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

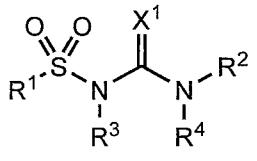
R^6 and R^7 together with the atom to which they are attached can form heterocyclyl or heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, S, P and O;

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] In one aspect,the present disclosure provides a compound of Formula Ie:



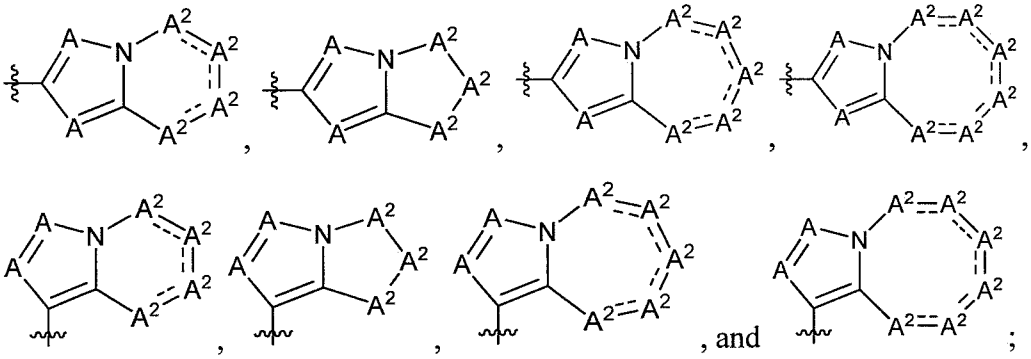
(Ie)

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

wherein:

X^1 is O or S;

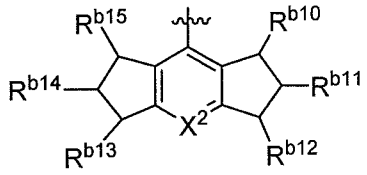
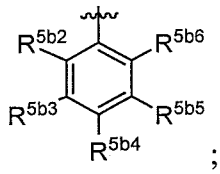
R^1 is selected from the group consisting of



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};

each R^{b10}, R^{b11}, R^{b12}, R^{b13}, R^{b14}, and R^{b15} is independently H, -OH, or oxo;

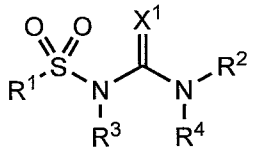
R^3 and R^4 are H;

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 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl$)_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$;

each R^{5a2} is independently H, D, halogen, OH, CN, $-NO_2$, $-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-

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] In one aspect, the present disclosure provides a compound of Formula If:



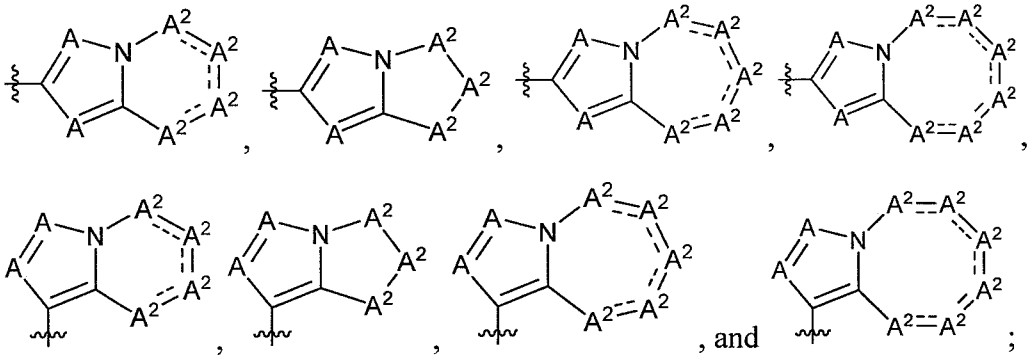
(If)

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

wherein:

X^1 is O or S;

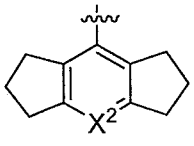
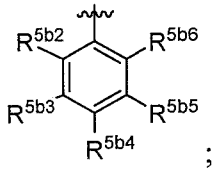
R^1 is selected from the group consisting of



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;

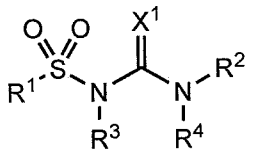
each R^{5a1} is independently H, D, halogen, OH, CN, $-NO_2$,$-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-NR^6C(O)R^6$, $-NR^6C(O)OR^6$, $-NR^6C(O)NR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-CH_2$-C_3-C_8cycloalkyl; wherein 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] In one aspect, the present disclosure provides a compound of Formula Ig:



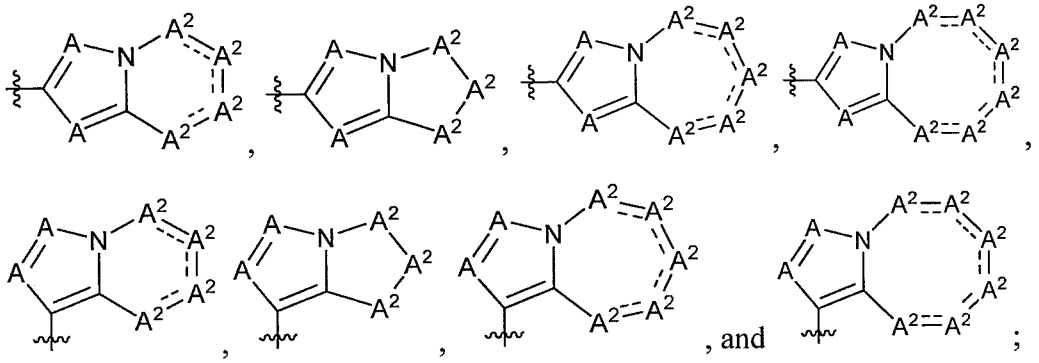
(Ig)

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

wherein:

X^1 is O or S;

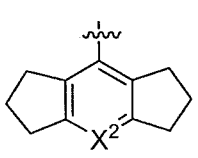
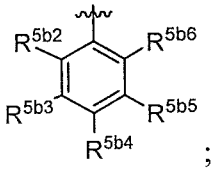
R^1 is selected from the group consisting of



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  ;

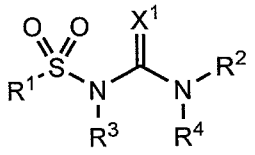
heterocyclyl, aryl, or heteroaryl are optionally substituted with halogen, -CN, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; and

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] In one aspect, the present disclosure provides a compound of Formula Ih:



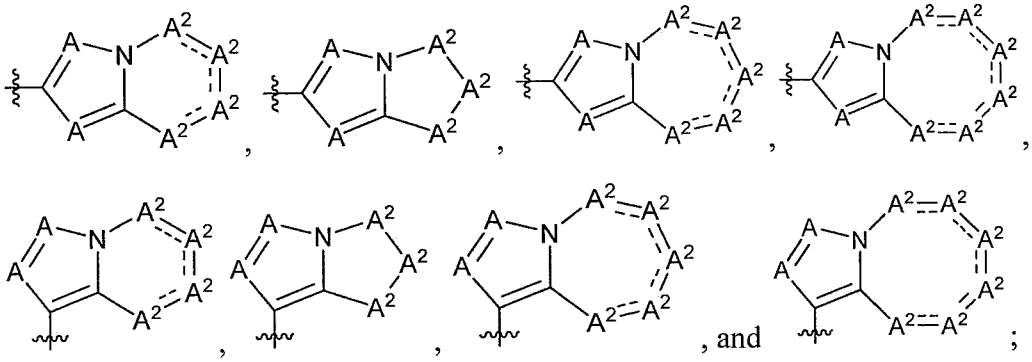
(Ih)

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

wherein:

X^1 is O or S;

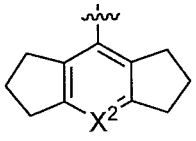
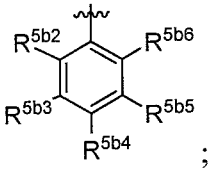
R^1 is selected from the group consisting of



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, $-NO_2$,$-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-NR^6C(O)R^6$, $-NR^6C(O)OR^6$, $-NR^6C(O)NR^6$, C1-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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl$)_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$;

each R^{5a2} is independently H, D, halogen, OH, -CN, $-NO_2$,$-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, 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 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl$)_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$, $-NR^6C(O)NR^6$, $-NR^6C(O)R^6$, or $-NR^6S(O)_2R^6$; or

wherein at least one R^{5a2} is $-NHR^6$, $-NR^6R^7$, 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl$)_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$, $-NR^6C(O)NR^6$, $-NR^6C(O)R^6$, or $-NR^6S(O)_2R^6$;

R^{5b1} is H, D, halogen, -CN,$-OR^6$, or C_1-C_6alkyl, C_3-C_8cycloalkyl, $-C(O)NR^6$, $-C(O)OR^6$; wherein the C_1-C_6alkyl, and C_3-C_8cycloalkyl, are optionally substituted with D, halogen, -CN, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), or $-N(C_1$-C_6alkyl$)_2$;

each R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} is independently 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_3-C_8cycloalkyl, or

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

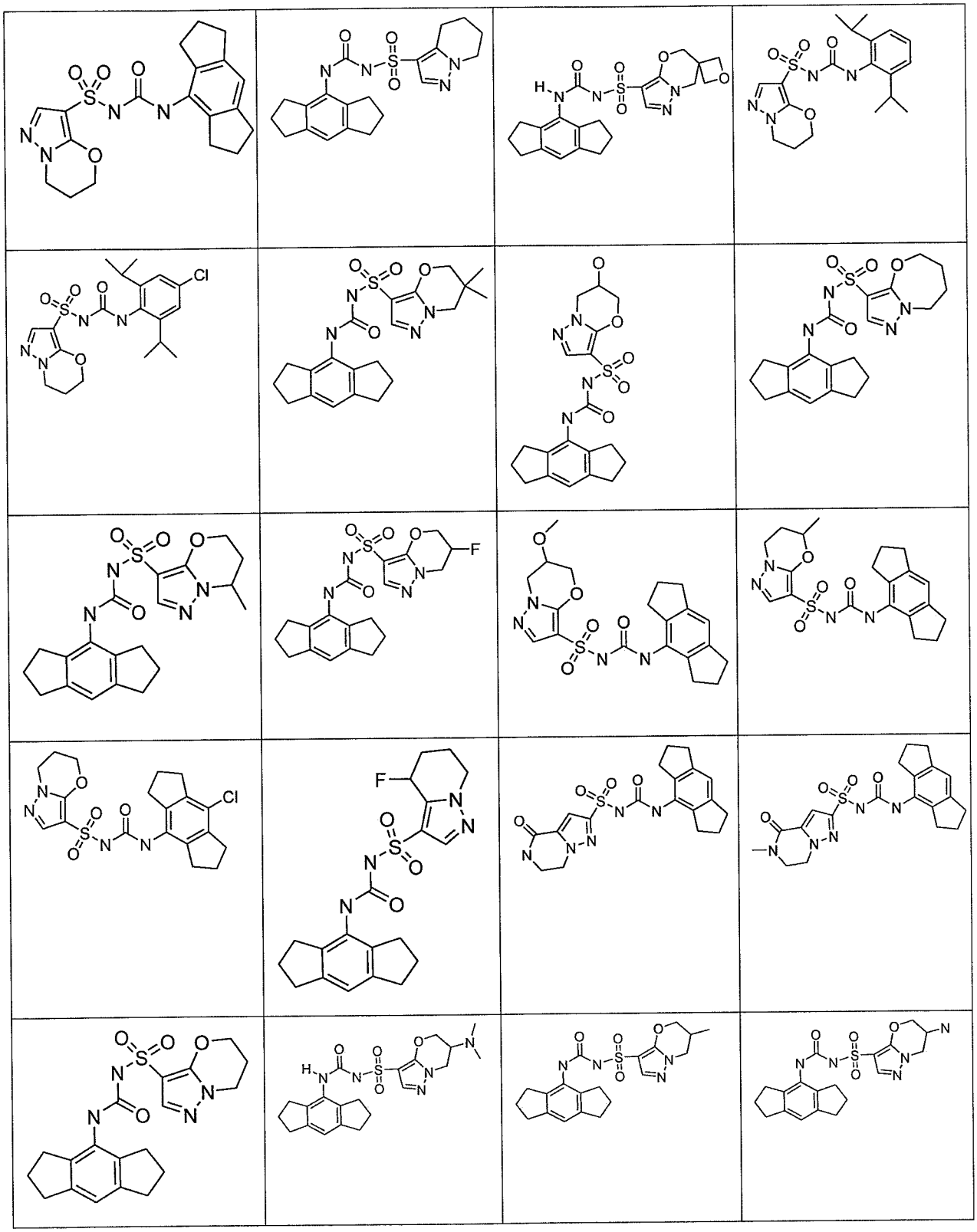
two adjacent R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} together with the atoms to which they are attached can form C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted with halogen, -CN, C_1-C_6alkyl, -OR^6,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

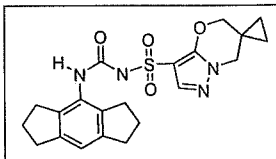
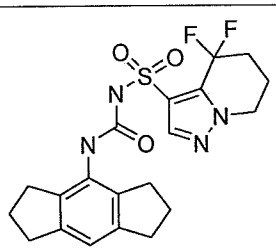
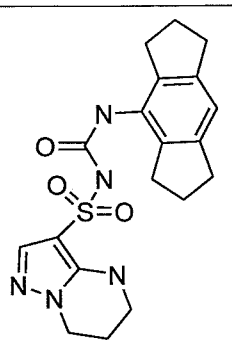
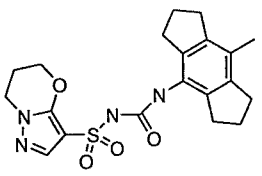
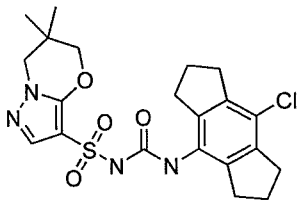
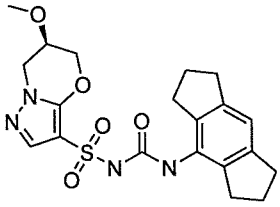
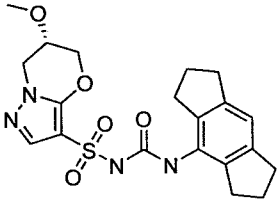
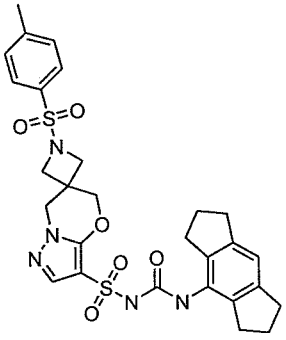
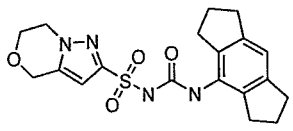
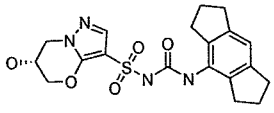
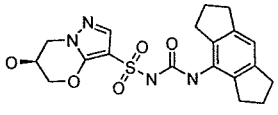
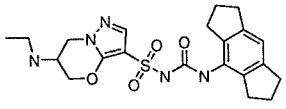
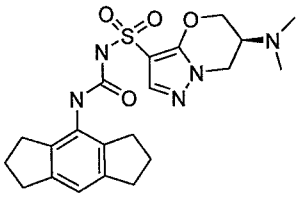
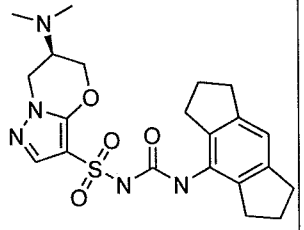
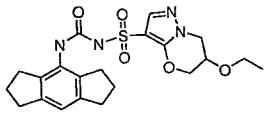
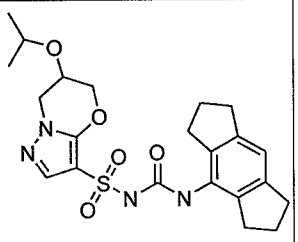
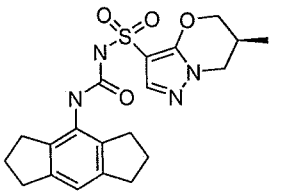
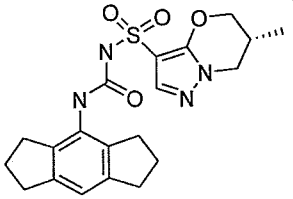
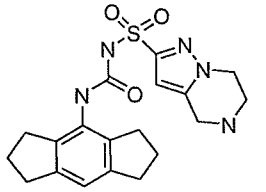
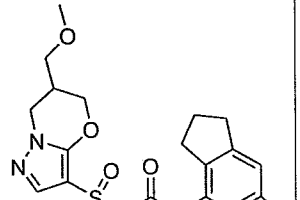
R^6 and R^7 are independently, at each occurrence, H, D, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, C_4-C_8cycloalkenyl, heterocyclyl, aryl, or heteroaryl; wherein the heterocyclyl and heteroaryl contain 1-5 heteroatoms selected from the group consisting of N, S, P and O; wherein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

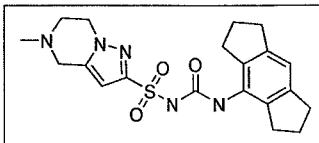
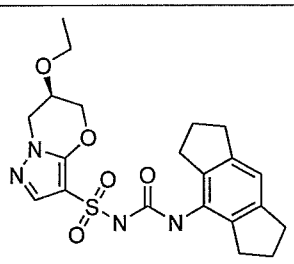
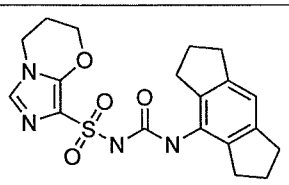
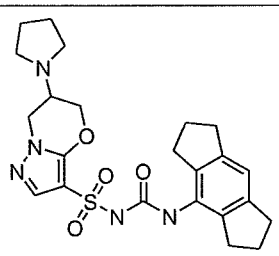
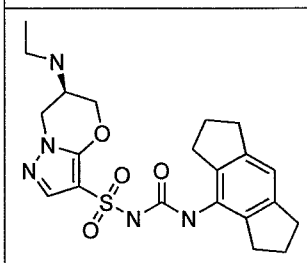
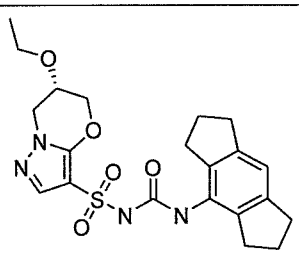
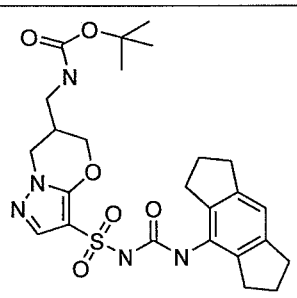
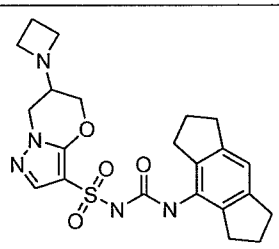
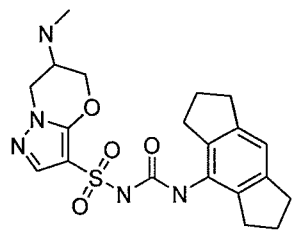
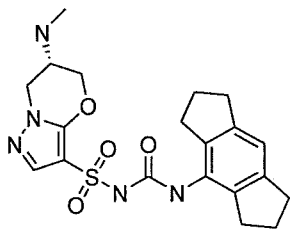
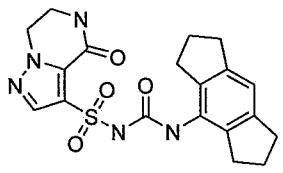
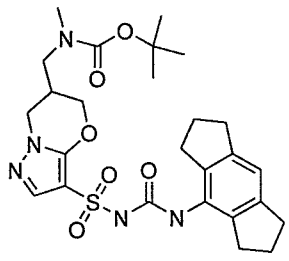
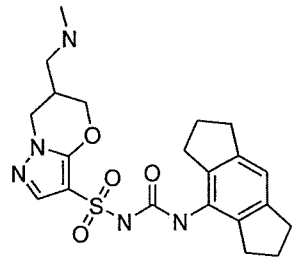
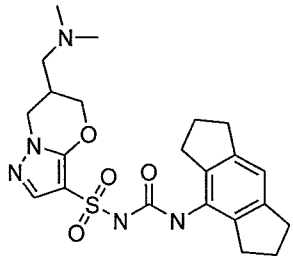
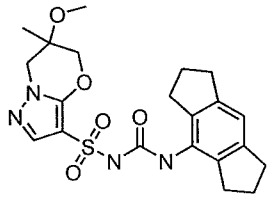
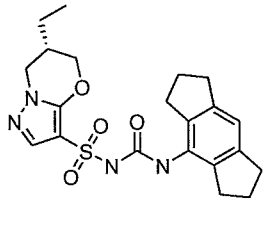
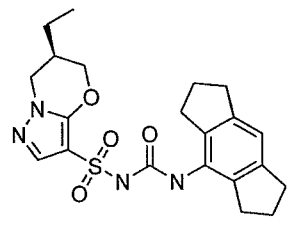
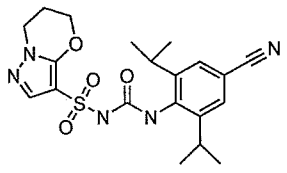
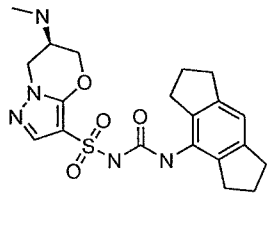
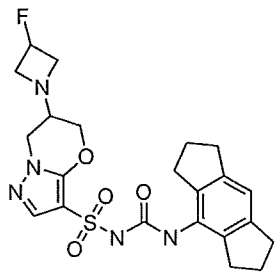
R^6 and R^7 together with the atom to which they are attached can form heterocyclyl or heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, S, P and O;

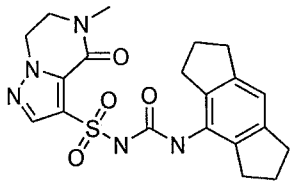
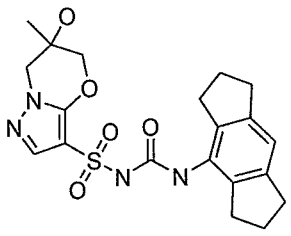
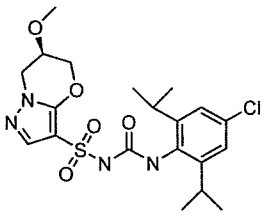
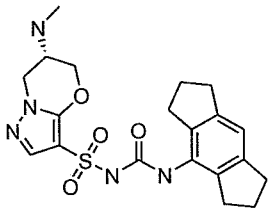
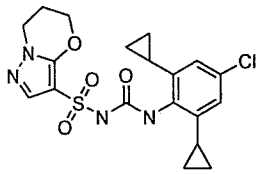
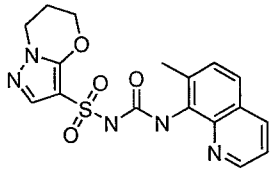
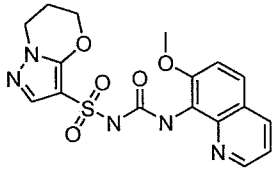
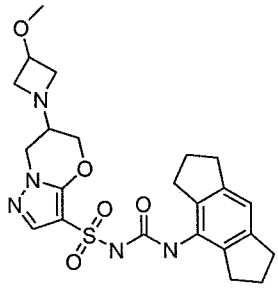
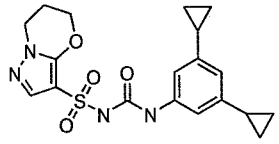
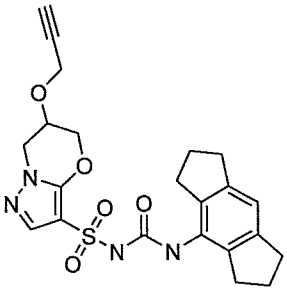
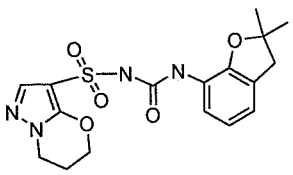
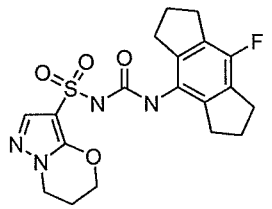
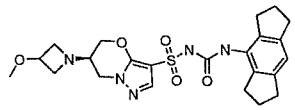
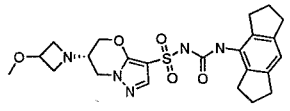
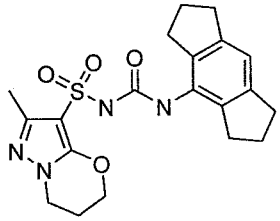
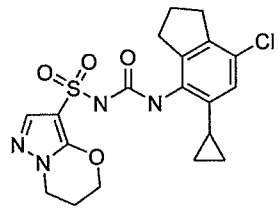
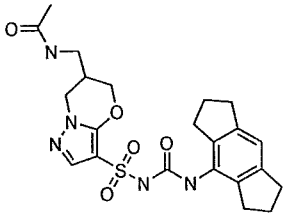
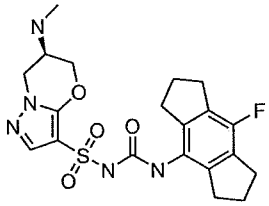
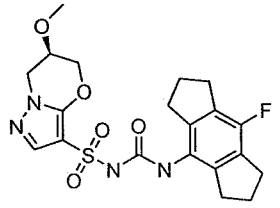
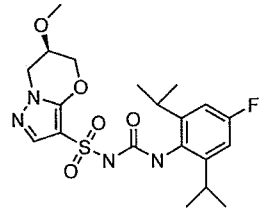
provided that when the ring comprising A and/or A^1 is an imidazole, then at least one A^2 is N, NR^{5a2}, O, S, or S(O)$_2$.

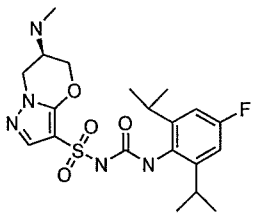
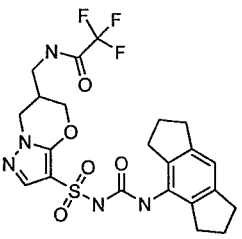
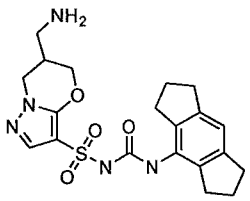
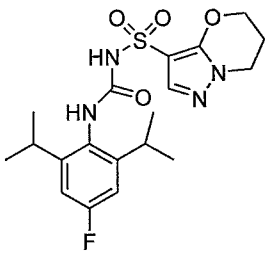
[0021a] In one aspect, the present disclosure provides a compound, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, selected from the group consisting of



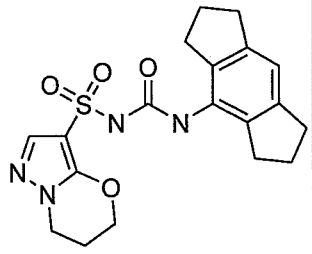
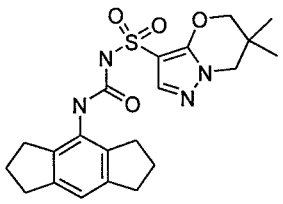
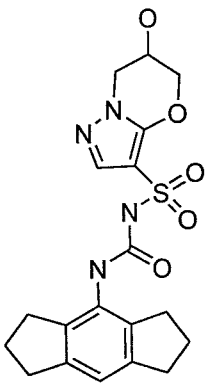
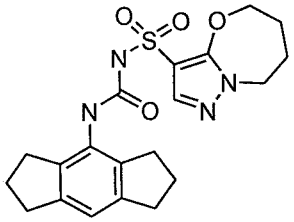
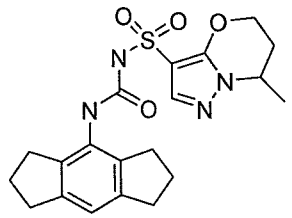
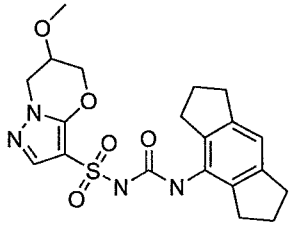
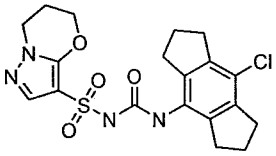
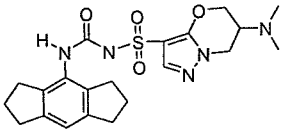
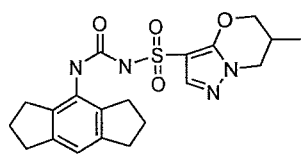
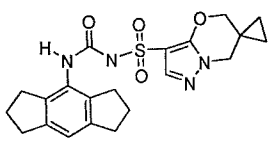
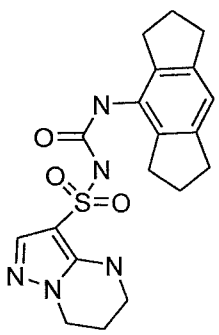
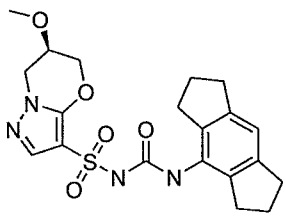
			
			
			
			
			

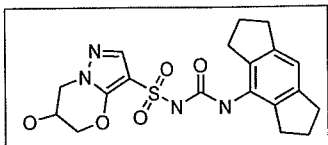
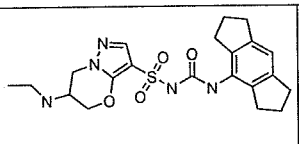
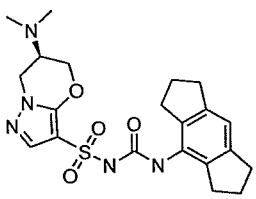
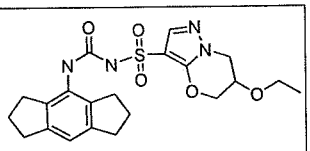
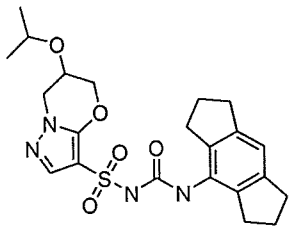
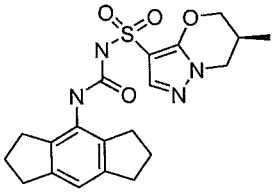
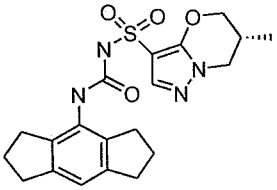
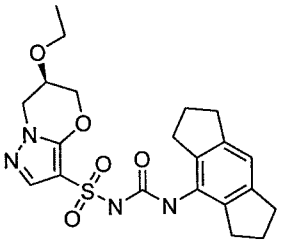
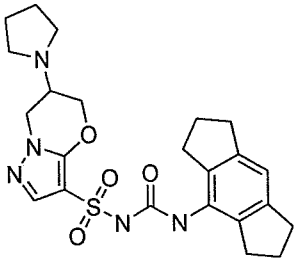
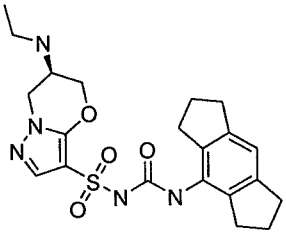
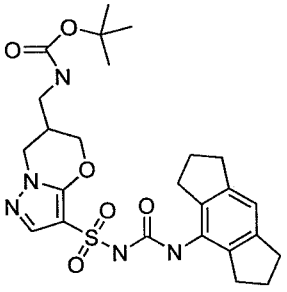
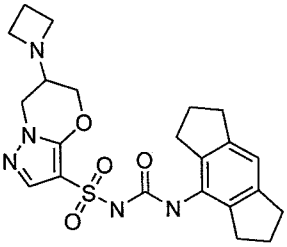
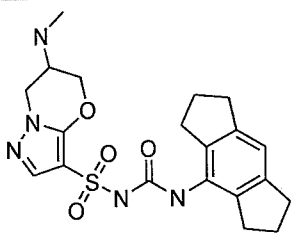
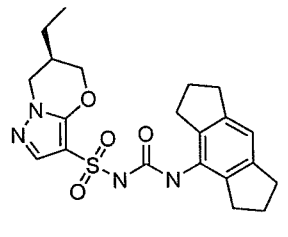
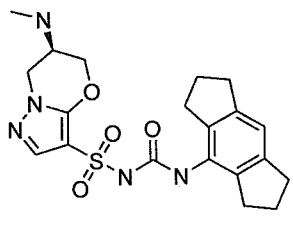
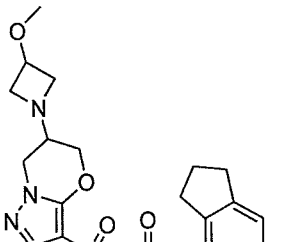
			
			
			
			
			

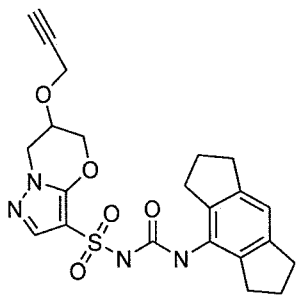
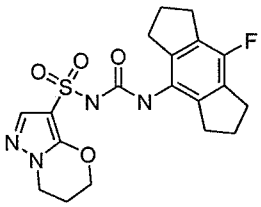
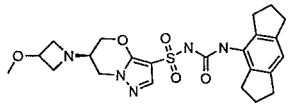
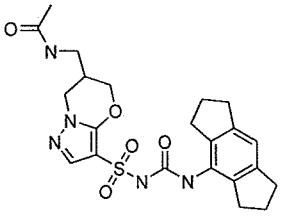
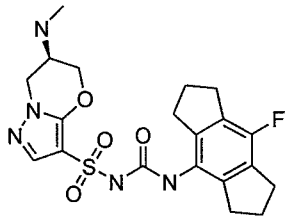
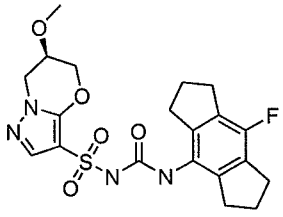
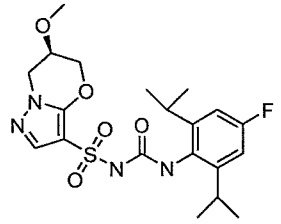
			
			
			
			
			

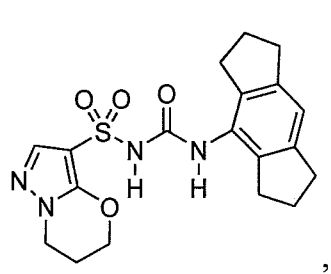
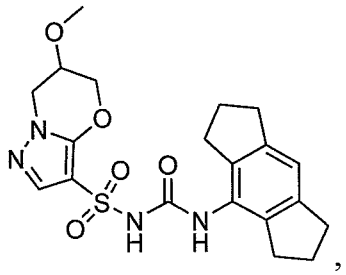
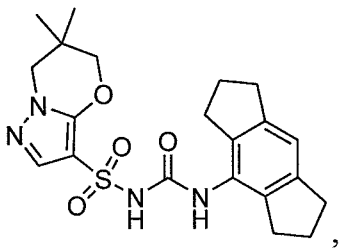
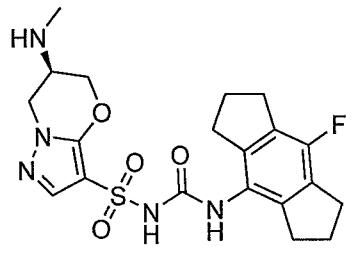
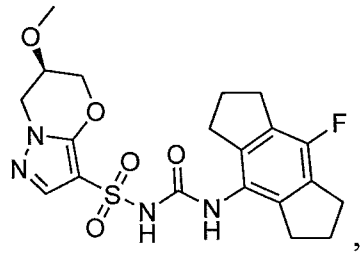
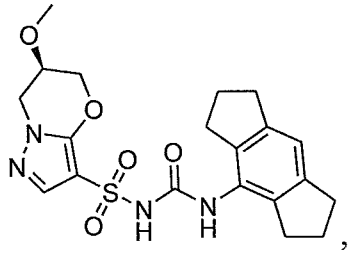
[0021b] In one aspect, the present disclosure provides a compound, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, selected from the group consisting of

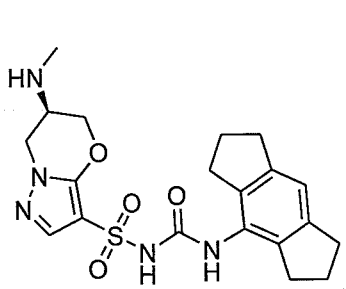
			
			
			

[0021c] In one aspect, the present disclosure provides a compound, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, selected from the group consisting of

 ,
 ,
 ,
 ,
 ,
 ,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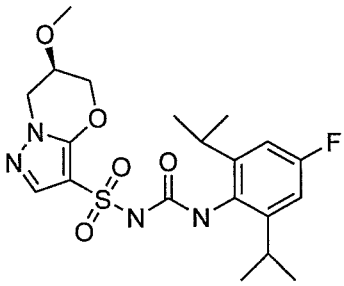
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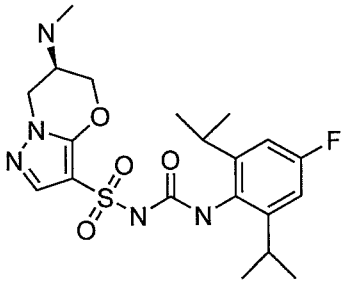
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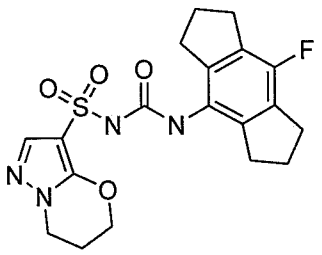
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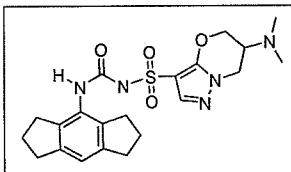
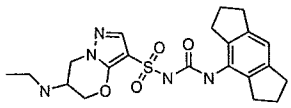
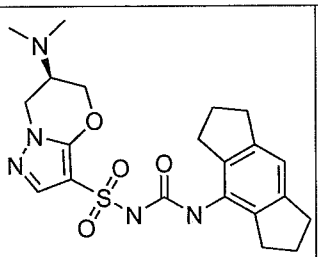
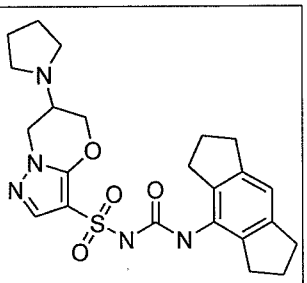
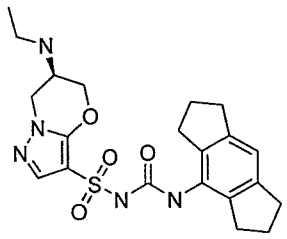
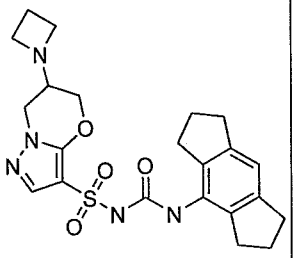
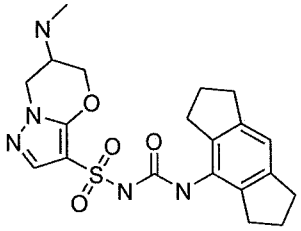
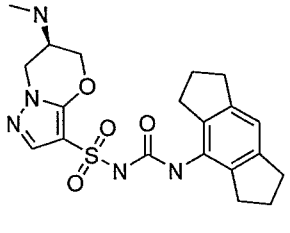
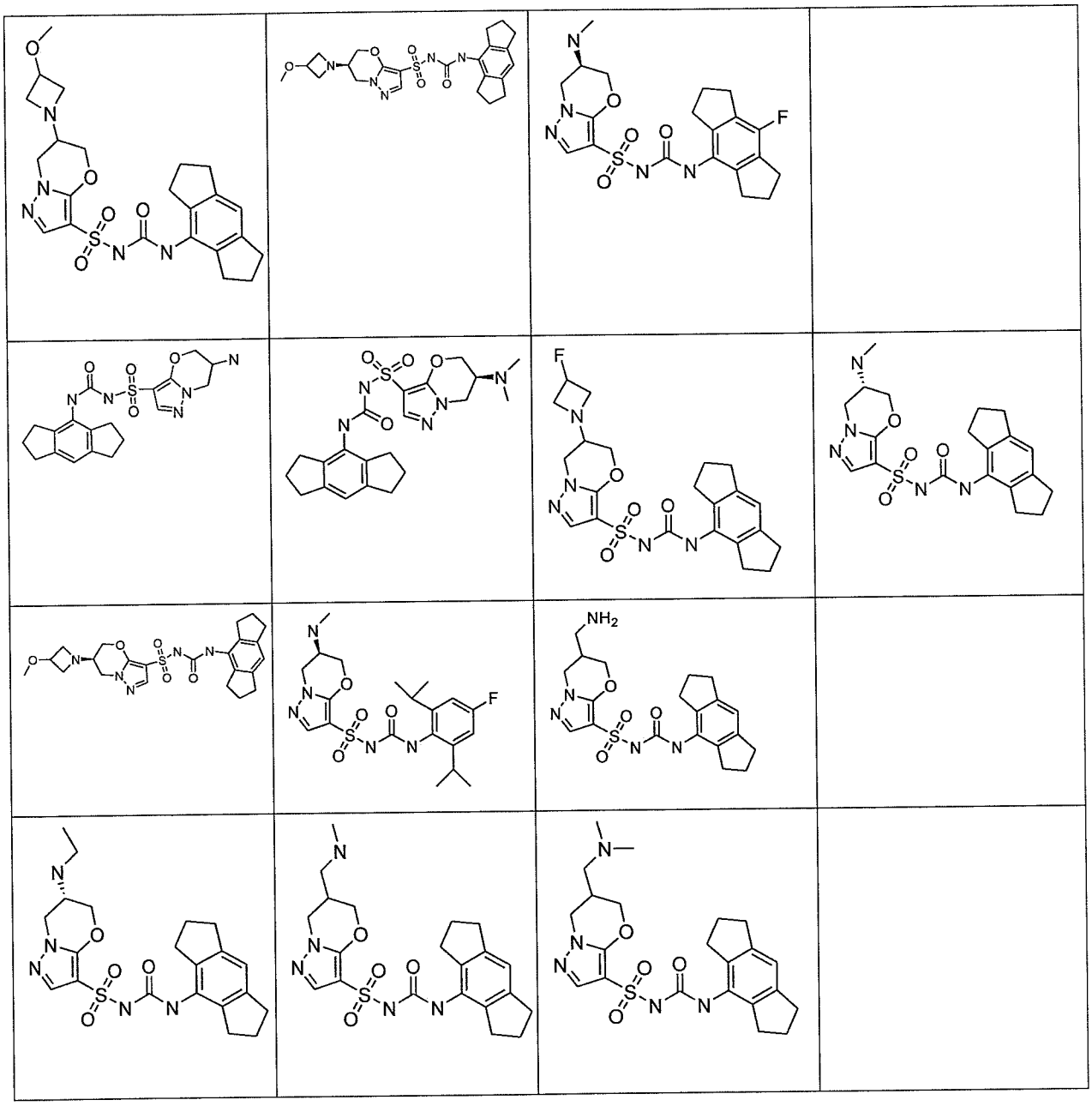
[0021d] In one aspect, the present disclosure provides a compound, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, selected from the group consisting of



[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 one aspect, the present disclosure provides use of a compound of the present disclosure, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, in the manufacture of a medicament for the treatment or prevention of a disease, disorder, or condition that is responsive to inhibition of inflammasome in a subject in need thereof.

[0023b] In one aspect, the present disclosure provides a compound of the present disclosure, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, for use in the manufacture of a medicament for treating a disease, disorder or condition that is responsive to inhibition of inflammasome.

[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.

[0030a] In one aspect, 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, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof.

[0030b] In one aspect, the present disclosure provides a method of inhibiting activation of an inflammasome comprising the step of exposing the biological target to a compound of the present disclosure, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer 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

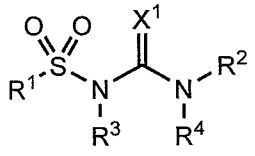
[0032] Figure 1 shows inhibition of IL-1β production in peripheral blood mononucleocytes (PBMCs) as a result of treatment with Compound 1, Compound 2, or Compound 3.

[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 If:



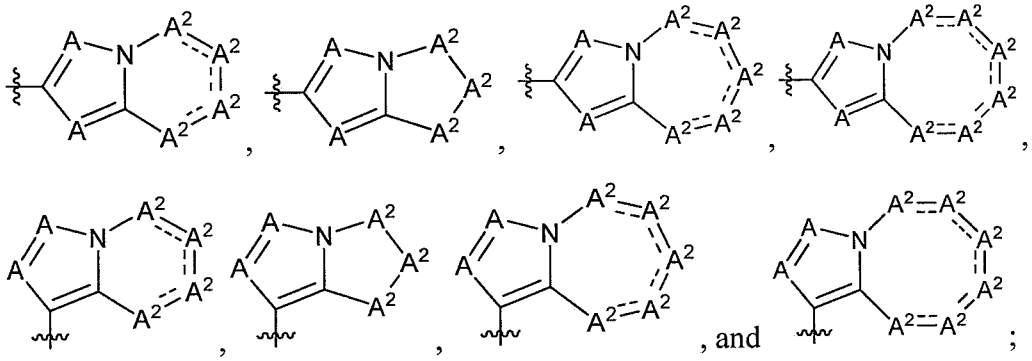
(If)

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

wherein:

X^1 is O or S;

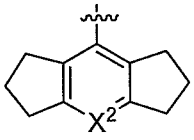
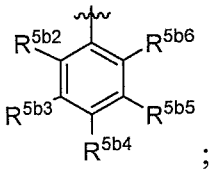
R^1 is selected from the group consisting of



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 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, -CN, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, -$NR^6C(O)OR^6$, or –$NR^6C(O)R^6$;

each R^{5a2} is independently H, D, halogen, OH, CN, –NO_2,–SR^6, –OR^6, –NHR^6, –NR^6R^7, -$C(O)R^6$, -$S(O)_2R^6$, -$C(O)OR^6$, -$C(O)NR^6$, 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 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, -CN, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, -$NR^6C(O)OR^6$, –$NR^6C(O)R^6$, -$NR^6C(O)NR^6$, -$NR^6C(O)R^6$, or –$NR^6S(O)_2R^6$; or

two R^{5a2} 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), -N(C_1-C_6alkyl)$_2$, –$S(O)_2$-R^6, -COR^6, -$NR^6C(O)OR^6$, –$NR^6C(O)R^6$, -$NR^6C(O)NR^6$, or -$NR^6S(O)_2R^6$; or

two geminal R^{5a2} can form an oxo group;

R^{5b1} is H, D, halogen, -CN,–OR^6, or C_1-C_6alkyl, C_3-C_8cycloalkyl, -$C(O)NR^6$, -$C(O)OR^6$; wherein the C_1-C_6alkyl, and C_3-C_8cycloalkyl, are optionally substituted with D, halogen, -CN, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$;

each R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} is independently 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_3-C_8cycloalkyl, or 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

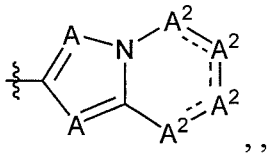
R^6 and R^7 together with the atom to which they are attached can form heterocyclyl or heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, S, P and O;

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 $S(O)_2$.

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

X^1 is O;

R^1 is selected from the group consisting of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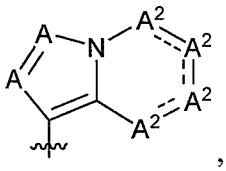
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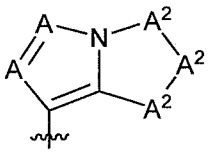
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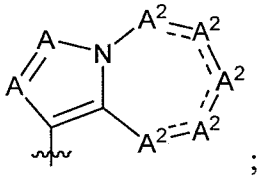

;

wherein ≡ represents a single bond;

each A^2 is independently $C(R^{5a2})_2$ or O;

X^2 is CR^{5b1};

each R^{5a1} is independently H or C_1-C_6alkyl; wherein the C_1-C_6alkyl is optionally substituted with D, halogen, -OR^6, -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, -$NR^6C(O)OR^6$, or –$NR^6C(O)R^6$;

each R^{5a2} is independently H, halogen, OH, –OR^6, –NHR^6, –NR^6R^7, C_1-C_6alkyl, or heterocyclyl; wherein the C_1-C_6alkyl and heterocyclyl are optionally substituted with D, halogen, -OR^6, -NH_2, NH(C_1-C_6alkyl), N(C_1-C_6alkyl)$_2$, -$NR^6C(O)OR^6$, or –$NR^6C(O)R^6$; or

two R^{5a2} 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), -N(C_1-C_6alkyl)$_2$, or –$S(O)_2$-R^6; or

two geminal R^{5a2} can form an oxo group;

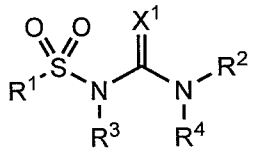
R^{5b1} is H, D, halogen, or C_1-C_6alkyl;

each R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} is independently H, D, halogen, -CN,–OR^6, C_1-C_6alkyl, or C_3-C_8cycloalkyl; wherein the C_1-C_6alkyl, and C_3-C_8cycloalkyl, are optionally substituted with D, halogen, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$; or

two 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, or heteroaryl, wherein C_3-C_8cycloalkyl, heterocyclyl, or heteroaryl are optionally substituted with halogen or C_1-C_6alkyl; and

R^6 and R^7 are independently, at each occurrence, H, D, C_1-C_8alkyl, C_2-C_8alkynyl, or aryl; wherein the C_1-C_8alkyl, C_2-C_8alkynyl, and aryl, are optionally substituted with D, halogen or C_1-C_6alkyl.

3. A compound of formula Ig:



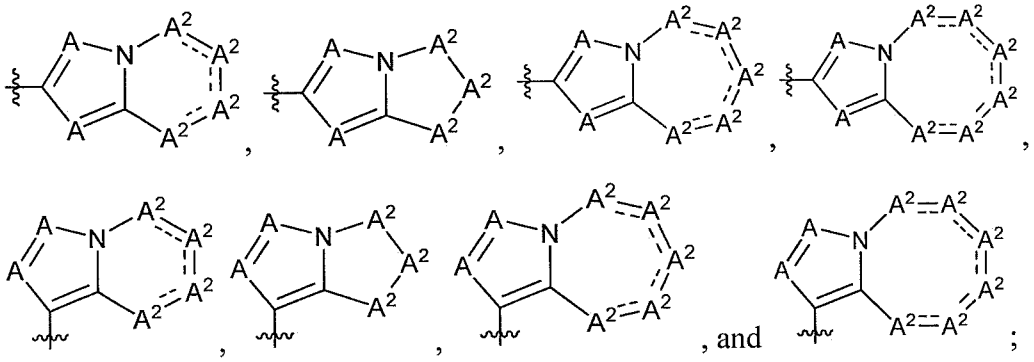
(Ig)

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

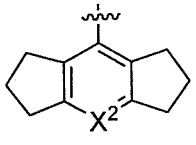
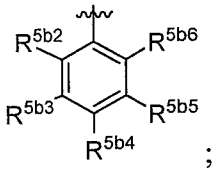


, and ;

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  ;

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 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $N(C_1$-C_6alkyl$)_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$;

each R^{5a2} is independently H, D, halogen, OH, CN, $-NO_2$,$-SR^6$, $-OR^6$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, 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 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NR^6C(O)OR^6$, $-NR^6C(O)R^6$, $-NR^6C(O)NR^6$, $-NR^6C(O)R^6$, or $-NR^6S(O)_2R^6$; or

two R^{5a2} 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, $-OR^6$,$-S(O)_2$-R^6; $-COR^6$, $NR^6C(O)OR^6$, $-NR^6C(O)R^6$, $-NR^6C(O)NR^6$, or $-NR^6S(O)_2R^6$; or

two geminal R^{5a2} can form an oxo group;

R^{5b1} is H, D, halogen, -CN,$-OR^6$, or C_1-C_6alkyl, C_3-C_8cycloalkyl, $-C(O)NR^6$, $-C(O)OR^6$; wherein the C_1-C_6alkyl, and C_3-C_8cycloalkyl, are optionally substituted with D, halogen, -CN, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), or $-N(C_1$-C_6alkyl$)_2$;

each R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} is independently 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_3-C_8cycloalkyl, or 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

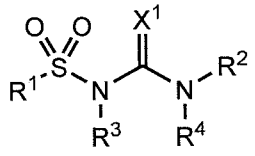
two adjacent R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} together with the atoms to which they are attached can form C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted with halogen, -CN, C_1-C_6alkyl, -OR^6,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

4. A compound of formula Ih:



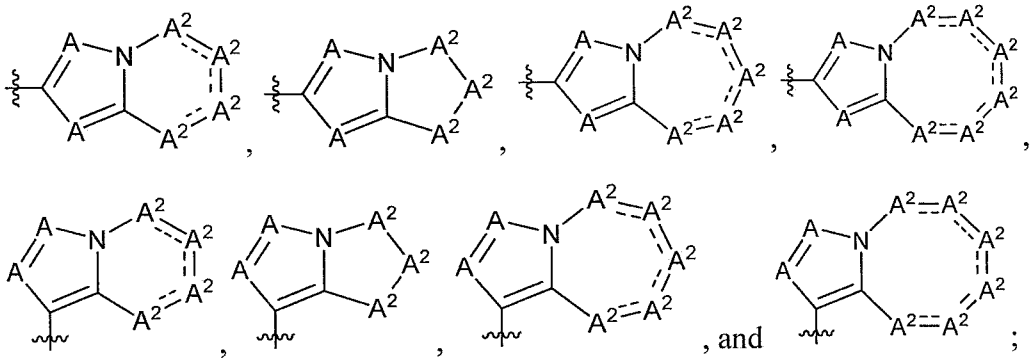
(Ih)

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

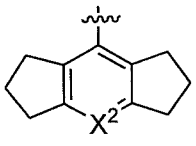
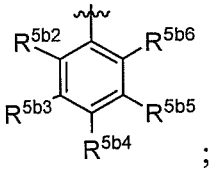


, and ;

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

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, $-NO_2$,$-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-NR^6C(O)R^6$, $-NR^6C(O)OR^6$, $-NR^6C(O)NR^6$, C1-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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl)$_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$;

each R^{5a2} is independently H, D, halogen, OH, -CN, $-NO_2$,$-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, 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 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl)$_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$, $-NR^6C(O)NR^6$, $-NR^6C(O)R^6$, or $-NR^6S(O)_2R^6$; or

wherein at least one R^{5a2} is $-NHR^6$, $-NR^6R^7$, 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl)$_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$, $-NR^6C(O)NR^6$, $-NR^6C(O)R^6$, or $-NR^6S(O)_2R^6$;

R^{5b1} is H, D, halogen, -CN,$-OR^6$, or C_1-C_6alkyl, C_3-C_8cycloalkyl, $-C(O)NR^6$, $-C(O)OR^6$; wherein the C_1-C_6alkyl, and C_3-C_8cycloalkyl, are optionally substituted with D, halogen, -CN, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), or $-N(C_1$-C_6alkyl)$_2$;

each R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} is independently 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_3-C_8cycloalkyl, or 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

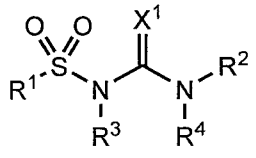
two adjacent R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} together with the atoms to which they are attached can form C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted with halogen, -CN, C_1-C_6alkyl, $-OR^6$,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

5. A compound of formula Ie:



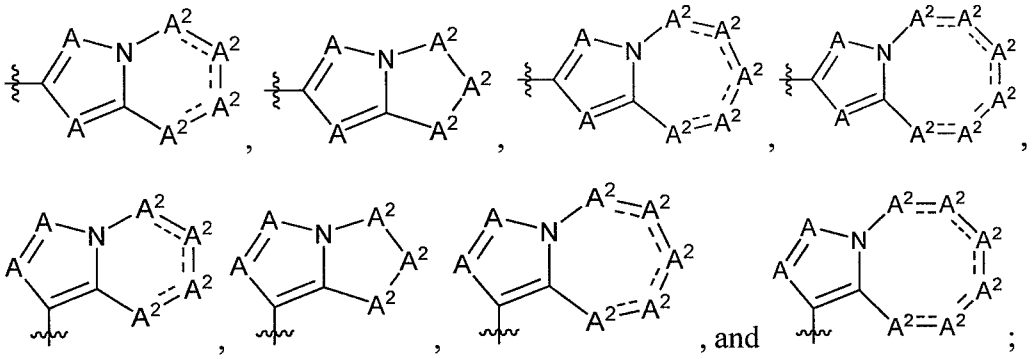
(Ie)

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

wherein:

X^1 is O or S;

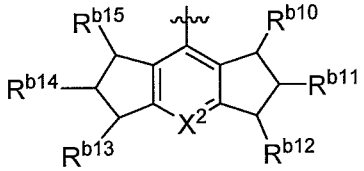
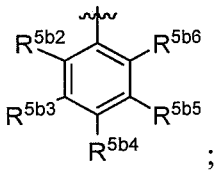
R^1 is selected from the group consisting of



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};

each R^{b10}, R^{b11}, R^{b12}, R^{b13}, R^{b14}, and R^{b15} is independently H, -OH, or oxo;

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 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl$)_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$;

each R^{5a2} is independently H, D, halogen, OH, CN, $-NO_2$,$-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, 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 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl$)_2$, $-NR^6C(O)OR^6$, $-NR^6C(O)R^6$, $NR^6C(O)NR^6$, $-NR^6C(O)R^6$, or $-NR^6S(O)_2R^6$; or

two R^{5a2} 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), -N(C_1-C_6alkyl)$_2$, –$S(O)_2$-R^6, -COR^6, $NR^6C(O)OR^6$, –$NR^6C(O)R^6$, -$NR^6C(O)NR^6$, or -$NR^6S(O)_2R^6$; or

two geminal R^{5a2} can form an oxo group;

R^{5b1} is H, D, halogen, -CN,–OR^6, or C_1-C_6alkyl, C_3-C_8cycloalkyl, -$C(O)NR^6$, -$C(O)OR^6$; wherein the C_1-C_6alkyl, and C_3-C_8cycloalkyl, are optionally substituted with D, halogen, -CN, -OR^6, -NH_2, -NH(C_1-C_6alkyl), or -N(C_1-C_6alkyl)$_2$;

each R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} is independently 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_3-C_8cycloalkyl, or 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

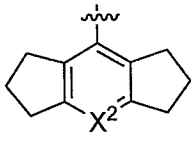
two adjacent R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} together with the atoms to which they are attached can form C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein C_3-C_8cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted with halogen, -CN, C_1-C_6alkyl, -OR^6,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

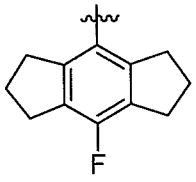
6. The compound of any one of claims 1 and 3-5, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein X^1 is O.

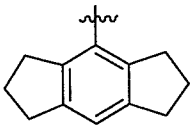
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^2 is  .

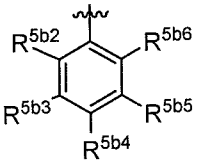
8. The compound of claim 7, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein X^2 is CR^{5b1}.

9. The compound of claim 8, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^{5b1} is H, halogen, or C_1-C_6alkyl.

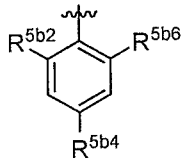
10. The compound of claim 8, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^{5b1} is H, fluoro, chloro, or methyl.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^2 is  .

12. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^2 is  .

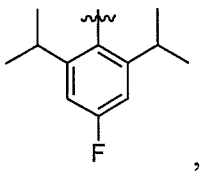
13. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^2 is  .

14. The compound of claim 13, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} is independently H, D, halogen, OH, CN, $-NO_2$, $-OR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, or C_3-C_8cycloalkyl.

15. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^2 is  .

16. The compound of claim 15, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each R^{5b2}, R^{5b3}, R^{5b4}, R^{5b5}, and R^{5b6} is independently selected from the group consisting of H, D, halogen, C_1-C_6alkyl, C_3-C_8cycloalkyl, and -CN.

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^2 is selected from the group consisting of



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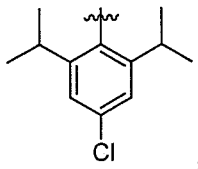

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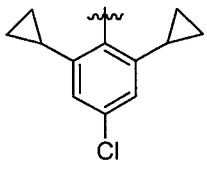

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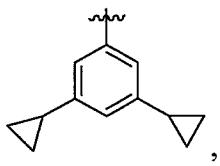
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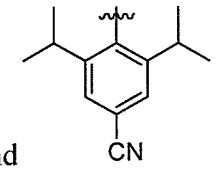

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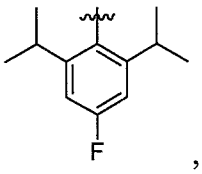
18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^2 is selected from the group consisting of



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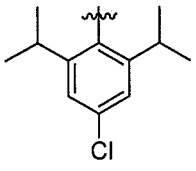
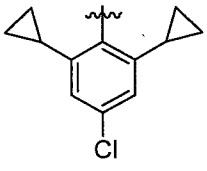
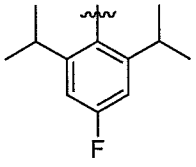


, and


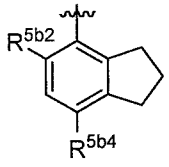
.

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^2 is



.

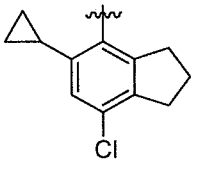
20. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^2 is



.

21. The compound of claim 20, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each R^{5b2} and R^{5b4} is selected from the group consisting of H, D, halogen, C_1-C_6alkyl, C_3-C_8cycloalkyl, and -CN.

22. The compound of any one of claims 20 and 21, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^2 is



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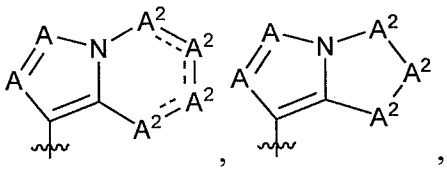
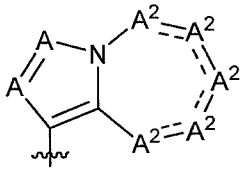
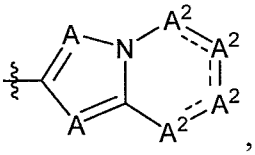
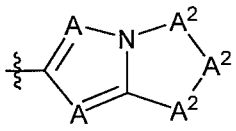
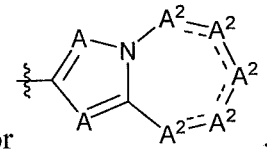
23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is  , ,  or .

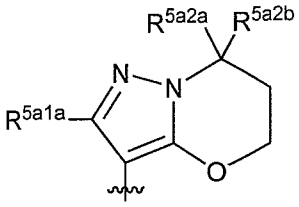
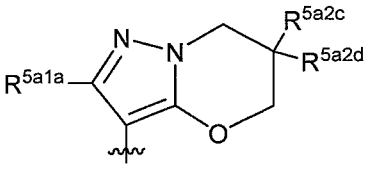
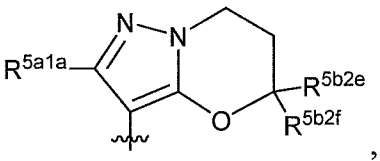
24. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is  ,  , or  .

25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein one A is CR^{5a1} and the other A is N.

26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each A^2 is independently $C(R^{5a2})_2$, NR^{5a2}, or O.

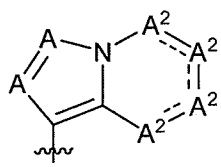
27. The compound of claim 26, wherein each R^{5a2} is independently H, $-NHR^6$, $-NR^6R^7$, C_1-C_6alkyl, or heterocyclyl containing N, wherein the C_1-C_6alkyl is substituted with $-NH_2$, $-NH(C_1$-C_6alkyl), or $-N(C_1$-C_6alkyl$)_2$, and wherein the heterocyclyl is optionally substituted with with D, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl$)_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$, $-NR^6C(O)NR^6$, $-NR^6C(O)R^6$, or $-NR^6S(O)_2R^6$.

28. The compound of claim 27, wherein R^1 is selected from the group consisting of


,

, and

,

wherein R^{5a1a} is 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 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl$)_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$. and

R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, R^{5a2e}, and R^{5a2f} are selected from 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 with D, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl$)_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$, $-NR^6C(O)NR^6$, $-NR^6C(O)R^6$, or $-NR^6S(O)_2R^6$.

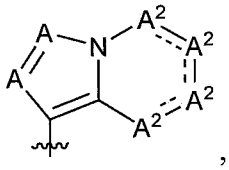
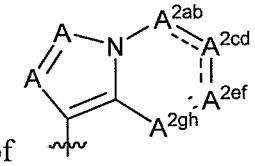
29. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is  .

30. The compound of claim 29, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein one A is CR^{5a1} and the other A is N.

31. The compound of any one of claims 29-30, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each A^2 is independently $C(R^{5a2})_2$, NR^{5a2}, or O.

32. The compound of any one of claims 29-30, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each R^{5a2} is independently H, halogen, OH, $-OR^6$, $-NHR^6$, $-NR^6R^7$, C_1-C_6alkyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-CH_2$-C_3-C_8cycloalkyl.

33. The compound of any one of claims 20-32, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein two R^{5a2} together with the atoms to which they are attached can form C_3-C_8cycloalkyl or heterocyclyl.

34. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is  , which is a formula of  , wherein

A^{2ab} is selected from CR^{5a2}, $C(R^{5a2a})(R^{5a2b})$, N, NR^{5a2}, O, S, or $S(O)_2$;

A^{2cd} is selected from CR^{5a2}, $C(R^{5a2c})(R^{5a2d})$, N, NR^{5a2}, O, S, or $S(O)_2$;

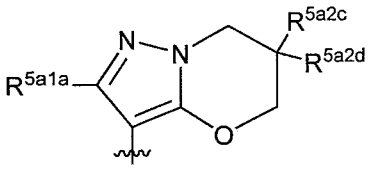
A^{2ef} is selected from CR^{5a2}, $C(R^{5a2e})(R^{5a2f})$, N, NR^{5a2}, O, S, or $S(O)_2$; and

A^{2gh} is selected from CR^{5a2}, $C(R^{5a2g})(R^{5a2h})$, N, NR^{5a2}, O, S, or $S(O)_2$;

each R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, R^{5a2e}, R^{5a2f}, R^{5a2g}, and R^{5a2h} are independently H, D, halogen, OH, CN, $-NO_2$,$-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, 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 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl)$_2$, $-NR^6C(O)OR^6$, $-NR^6C(O)R^6$, $NR^6C(O)NR^6$, $-NR^6C(O)R^6$, or $-NR^6S(O)_2R^6$; or

two R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, R^{5a2e}, R^{5a2f}, R^{5a2g}, and R^{5a2h} 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), $-N(C_1$-C_6alkyl)$_2$, $-S(O)_2$-R^6, $-COR^6$, $NR^6C(O)OR^6$, $-NR^6C(O)R^6$, $-NR^6C(O)NR^6$, or $-NR^6S(O)_2R^6$; or

two geminal R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, R^{5a2e}, R^{5a2f}, R^{5a2g}, and R^{5a2h} can form an oxo group.

35. The compound of claim 34, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is.  , wherein

wherein R^{5a1a} is 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 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl)$_2$, $-NR^6C(O)OR^6$, or $-NR^6C(O)R^6$;

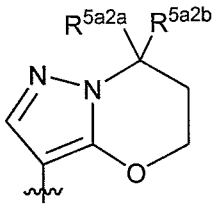
R^{5a2c} and R^{5a2d} are each independently H, D, halogen, OH, CN, $-NO_2$,$-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-CH_2$-C_3-C_8cycloalkyl;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

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

36. The compound of claim 35, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each R^{5a2c} and R^{5a2d} is independently H, halogen, OH, $-OR^6$, $-NHR^6$, $-NR^6R^7$, C_1-C_6alkyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or -CH_2-C_3-C_8cycloalkyl.

37. The compound of any one of claims 35-36, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^{5a2c} and R^{5a2d} together with the atoms to which they are attached can form C_3-C_8cycloalkyl or heterocyclyl.

38. The compound of claim 34, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is.  , wherein

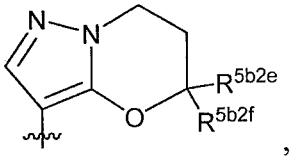
R^{5a2a} and R^{5a2b} are each independently H, D, halogen, OH, CN, $-NO_2$,$-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-CH_2$-C_3-C_8cycloalkyl;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

R^{5a2a} and 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), $-N(C_1$-C_6alkyl)$_2$, $-S(O)_2$-R^6, $-COR^6$, $NR^6C(O)OR^6$, $-NR^6C(O)R^6$, $-NR^6C(O)NR^6$, or $-NR^6S(O)_2R^6$; or

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

39. The compound of claim 38, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each R^{5a2a} and R^{5a2b} is independently H, halogen, OH, $-OR^6$, $-NHR^6$, $-NR^6R^7$, C_1-C_6alkyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-CH_2$-C_3-C_8cycloalkyl.

40. The compound of any one of claims 38-39, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^{5a2a} and R^{5a2b} together with the atoms to which they are attached can form C_3-C_8cycloalkyl or heterocyclyl.

41. The compound of claim 33, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is.  , wherein

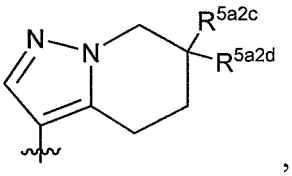
R^{5a2e} and R^{5a2f} are each independently independently H, D, halogen, OH, CN, $-NO_2$, $-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl,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

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

42. The compound of claim 41, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each R^{5a2e} and R^{5a2f} is independently H, halogen, OH, $-OR^6$, $-NHR^6$, $-NR^6R^7$, C_1-C_6alkyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or -CH_2-C_3-C_8cycloalkyl.

43. The compound of any one of claims 41-42, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^{5a2e} and R^{5a2f} together with the atoms to which they are attached can form C_3-C_8cycloalkyl or heterocyclyl.

44. The compound of claim 34, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is. 

, wherein

R^{5a2c} and R^{5a2d} are each independently H, D, halogen, OH, CN, $-NO_2$,$-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, 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 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, -CN, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, -$NR^6C(O)OR^6$, –$NR^6C(O)R^6$, $NR^6C(O)NR^6$, -$NR^6C(O)R^6$, or –$NR^6S(O)_2R^6$; or

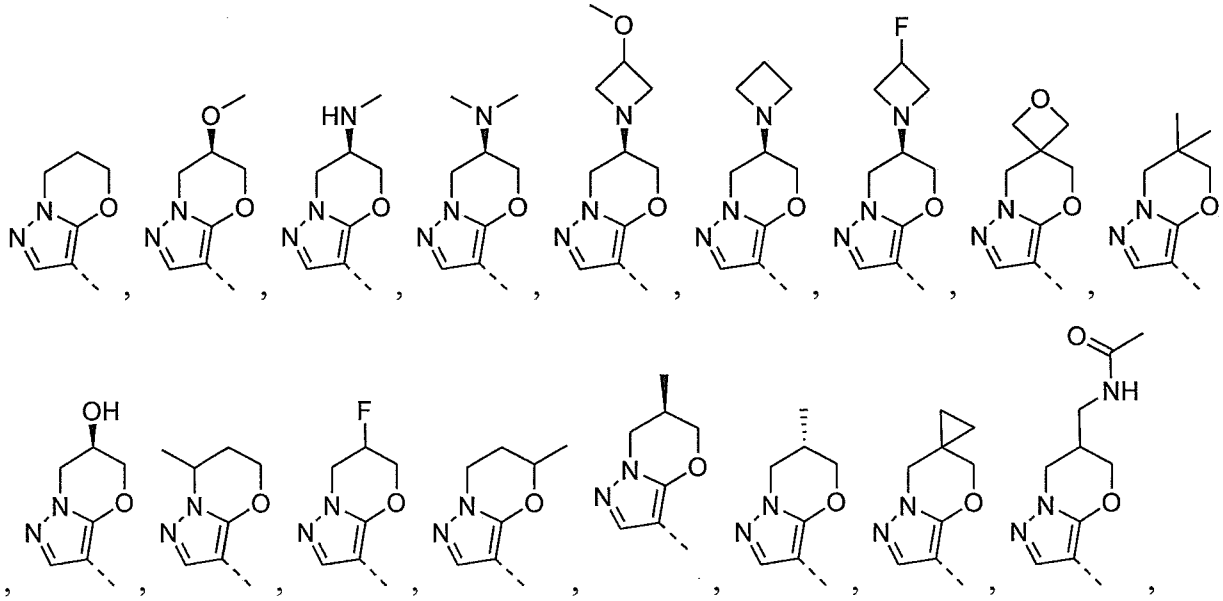
R^{5a2c} and R^{5a2d} together with the atoms to which they are attached can form C_3-C_8cycloalkyl or heterocyclyl; wherein the heterocyclyl contains 1-3 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_3-C_8cycloalkyl and heterocyclyl are optionally substituted with D, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, –$S(O)_2$-R^6, -COR^6, $NR^6C(O)OR^6$, –$NR^6C(O)R^6$, -$NR^6C(O)NR^6$, or -$NR^6S(O)_2R^6$; or

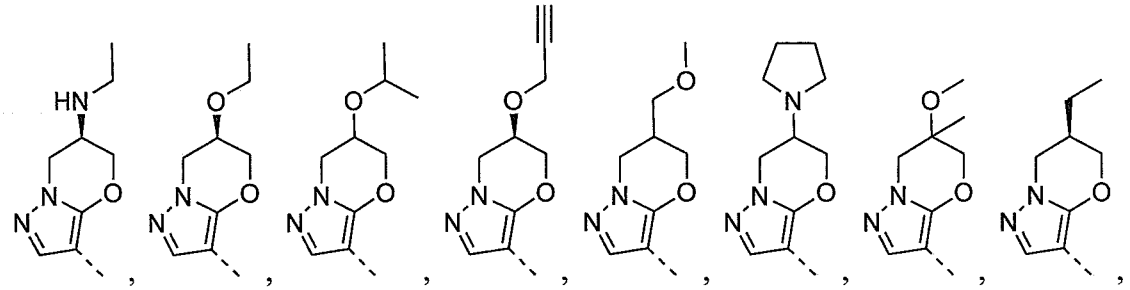
R^{5a2c} and R^{5a2d} can form an oxo group.

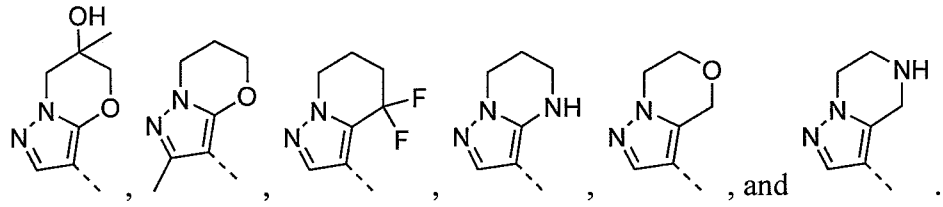
45. The compound of claim 44, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each R^{5a2c} and R^{5a2d} is independently H, halogen, OH, –OR^6, –NHR^6, –NR^6R^7, C_1-C_6alkyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or -CH_2-C_3-C_8cycloalkyl.

46. The compound of any one of claims 44-45, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^{5a2c} and R^{5a2d} together with the atoms to which they are attached can form C_3-C_8cycloalkyl or heterocyclyl.

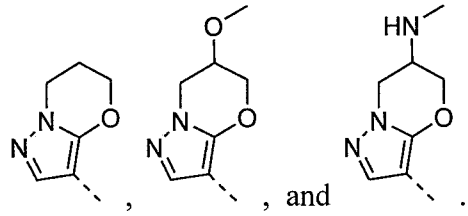
47. The compound of claim 29, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is selected from the group consisting of



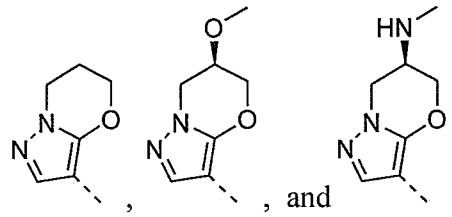


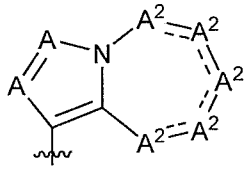


48. The compound of claim 29, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is selected from the group consisting of



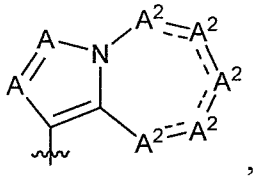
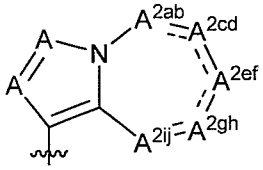
49. The compound of claim 29, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is selected from the group consisting of



50. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is  .

51. The compound of claim 50, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein one A is CR^{5a1} and the other A is N.

52. The compound of any one of claims 50-51, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each A^2 is independently $C(R^{5a2})_2$, NR^{5a2}, or O.

53. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is  , which is a formula of  , wherein.

A^{2ab} is selected from CR^{5a2}, $C(R^{5a2a})(R^{5a2b})$, N, NR^{5a2}, O, S, or $S(O)_2$;

A^{2cd} is selected from CR^{5a2}, $C(R^{5a2c})(R^{5a2d})$, N, NR^{5a2}, O, S, or $S(O)_2$;

A^{2ef} is selected from CR^{5a2}, $C(R^{5a2e})(R^{5a2f})$, N, NR^{5a2}, O, S, or $S(O)_2$; and

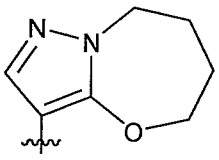
A^{2gh} is selected from CR^{5a2}, $C(R^{5a2g})(R^{5a2h})$, N, NR^{5a2}, O, S, or $S(O)_2$;

A^{2ij} is selected from CR^{5a2}, $C(R^{5a2i})(R^{5a2j})$, N, NR^{5a2}, O, S, or $S(O)_2$;

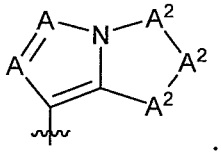
each R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, R^{5a2e}, R^{5a2f}, R^{5a2g}, R^{5a2h}, R^{5a2i}, and R^{5a2j} are independently H, D, halogen, OH, CN, $-NO_2$, $-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-CH_2$-C_3-C_8cycloalkyl; wherein the 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl)$_2$, $-NR^6C(O)OR^6$, $-NR^6C(O)R^6$, $NR^6C(O)NR^6$, $-NR^6C(O)R^6$, or $-NR^6S(O)_2R^6$; or

two R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, R^{5a2e}, R^{5a2f}, R^{5a2g}, R^{5a2h}, R^{5a2i}, and R^{5a2j} 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), $-N(C_1$-C_6alkyl)$_2$, $-S(O)_2$-R^6, $-COR^6$, $NR^6C(O)OR^6$, $-NR^6C(O)R^6$, $-NR^6C(O)NR^6$, or $-NR^6S(O)_2R^6$; or

two geminal R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, R^{5a2e}, R^{5a2f}, R^{5a2g}, R^{5a2h}, R^{5a2i}, and R^{5a2j} can form an oxo group.

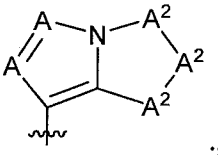
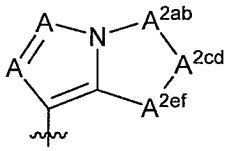
54. The compound of claim 50, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is  .

R^1 is 3B

55. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is  .

56. The compound of claim 55, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein one A is CR^{5a1} and the other A is N.

57. The compound of any one of claims 55-56, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each A^2 is independently $C(R^{5a2})_2$, NR^{5a2}, or O.

58. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is  ., which is a formula of  ., wherein.

A^{2ab} is selected from $C(R^{5a2a})(R^{5a2b})$, NR^{5a2}, O, S, or $S(O)_2$;

A^{2cd} is selected from $C(R^{5a2c})(R^{5a2d})$, NR^{5a2}, O, S, or $S(O)_2$;

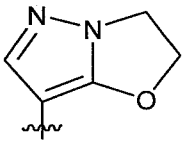
A^{2ef} is selected from $C(R^{5a2e})(R^{5a2f})$, NR^{5a2}, O, S, or $S(O)_2$; and

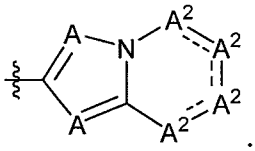
each R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, R^{5a2e}, and R^{5a2f} are independently H, D, halogen, OH, CN, $-NO_2$, $-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or

-CH_2-C_3-C_8cycloalkyl; wherein the 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, -CN, halogen, C_1-C_6alkyl, -OR^6, -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, -$NR^6C(O)OR^6$, –$NR^6C(O)R^6$, $NR^6C(O)NR^6$, -$NR^6C(O)R^6$, or –$NR^6S(O)_2R^6$; or

two R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, 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), -N(C_1-C_6alkyl)$_2$, –S(O)$_2$-R^6, -COR^6, $NR^6C(O)OR^6$, –$NR^6C(O)R^6$, -$NR^6C(O)NR^6$, or -$NR^6S(O)_2R^6$; or

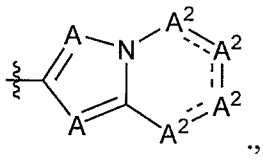
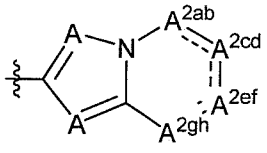
two geminal R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, R^{5a2e}, and R^{5a2f} can form an oxo group.

59. The compound of claim 55, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is  .

60. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is  .

61. The compound of claim 60, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein one A is CR^{5a1} and the other A is N.

62. The compound of any one of claims 60-61, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein each A^2 is independently $C(R^{5a2})_2$, NR^{5a2}, or O.

63. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein R^1 is  ., which is a formula of  ., wherein.

A^{2ab} is selected from CR^{5a2}, $C(R^{5a2a})(R^{5a2b})$, N, NR^{5a2}, O, S, or $S(O)_2$;

A^{2cd} is selected from CR^{5a2}, $C(R^{5a2c})(R^{5a2d})$, N, NR^{5a2}, O, S, or $S(O)_2$;

A^{2ef} is selected from CR^{5a2}, $C(R^{5a2e})(R^{5a2f})$, N, NR^{5a2}, O, S, or $S(O)_2$; and

A^{2gh} is selected from CR^{5a2}, $C(R^{5a2g})(R^{5a2h})$, N, NR^{5a2}, O, S, or $S(O)_2$;

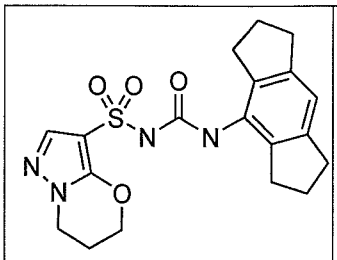
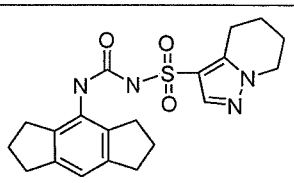
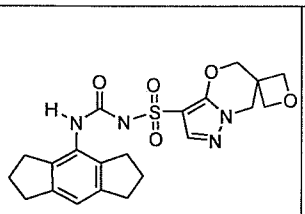
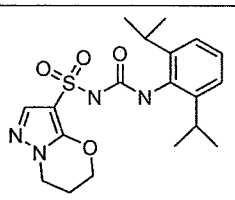
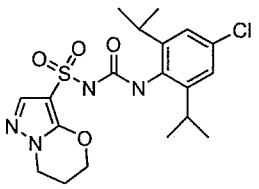
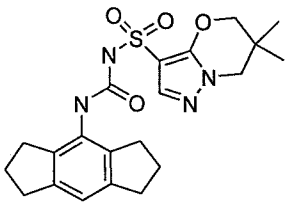
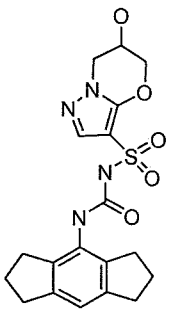
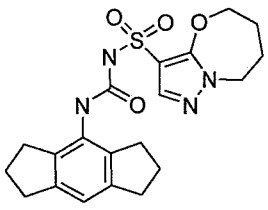
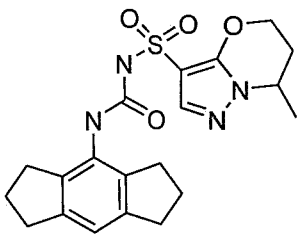
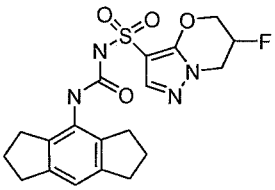
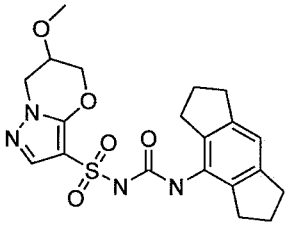
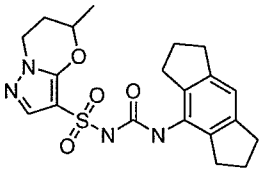
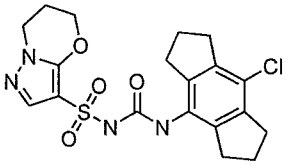
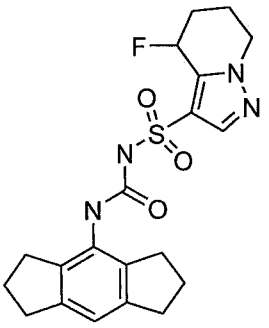
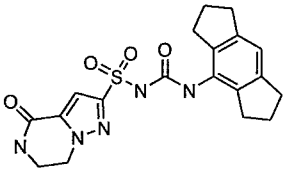
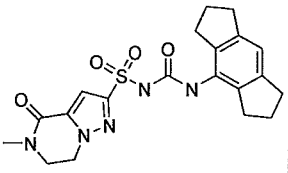
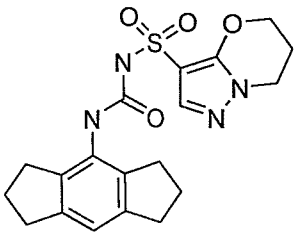
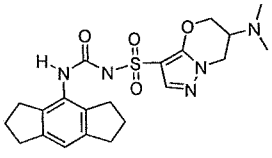
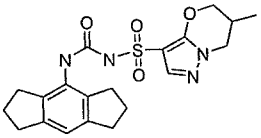
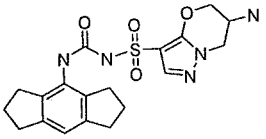
each R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, R^{5a2e}, R^{5a2f}, R^{5a2g}, and R^{5a2h} are independently H, D, halogen, OH, CN, $-NO_2$,$-SR^6$, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-C(O)R^6$, $-S(O)_2R^6$, $-C(O)OR^6$, $-C(O)NR^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl, or $-CH_2$-C_3-C_8cycloalkyl; wherein the 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, -CN, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl)$_2$, $-NR^6C(O)OR^6$, $-NR^6C(O)R^6$, $NR^6C(O)NR^6$, $-NR^6C(O)R^6$, or $-NR^6S(O)_2R^6$ or

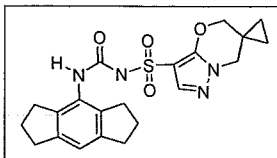
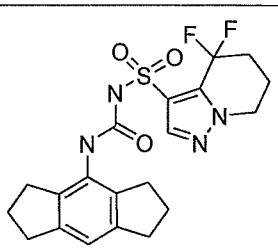
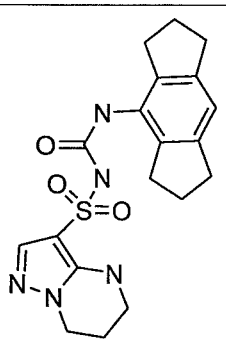
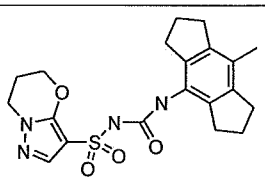
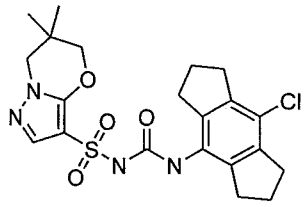
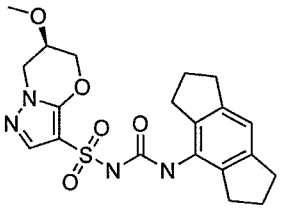
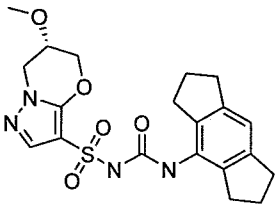
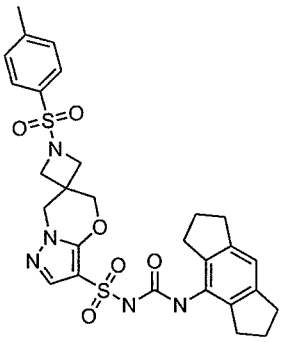
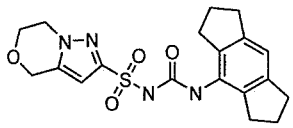
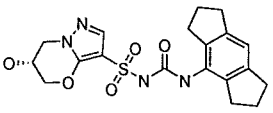
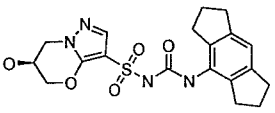
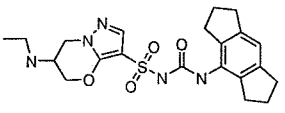
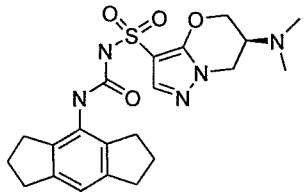
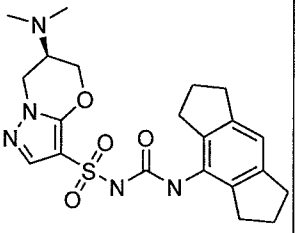
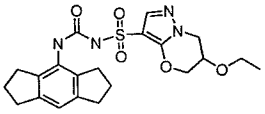
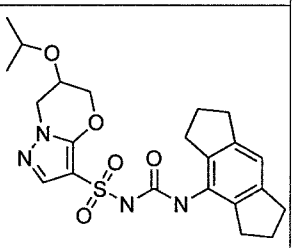
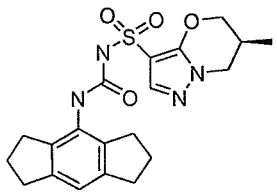
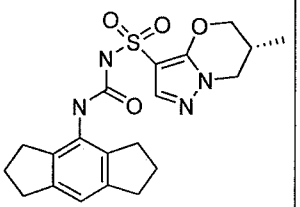
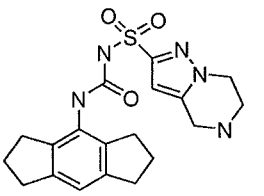
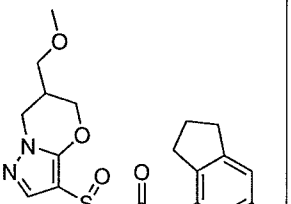
two R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, R^{5a2e}, R^{5a2f}, R^{5a2g}, and R^{5a2h} together with the atoms to which they are attached can form C_3-C_8cycloalkyl or heterocyclyl; wherein the heterocyclyl contains 1-3 heteroatoms selected from the group consisting of N, S, P and O; wherein the C_3-C_8cycloalkyl and heterocyclyl are optionally substituted with D, halogen, C_1-C_6alkyl, $-OR^6$, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl)$_2$, $-S(O)_2$-R^6, $-COR^6$, $NR^6C(O)OR^6$, $-NR^6C(O)R^6$, $-NR^6C(O)NR^6$, or $-NR^6S(O)_2R^6$ or

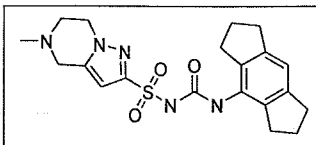
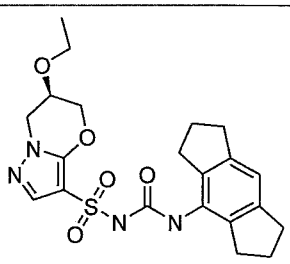
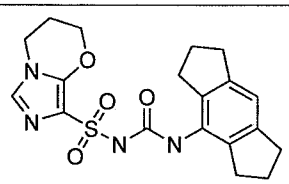
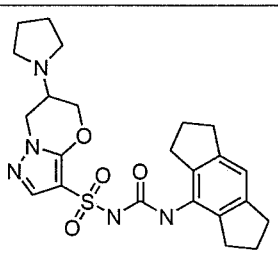
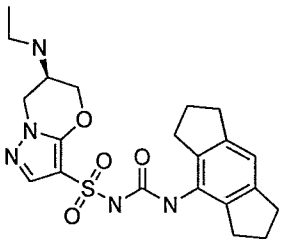
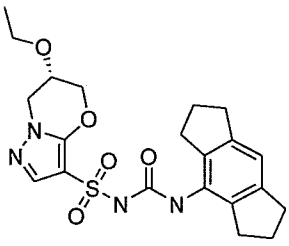
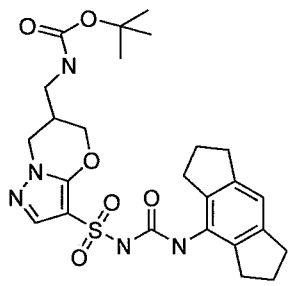
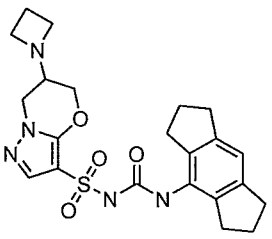
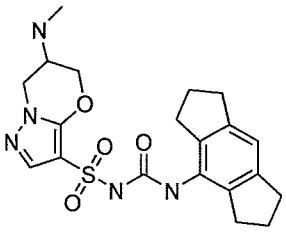
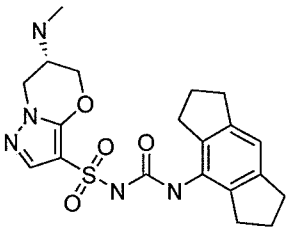
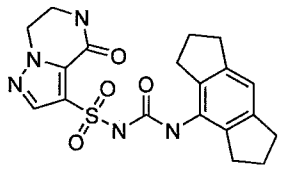
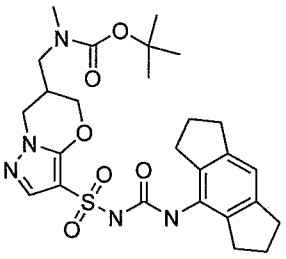
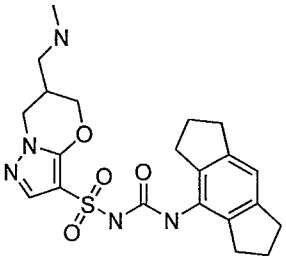
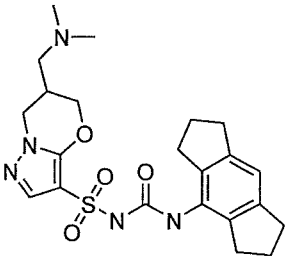
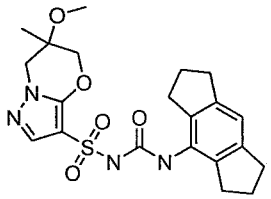
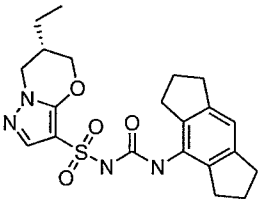
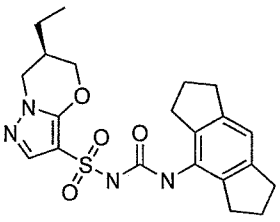
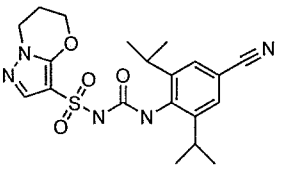
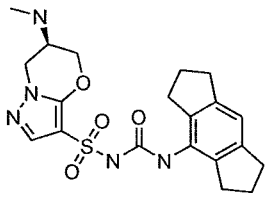
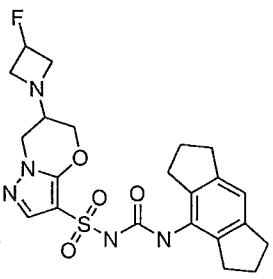
two geminal R^{5a2a}, R^{5a2b}, R^{5a2c}, R^{5a2d}, R^{5a2e}, R^{5a2f}, R^{5a2g}, and R^{5a2h} can form an oxo group.

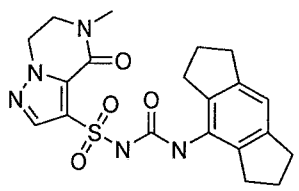
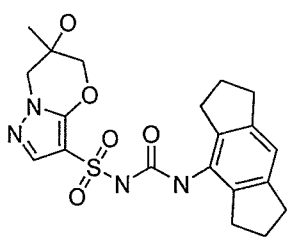
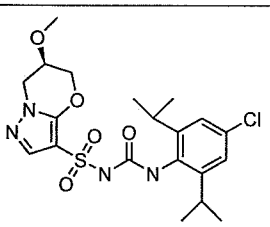
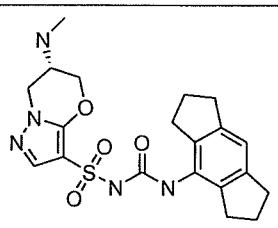
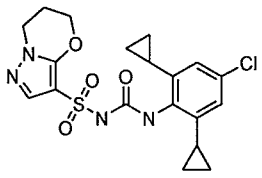
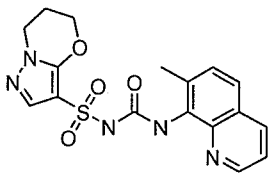
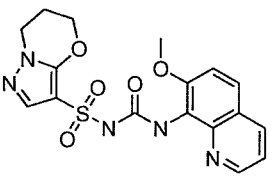
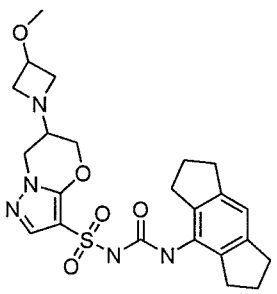
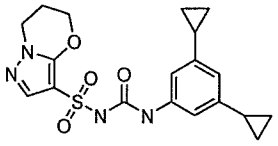
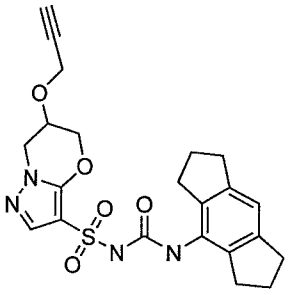
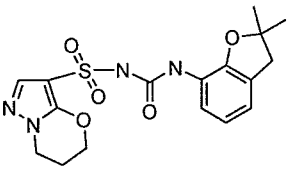
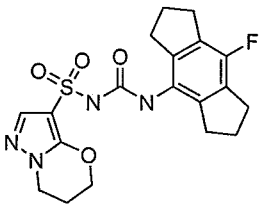
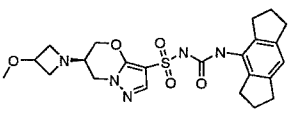
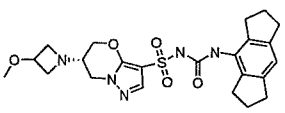
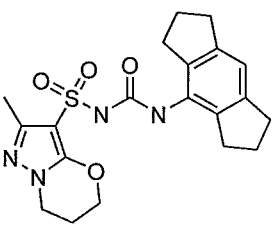
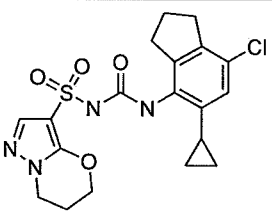
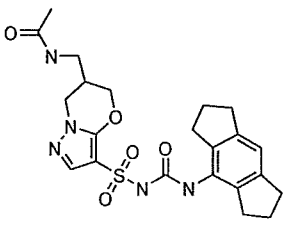
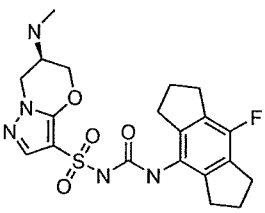
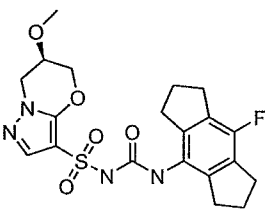
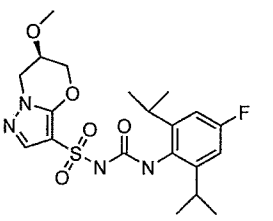
64. The compound of any one of claims 1-63, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, wherein the ⎓ are single bonds in the ring comprising A^2, thereby forming a saturated ring.

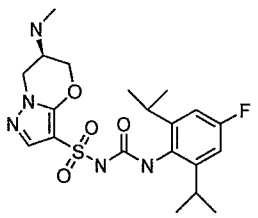
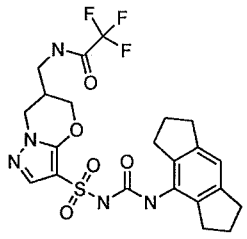
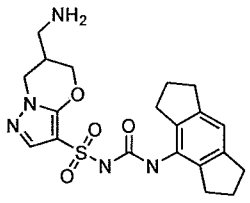
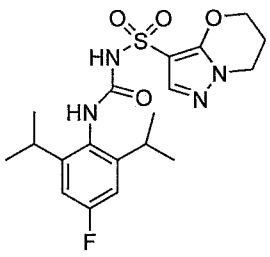
65. A compound, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, selected from the group consisting of

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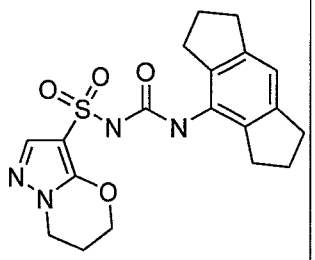
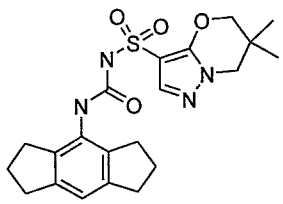
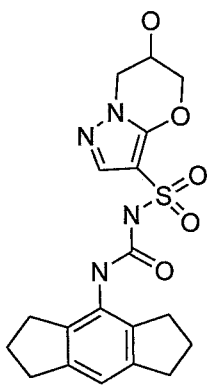
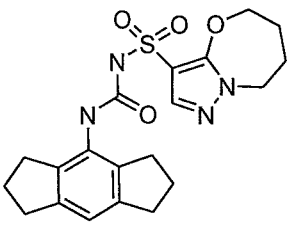
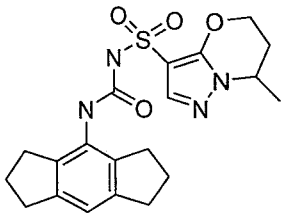
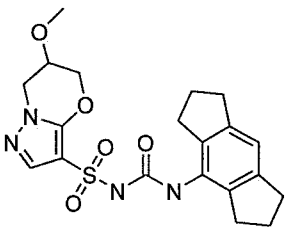
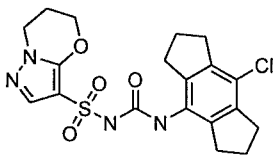
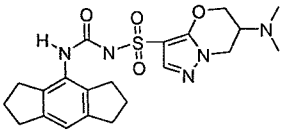
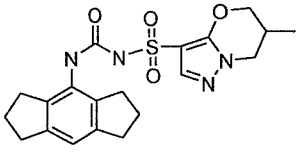
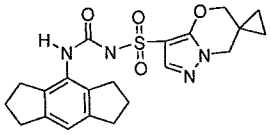
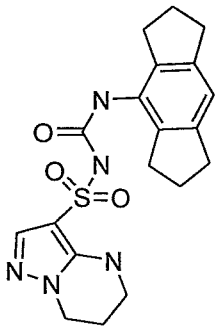
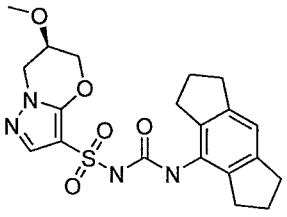
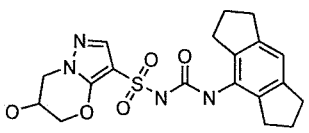
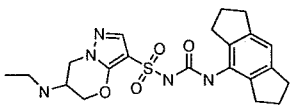
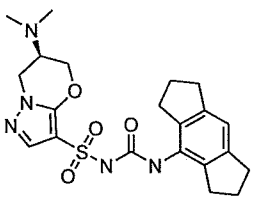
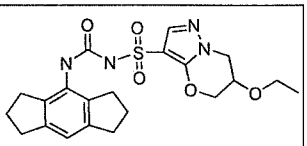
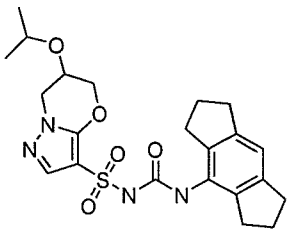
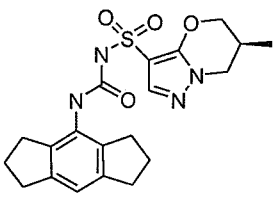
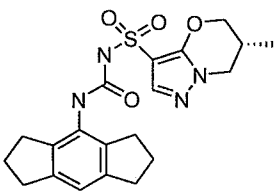
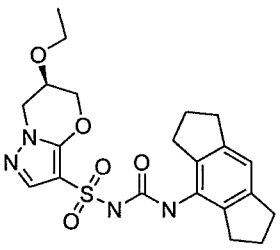
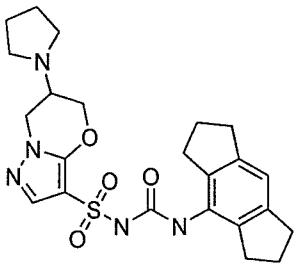
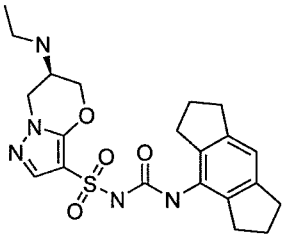
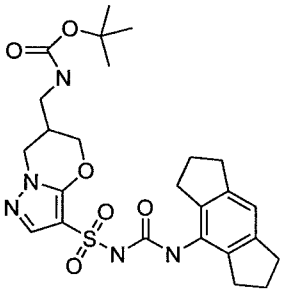
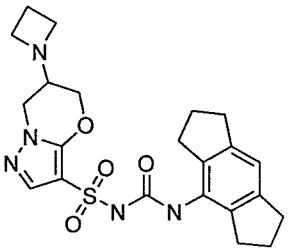
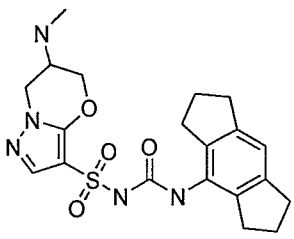
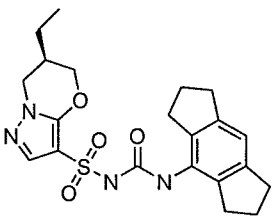
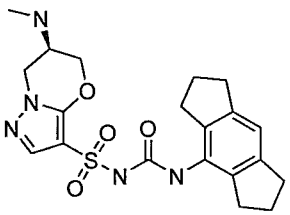
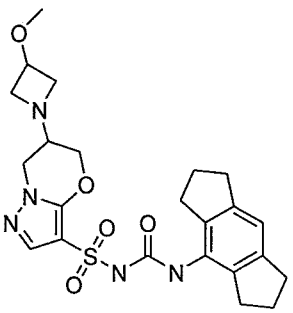
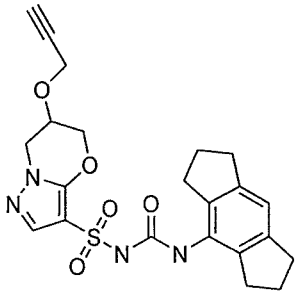
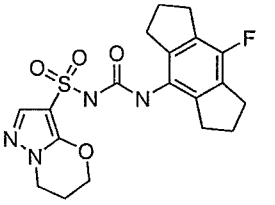
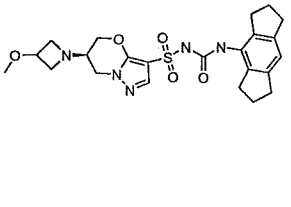
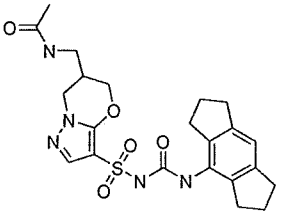
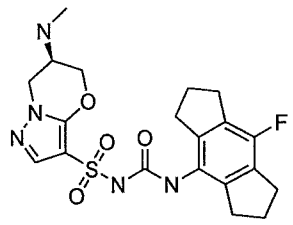
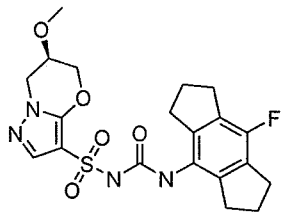
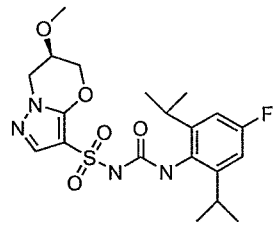
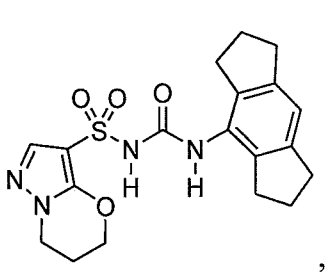
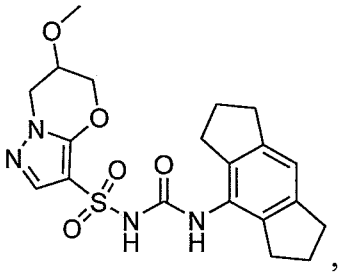
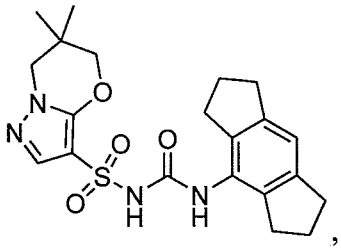
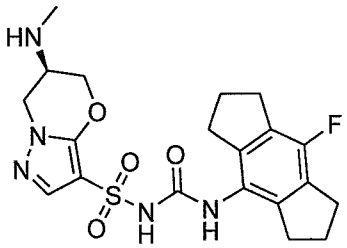
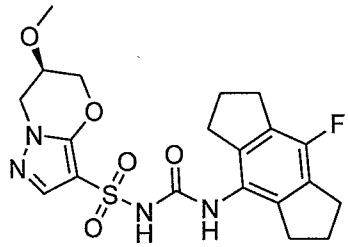
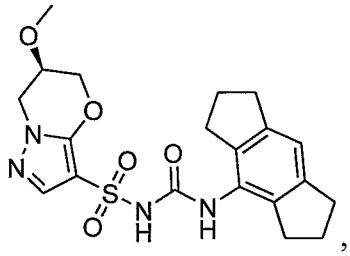
			
			
			

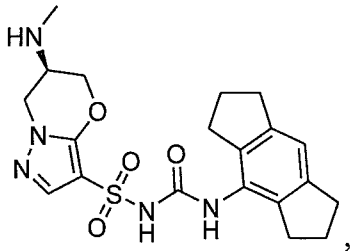
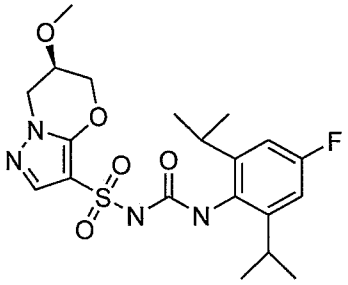
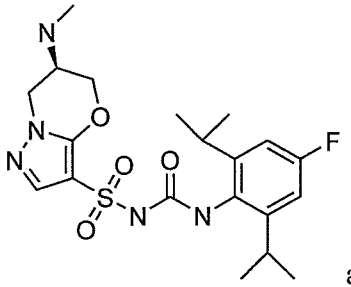
			
			
			
			
			

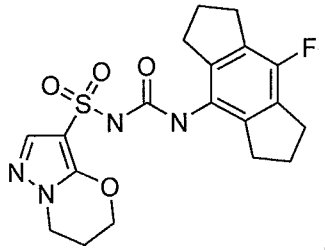
			

67. A compound, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, selected from the group consisting of

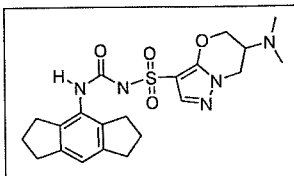
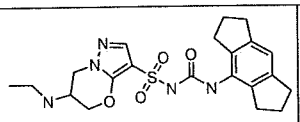
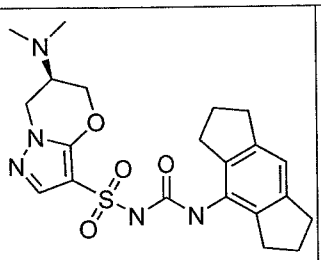
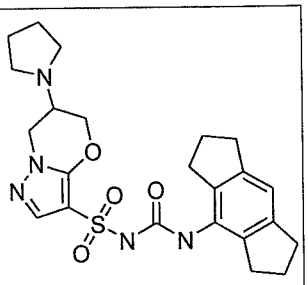
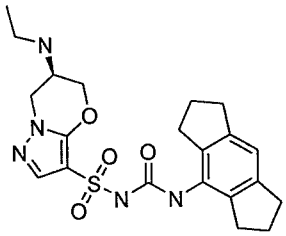
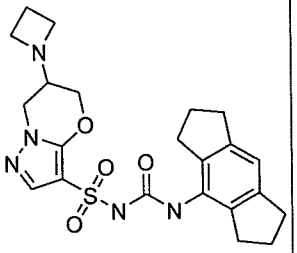
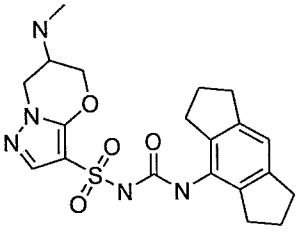
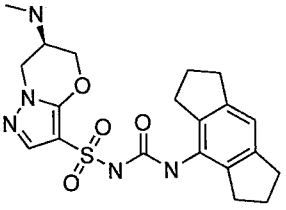
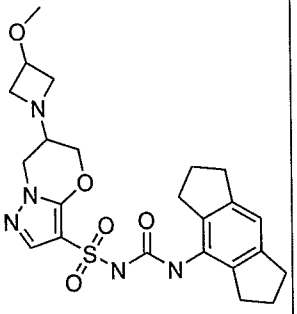
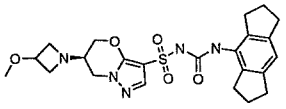
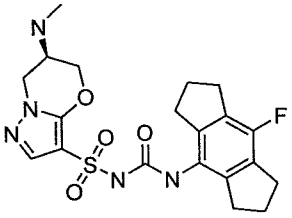
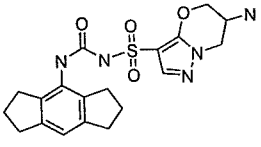
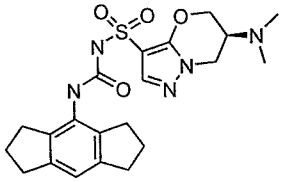
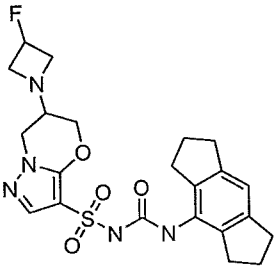
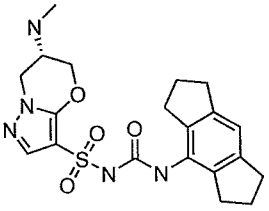
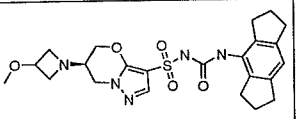
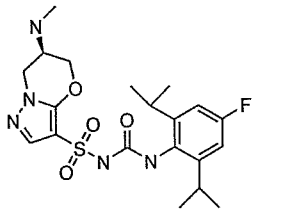
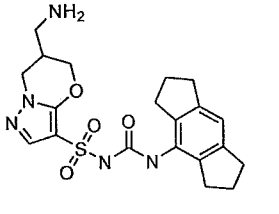
 ,  ,  ,

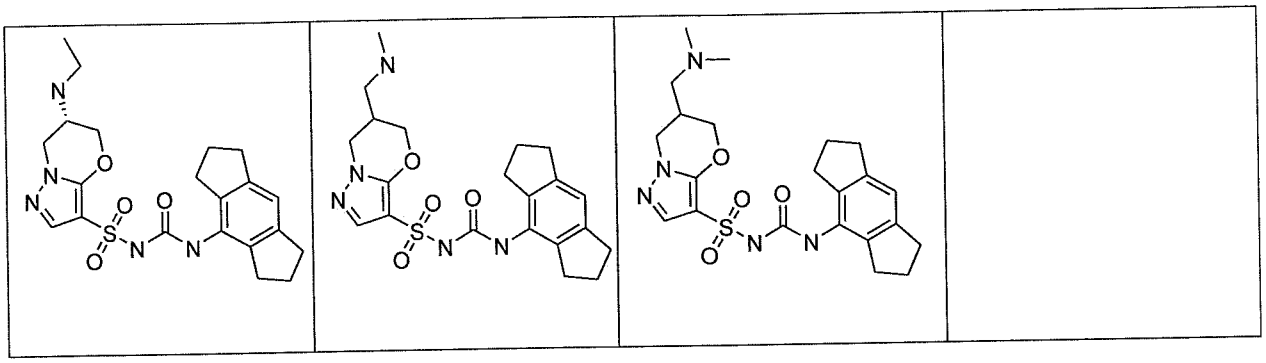
 ,  ,  ,

 ,  ,  and

 .

68. A compound, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, selected from the group consisting of



69. A pharmaceutical composition comprising a compound of any one of claims 1-68, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

70. Use of a compound of any one of claims 1-68, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, in the manufacture of a medicament for the treatment or prevention of a disease, disorder, or condition that is responsive to inhibition of inflammasome in a subject in need thereof.

71. The use of claim 70, wherein the disease, disorder or condition is one which is responsive to inhibition of activation of the NLRP3 inflammasome.

72. The use of claim 70 or 71, wherein the disease, disorder or condition is responsive to modulation of one or more of IL-6, IL-1β, IL-17, IL-18, IL-1α, IL-37, IL-22, IL-33 and Th17 cells.

73. The use of claim 70 or 71, wherein the disease, disorder or condition is responsive to modulation of one or more of IL-1β and IL-18.

74. The use of any one of claims 70-73, wherein the disease, disorder or condition is a disease, disorder or condition of the immune system.

75. The use of any one of claims 70-73, wherein the disease, disorder or condition is an inflammatory disease disorder or condition or an autoimmune disease disorder or condition.

76. The use of any one of claims 70-73, wherein the disease, disorder or condition is a disease, disorder or condition of the liver.

77. The use of any one of claims 70-73, wherein the disease, disorder or condition is a disease, disorder or condition of the lung.

78. The use of any one of claims 70-73, wherein the disease, disorder or condition is a disease, disorder or condition of the skin.

79. The use of any one of claims 70-73, wherein the disease, disorder or condition is a disease, disorder or condition of the cardiovascular system.

80. The use of any one of claims 70-73, wherein the disease, disorder or condition is a cancer, tumor or other malignancy.

81. The use of any one of claims 70-73, wherein the disease, disorder or condition is a disease, disorder or condition is of the renal system.

82. The use of any one of claims 70-73, wherein the disease, disorder or condition is a disease, disorder or condition is of the gastro-intestinal tract.

83. The use of any one of claims 70-73, wherein the disease, disorder or condition is a disease, disorder or condition is of the respiratory system.

84. The use of any one of claims 70-73, wherein the disease, disorder or condition is a disease, disorder or condition is of the endocrine system.

85. The use of any one of claims 70-73, wherein the disease, disorder or condition is a disease, disorder or condition is of the central nervous system (CNS).

86. The use of any one of claims 70-73, wherein the disease, disorder or condition is 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.

87. The use of claim 86, wherein the disorder is selected from the group consisting of a bacterial infection, a viral infection, a fungal infection, inflammatory bowel disease, celiac disease, colitis, intestinal hyperplasia, cancer, metabolic syndrome, obesity, rheumatoid arthritis, liver disease, hepatic steatosis, fatty liver disease, liver fibrosis, non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

88. The use of claim 87, wherein the disorder is non-alcoholic steatohepatitis (NASH).

89. The use of any one of claims 70-88, wherein the medicament is for treatment or prevention of the disease, disorder or condition performed on a mammal.

90. The use of claim 89, wherein the mammal is a human subject.

91. A method of modulating the activity of a biological target comprising the step of exposing the biological target to a compound of any one of claims 1-68, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof.

92. The method of claim 91, wherein 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.

93. The method of claim 91, wherein the biological target may be selected from the group consisting of IL-1β and IL-18.

94. A method of inhibiting activation of an inflammasome comprising the step of exposing the biological target to a compound of any one of claims 1-68, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof.

95. The method of claim 94, wherein the inflammasome is NLRP3 inflammasome.

96. The method of claim 94 or 95, wherein inhibition of inflammasome is associated with one or more of IL-6, IL-1β, IL-17, IL-18, IL-1α, IL-37, IL-22, IL-33 and Th17 cells.

97. The method of claim 96, wherein inhibition of inflammasome is associated with one or more of IL-1β and IL-18.

98. A compound of any one of claims 1-68, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, isomer, or tautomer thereof, for use in the manufacture of a medicament for treating a disease, disorder or condition that is responsive to inhibition of inflammasome.