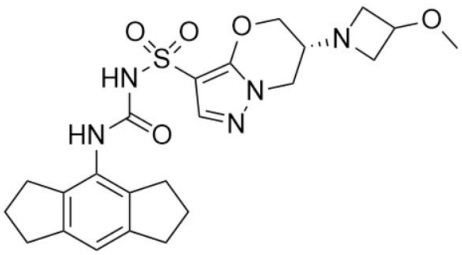
, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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



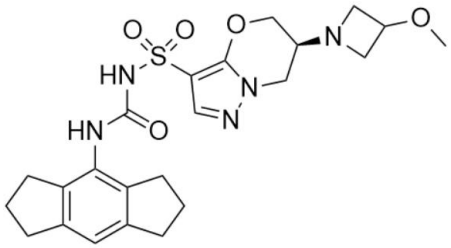
, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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



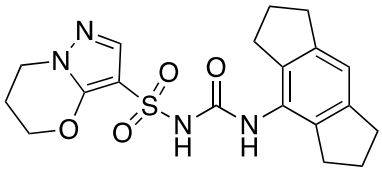
, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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



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

40. The compound of claim 1, wherein the compound is



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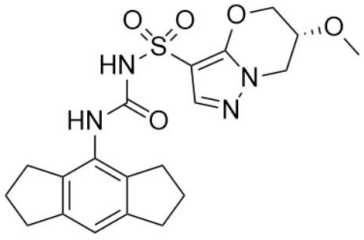
41. The compound of claim 1, wherein the compound is



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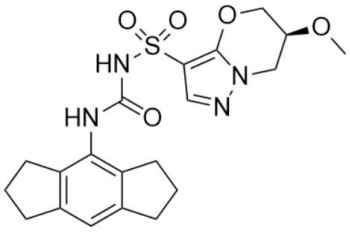
42. The compound of claim 1, wherein the compound is



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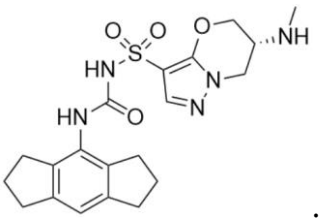
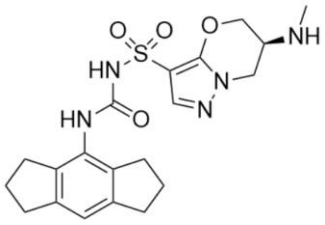
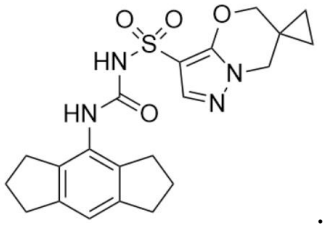
43. The compound of claim 1, wherein the compound is



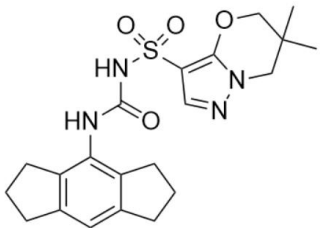
44. The compound of claim 1, wherein the compound is



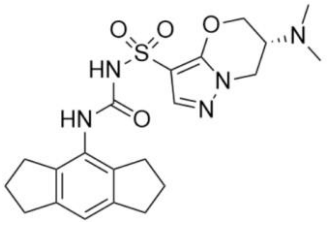
45. The compound of claim 1, wherein the compound is



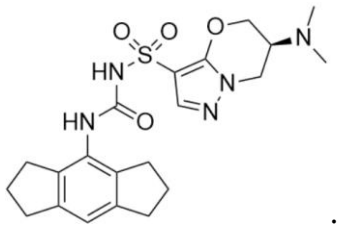
46. The compound of claim 1, wherein the compound is



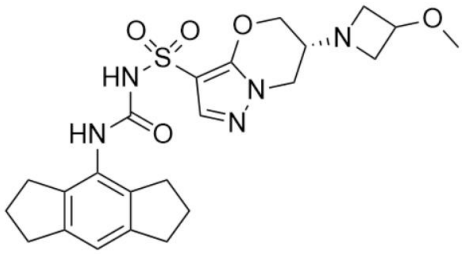
47. The compound of claim 1, wherein the compound is



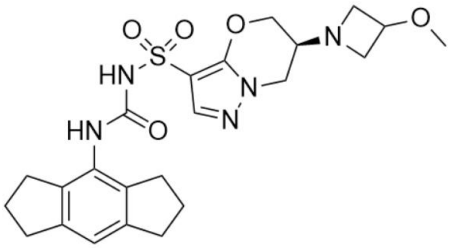
48. The compound of claim 1, wherein the compound is



49. The compound of claim 1, wherein the compound is



50. The compound of claim 1, wherein the compound is



51. A pharmaceutical composition comprising a compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

52. A pharmaceutical composition comprising a compound of any one of claims 40 to 50, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

53. A compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, or a compound of any one of claims 40 to 50, for use in therapy.

54. Use of a compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, or a compound of any one of claims 40 to 50, in the manufacture of a medicament for the treatment of a disease, disorder, or condition that is of the immune system, the cardiovascular system, the endocrine system, the gastrointestinal tract, the renal system, the respiratory system, the central nervous system, that is a cancer or other malignancy, or that is caused by or associated with a pathogen.

55. Use of a compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, or a compound of any one of claims 40 to 50, in the manufacture of a medicament for the treatment of an inflammatory or autoimmune disease, disorder, or condition.

56. Use of a compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, or a compound of any one of claims 40 to 50, in the manufacture of a medicament for the treatment of a disease, disorder, or condition selected from the group consisting of constitutive inflammation, the cryopyrin-associated periodic syndromes (CAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), neonatal-onset multisystem inflammatory disease (NOMID), autoinflammatory diseases, familial Mediterranean fever (FMF), TNF receptor associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), hyperimmunoglobulinemia D, periodic fever syndrome (HIDS), deficiency of interleukin 1 receptor (DIRA) antagonist, Majeed syndrome, pyogenic arthritis, pyoderma gangrenosum and acne (PAPA), haploinsufficiency of A20 (HA20), pediatric granulomatous arthritis (PGA), PLCG2-associated antibody deficiency and immune dysregulation (PLAID), PLCG2-associated autoinflammation, antibody deficiency and immune dysregulation (APLAID), sideroblastic anemia with B-cell immunodeficiency, periodic fevers, developmental delay (SIFD), Sweet's syndrome, chronic nonbacterial osteomyelitis (CNO), chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, osteitis syndrome (SAPHO), autoimmune diseases including multiple sclerosis (MS), type-1 diabetes, psoriasis, rheumatoid arthritis, Behcet's disease, Sjogren's syndrome, Schnitzler syndrome, respiratory diseases, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disorder (COPD), steroid-resistant asthma, asbestosis, silicosis, cystic fibrosis, central nervous system diseases, Parkinson's disease, Alzheimer's disease, motor neuron disease, Huntington's disease, cerebral malaria, brain injury from pneumococcal meningitis, metabolic diseases, Type 2 diabetes, atherosclerosis, obesity, gout, pseudo-gout, ocular disease, disease of the ocular epithelium, age-related macular degeneration (AMD), corneal infection, uveitis, dry eye, kidney disease, chronic kidney disease, oxalate nephropathy, diabetic nephropathy, liver disease, non-alcoholic steatohepatitis, alcoholic liver disease, inflammatory reactions in skin, contact hypersensitivity, sunburn, inflammatory reactions in the joints, osteoarthritis, systemic juvenile idiopathic arthritis, adult-onset Still's disease, relapsing polychondritis, viral infections,

alpha virus infection, Chikungunya virus infection, Ross River virus infection, flavivirus infection, Dengue virus infection, Zika virus infection, flu, HIV infection, hidradenitis suppurativa (HS), cyst-causing skin diseases, cancers, lung cancer metastasis, pancreatic cancers, gastric cancers, myelodisplastic syndrome, leukemia, polymyositis, stroke, myocardial infarction, Graft versus Host Disease, hypertension, colitis, helminth infection, bacterial infection, abdominal aortic aneurism, wound healing, depression, psychological stress, pericarditis, Dressler's syndrome, ischaemia reperfusion injury, and any disease where an individual has been determined to carry a germ line or somatic non-silent mutation in NLRP3.

57. Use of a compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, or a compound of any one of claims 40 to 50, in the manufacture of a medicament for the treatment of a disease, disorder, or condition selected from the group consisting of cryopyrin-associated periodic syndromes (CAPS), atherosclerosis, gout, pseudo-gout, rheumatoid arthritis, systemic juvenile idiopathic arthritis, non-alcoholic steatohepatitis, myocardial infarction, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and type-1 diabetes.