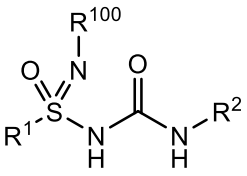
3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl,-OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6 membered heteroaryl.

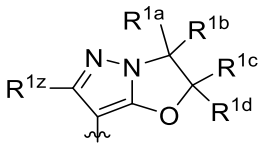
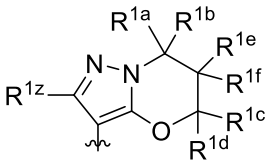
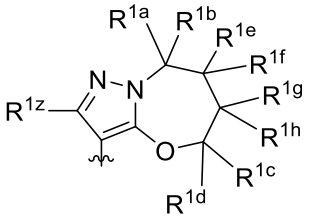
[0019a] In one aspect, the present disclosure provides a compound having the structure of Formula (I-5),


(I-5),

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

R^{100} is selected from the group consisting of H, Cl, D, -CN, -C(O)R^{3b}, and C_1-C_6alkyl; wherein the C_1-C_6alkyl is independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, -OR^{3a}, C_6aryl, and 5-6-membered heteroaryl;

R^1 is selected from the group consisting of


,

, and

;

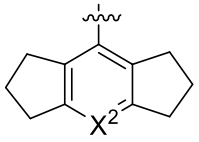
R^{1z} is H, D, halogen, -CN, or C_1-C_6alkyl; wherein the C_1-C_6alkyl

is independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, and -OR^{7a};

each R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f}, R^{1g}, and R^{1h} is independently selected from the group consisting of H, D, halogen, -CN, $–NO_2$, $–SR^{11a}$, $–OR^{11a}$, $-C(O)R^{11b}$, $-P(O)R^{11b}R^{12b}$, $-S(O)_2R^{11b}$, $-S(O)R^{11b}$, $–NR^{11a}R^{12a}$, $-NR^{11a}C(O)R^{12a}$, $-NR^{11a}C(O)OR^{12a}$, $-NR^{11a}C(O)NR^{12a}$, $–NR^{11a}S(O)_2R^{12a}$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl, $-OR^{11a}$, $-C(O)R^{11b}$, $-P(O)R^{11b}R^{12b}$, $-S(O)_2R^{11b}$, $-S(O)R^{11b}$, $–NR^{11a}R^{12a}$, $–NR^{11a}C(O)R^{12a}$, $-NR^{11a}C(O)OR^{12a}$, $-NR^{11a}C(O)NR^{12a}$, $–NR^{11a}S(O)_2R^{12a}$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl; or

two of the following groups, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f}, R^{1g}, and R^{1h}, when present, together with the atoms to which they are attached can form a C_3-C_{10}cycloalkyl or a 3-7-membered heterocyclyl; wherein the C_3-C_{10}cycloalkyl and 3-7-membered heterocyclyl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl, $-OR^{13a}$, $-C(O)R^{13b}$, $-P(O)R^{13b}R^{14b}$, $-S(O)_2R^{13b}$, $-S(O)R^{13b}$, $–NR^{13a}R^{14a}$, $–NR^{13a}C(O)R^{14a}$, $-NR^{13a}C(O)OR^{14a}$, $-NR^{13a}C(O)NR^{14a}$, and $–NR^{13a}S(O)_2R^{14a}$; or

two geminal groups R^{1a} and R^{1b}; R^{1c} and R^{1d}; R^{1e} and R^{1f}; or R^{1g} and R^{1h}, when present, form an oxo group;

R^2 is selected from the group consisting of 5-membered heteroaryl, 

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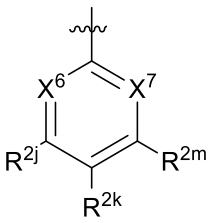

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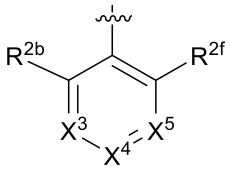
and  ; wherein the 5-membered heteroaryl is unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, oxo, -OR^{23a}, -$C(O)R^{23b}$, -$P(O)R^{23b}R^{24b}$, -$S(O)_2R^{23b}$, -$S(O)R^{23b}$, -$NR^{23a}R^{24a}$, –$NR^{23a}C(O)R^{24a}$, -$NR^{23a}C(O)OR^{24a}$, -$NR^{23a}C(O)NR^{24a}$, –$NR^{23a}S(O)_2R^{24a}$, -$(CH_2)_{1-4}$$C_3$-$C_{10}$cycloalkyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl;

X^2 is N or CR^{2a};

X^3 is N or CR^{2c};

X^4 is N or CR^{2d};

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

X^6 and X^7 are independently N or CR^{2n}, wherein at least one of X^6 and X^7 is N;

R^{2a} is H, D, halogen, -CN, –OR^{15a}, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, -$C(O)NR^{15a}R^{16a}$, -$C(O)OR^{15a}$, –$NR^{15a}R^{16a}$, –$NR^{15a}C(O)R^{16a}$, -$NR^{15a}C(O)OR^{16a}$, -$NR^{15a}C(O)NR^{16a}$, or –$NR^{15a}S(O)_2R^{16a}$, wherein the C_1-C_6alkyl and C_3-C_{10}cycloalkyl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, halogen, -CN, -OR^{15a}, -$C(O)R^{15b}$, -$NR^{15a}R^{16a}$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl;

each R^{2b}, R^{2c}, R^{2d}, R^{2e}, and R^{2f} is independently H, D, halogen, -CN, –NO_2, –SR^{17a}, –OR^{17a}, -$C(O)R^{17b}$, -$P(O)R^{17b}R^{18b}$, -$S(O)_2R^{17b}$, -$S(O)R^{17b}$, –$NR^{17a}R^{18a}$, –$NR^{17a}C(O)R^{18a}$, -$NR^{17a}C(O)OR^{18a}$, -$NR^{17a}C(O)NR^{18a}$, –$NR^{17a}S(O)_2R^{18a}$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, or 5-6-membered heteroaryl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, -OR^{17a}, -$C(O)R^{17b}$, -$P(O)R^{17b}R^{18b}$, -$S(O)_2R^{17b}$, -$S(O)R^{17b}$, –$NR^{17a}R^{18a}$, –$NR^{17a}C(O)R^{18a}$, -$NR^{17a}C(O)OR^{18a}$, -$NR^{17a}C(O)NR^{18a}$, –$NR^{17a}S(O)_2R^{18a}$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl; or

two adjacent R^{2b}, R^{2c}, R^{2d}, R^{2e}, and R^{2f} together with the atoms to which they are attached can form C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, or 5-6-membered

heteroaryl; wherein the C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, D, -CN, C_1-C_6alkyl, -OR^{19a}, and $NR^{19a}R^{20a}$;

each R^{2j}, R^{2k}, R^{2m}, and R^{2n} is independently H, D, halogen, -CN, $–NO_2$, $–SR^{17a}$, $–OR^{17a}$, -$C(O)R^{17b}$, -$P(O)R^{17b}R^{18b}$, -$S(O)_2R^{17b}$, -$S(O)R^{17b}$, $–NR^{17a}R^{18a}$, -$NR^{17a}C(O)R^{18a}$, -$NR^{17a}C(O)OR^{18a}$, -$NR^{17a}C(O)NR^{18a}$, $–NR^{17a}S(O)_2R^{18a}$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, or 5-6-membered heteroaryl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, -OR^{17a}, -$C(O)R^{17b}$, -$P(O)R^{17b}R^{18b}$, -$S(O)_2R^{17b}$, -$S(O)R^{17b}$, $–NR^{17a}R^{18a}$, $–NR^{17a}C(O)R^{18a}$, -$NR^{17a}C(O)OR^{18a}$, -$NR^{17a}C(O)NR^{18a}$, $–NR^{17a}S(O)_2R^{18a}$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl; or

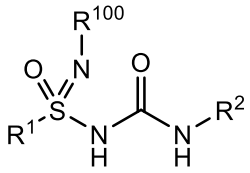
two adjacent R^{2j}, R^{2k}, R^{2m}, and R^{2n} together with the atoms to which they are attached can form C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, or 5-6-membered heteroaryl, wherein the C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, D, -CN, C_1-C_6alkyl, -OR^{19a}, and $NR^{19a}R^{20a}$;

R^{3a}, R^{7a}, R^{11a}, R^{12a}, R^{13a}, R^{14a}, R^{15a}, R^{16a}, R^{17a}, R^{18a}, R^{19a}, R^{20a}, R^{23a}, and R^{24a} are independently, at each occurrence, H, D, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_{10}cycloalkyl, C_4-C_8cycloalkenyl, C_6aryl, 3-7-membered heterocyclyl, or 5-6-membered heteroaryl; wherein the C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_{10}cycloalkyl, C_4-C_8cycloalkenyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are

independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl, -OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl; and

R^{3b}, R^{11b}, R^{12b}, R^{13b}, R^{14b}, R^{15b}, R^{17b}, R^{18b}, R^{23b}, and R^{24b} are independently, at each occurrence, H, D, -OH, -O(C_1-C_6alkyl), -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, -$NHS(O)_2CH_3$, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_{10}cycloalkyl, C_4-C_8cycloalkenyl, C_6aryl, 3-7-membered heterocyclyl, or 5-6-membered heteroaryl; wherein the C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_{10}cycloalkyl, C_4-C_8cycloalkenyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl, -OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl.

[0020] The present disclosure provides a compound having the structure of Formula (I-6),



(I-6)

and pharmaceutically acceptable salts, solvates, isomers, prodrugs, and tautomers thereof, wherein:

R^{100} is selected from the group consisting of H, Cl, D, -CN, –NO_2, –OR^{3a},-$C(O)R^{3b}$, -$S(O)_2R^{3b}$, -$S(O)R^{3b}$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6 membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl, -OR^{3a},-$C(O)R^{3b}$, -$P(O)R^{3b}R^{4b}$, -$S(O)_2R^{3b}$,-$S(O)R^{3b}$, -$NR^{3a}R^{4a}$, –$NR^{3a}C(O)R^{4a}$, -$NR^{3a}C(O)OR^{4a}$, -$NR^{3a}C(O)NR^{4a}$, –$NR^{3a}S(O)_2R^{4a}$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of

heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl,-OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6 membered heteroaryl.

[0021] The present disclosure provides pharmaceutical compositions comprising one or more compounds of the present disclosure, e.g., compounds of Formula (I), any variations thereof detailed herein, one or more of Compound Nos. 1-210 in Table 1, and pharmaceutically acceptable salts, solvates (e.g., hydrates), isomers, prodrugs, and tautomers thereof, and a pharmaceutically acceptable carrier.

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

[0022] The present disclosure provides methods of treating disorders including the step of administering an effective amount of one or more compounds of the present disclosure, e.g., compounds of Formula (I), any variations thereof detailed herein, one or more of Compound Nos. 1-210 in Table 1, and pharmaceutically acceptable salts, solvates (e.g., hydrates), isomers, prodrugs, and tautomers thereof, to thereby treat the disorder in a subject in need thereof.

[0023] The present disclosure provides a method of treating disorders including the step of administering an effective amount of one or more pharmaceutical compositions of the present disclosure to thereby treat the disorder in a subject in need thereof.

[0024] The present disclosure provides one or more compounds of the present disclosure, e.g., compounds of Formula (I), any variations thereof detailed herein, one or more of Compound Nos. 1-210 in Table 1, and pharmaceutically acceptable salts, solvates (e.g., hydrates), isomers, prodrugs, and tautomers thereof, or one or more pharmaceutical compositions of the present disclosure for use in the treatment of a disorder in a subject in need thereof.

[0024a] In another aspect, the present disclosure provides a compound of the disclosure, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, or a pharmaceutical composition of the disclosure, for use as a medicament.

[0025] The present disclosure provides for the use of one or more compounds of the present disclosure, e.g., compounds of Formula (I), any variations thereof detailed herein, one or more of Compound Nos. 1-210 in Table 1, and pharmaceutically acceptable salts, solvates (e.g.,

hydrates), isomers, prodrugs, and tautomers thereof, for the treatment of a disorder in a subject in need thereof.

[0026] The present disclosure provides for the use of one or more pharmaceutical compositions of the present disclosure for the treatment of a disorder in a subject in need thereof.

[0027] The present disclosure provides for the use of one or more compounds of the present disclosure, e.g., compounds of Formula (I), any variations thereof detailed herein, one or more of Compound Nos. 1-210 in Table 1, and pharmaceutically acceptable salts, solvates (e.g., hydrates), isomers, prodrugs, and tautomers thereof, in the manufacture of a medicament for the treatment of a disorder.

[0027a] In another aspect, the present disclosure provides for the use of a compound of the disclosure, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, or a pharmaceutical composition of the disclosure, in the manufacture of a medicament for the treatment of a disorder, wherein the disorder is a disorder of the immune system, a disorder of the liver, a disorder of the lung, a disorder of the skin, a disorder of the cardiovascular system, a disorder of the renal system, a disorder of the gastro-intestinal tract, a disorder of the respiratory system, a disorder of the endocrine system, a disorder of the central nervous system (CNS), an inflammatory disorder, an autoimmune disorder, or a cancer, tumor, or other malignancy.

[0028] The present disclosure provides for the use of one or more pharmaceutical compositions of the present disclosure in the manufacture of a medicament for the treatment of a disorder.

[0029] In some examples, the disorder is responsive to inflammasome inhibition.

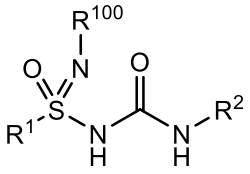
[0030] In some examples, the disorder is responsive to inhibition of activation of the NLRP3 inflammasome.

[0031] In some examples, the disorder is a disorder 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.

[0032] The present disclosure provides methods of modulating the activity of a biological target comprising the step of exposing the biological target to one or more compounds of the present disclosure, e.g., compounds of Formula (I), any variations thereof detailed herein, one or more of Compound Nos. 1-210 in Table 1, and pharmaceutically acceptable salts, solvates (e.g., hydrates), isomers, prodrugs, and tautomers thereof.

CLAIMS

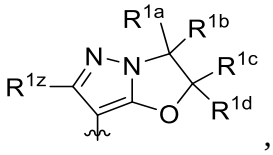
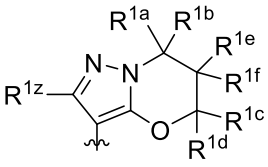
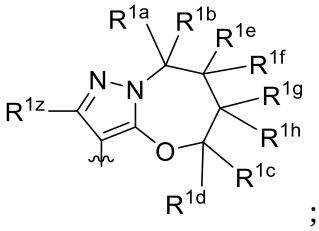
1. A compound having the structure of Formula (I-5),


(I-5),

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

R^{100} is selected from the group consisting of H, Cl, D, -CN, -C(O)R^{3b}, and C_1-C_6alkyl; wherein the C_1-C_6alkyl is independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, -OR^{3a}, C_6aryl, and 5-6-membered heteroaryl;

R^1 is selected from the group consisting of

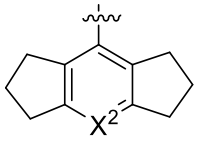

, 
, and 
;

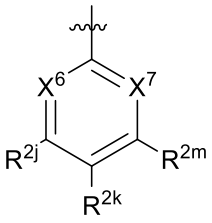
R^{1z} is H, D, halogen, -CN, or C_1-C_6alkyl; wherein the C_1-C_6alkyl is independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, and -OR^{7a};

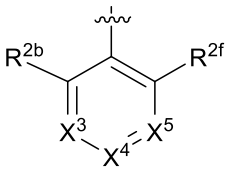
each R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f}, R^{1g}, and R^{1h} is independently selected from the group consisting of H, D, halogen, -CN, –NO_2, –SR^{11a}, –OR^{11a}, -C(O)R^{11b}, -P(O)$R^{11b}R^{12b}$, -S(O)$_2R^{11b}$, -S(O)R^{11b}, –N$R^{11a}R^{12a}$, -NR^{11a}C(O)R^{12a}, -NR^{11a}C(O)OR^{12a}, -NR^{11a}C(O)NR^{12a}, –NR^{11a}S(O)$_2R^{12a}$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl, -OR^{11a}, -C(O)R^{11b}, -P(O)$R^{11b}R^{12b}$, -S(O)$_2R^{11b}$, -S(O)R^{11b}, –N$R^{11a}R^{12a}$, –NR^{11a}C(O)R^{12a}, -NR^{11a}C(O)OR^{12a}, -NR^{11a}C(O)NR^{12a}, –NR^{11a}S(O)$_2R^{12a}$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl; or

two of the following groups, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f}, R^{1g}, and R^{1h}, when present, together with the atoms to which they are attached can form a C_3-C_{10}cycloalkyl or a 3-7-membered heterocyclyl; wherein the C_3-C_{10}cycloalkyl and 3-7-membered heterocyclyl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl, $-OR^{13a}$, $-C(O)R^{13b}$, $-P(O)R^{13b}R^{14b}$, $-S(O)_2R^{13b}$, $-S(O)R^{13b}$, $–NR^{13a}R^{14a}$, $–NR^{13a}C(O)R^{14a}$, $-NR^{13a}C(O)OR^{14a}$, $-NR^{13a}C(O)NR^{14a}$, and $–NR^{13a}S(O)_2R^{14a}$; or

two geminal groups R^{1a} and R^{1b}; R^{1c} and R^{1d}; R^{1e} and R^{1f}; or R^{1g} and R^{1h}, when present, form an oxo group;

R^2 is selected from the group consisting of 5-membered heteroaryl, 

, 

, and 

; wherein the 5-membered heteroaryl is unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, oxo, $-OR^{23a}$, $-C(O)R^{23b}$, $-P(O)R^{23b}R^{24b}$, $-S(O)_2R^{23b}$, $-S(O)R^{23b}$, $-NR^{23a}R^{24a}$, $–NR^{23a}C(O)R^{24a}$, $-NR^{23a}C(O)OR^{24a}$, $-NR^{23a}C(O)NR^{24a}$, $–NR^{23a}S(O)_2R^{24a}$, $-(CH_2)_{1-4}C_3$-C_{10}cycloalkyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl;

X^2 is N or CR^{2a};

X^3 is N or CR^{2c};

X^4 is N or CR^{2d};

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

X^6 and X^7 are independently N or $CR^{2n,}$, wherein at least one of X^6 and X^7 is N;

R^{2a} is H, D, halogen, -CN, $–OR^{15a}$, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, $-C(O)NR^{15a}R^{16a}$, $-C(O)OR^{15a}$, $–NR^{15a}R^{16a}$, $–NR^{15a}C(O)R^{16a}$, $-NR^{15a}C(O)OR^{16a}$, $-NR^{15a}C(O)NR^{16a}$, or $–NR^{15a}S(O)_2R^{16a}$, wherein the C_1-C_6alkyl and C_3-C_{10}cycloalkyl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, halogen, -CN, $-OR^{15a}$, $-C(O)R^{15b}$, $-NR^{15a}R^{16a}$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl;

each R^{2b}, R^{2c}, R^{2d}, R^{2e}, and R^{2f} is independently H, D, halogen, -CN, $–NO_2$, $–SR^{17a}$, $–OR^{17a}$, $-C(O)R^{17b}$, $-P(O)R^{17b}R^{18b}$, $-S(O)_2R^{17b}$, $-S(O)R^{17b}$, $–NR^{17a}R^{18a}$, $–NR^{17a}C(O)R^{18a}$, $-NR^{17a}C(O)OR^{18a}$, $-NR^{17a}C(O)NR^{18a}$, $–NR^{17a}S(O)_2R^{18a}$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, or 5-6-membered heteroaryl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, $-OR^{17a}$, $-C(O)R^{17b}$, $-P(O)R^{17b}R^{18b}$, $-S(O)_2R^{17b}$, $-S(O)R^{17b}$, $–NR^{17a}R^{18a}$, $–NR^{17a}C(O)R^{18a}$, $-NR^{17a}C(O)OR^{18a}$, $-NR^{17a}C(O)NR^{18a}$, $–NR^{17a}S(O)_2R^{18a}$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl; or

two adjacent R^{2b}, R^{2c}, R^{2d}, R^{2e}, and R^{2f} together with the atoms to which they are attached can form C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, or 5-6-membered heteroaryl; wherein the C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, D, -CN, C_1-C_6alkyl, $-OR^{19a}$, and $NR^{19a}R^{20a}$;

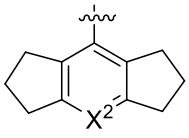
each R^{2j}, R^{2k}, R^{2m}, and R^{2n} is independently H, D, halogen, -CN, $–NO_2$, $–SR^{17a}$, $–OR^{17a}$, $-C(O)R^{17b}$, $-P(O)R^{17b}R^{18b}$, $-S(O)_2R^{17b}$, $-S(O)R^{17b}$, $–NR^{17a}R^{18a}$, $-NR^{17a}C(O)R^{18a}$, $-NR^{17a}C(O)OR^{18a}$, $-NR^{17a}C(O)NR^{18a}$, $–NR^{17a}S(O)_2R^{18a}$, C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, or 5-6-membered heteroaryl; wherein the C_1-C_6alkyl, C_2-C_6alkenyl, C_4-C_8cycloalkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, $-OR^{17a}$, $-C(O)R^{17b}$, $-P(O)R^{17b}R^{18b}$, $-S(O)_2R^{17b}$, $-S(O)R^{17b}$, $–NR^{17a}R^{18a}$, $–NR^{17a}C(O)R^{18a}$, $-NR^{17a}C(O)OR^{18a}$, $-NR^{17a}C(O)NR^{18a}$, $–NR^{17a}S(O)_2R^{18a}$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl; or

two adjacent R^{2j}, R^{2k}, R^{2m}, and R^{2n} together with the atoms to which they are attached can form C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, or 5-6-membered heteroaryl, wherein the C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, D, -CN, C_1-C_6alkyl, $-OR^{19a}$, and $NR^{19a}R^{20a}$;

R^{3a}, R^{7a}, R^{11a}, R^{12a}, R^{13a}, R^{14a}, R^{15a}, R^{16a}, R^{17a}, R^{18a}, R^{19a}, R^{20a}, R^{23a}, and R^{24a} are independently, at each occurrence, H, D, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-

C_{10}cycloalkyl, C_4-C_8cycloalkenyl, C_6aryl, 3-7-membered heterocyclyl, or 5-6-membered heteroaryl; wherein the C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_{10}cycloalkyl, C_4-C_8cycloalkenyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl, -OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl; and

R^{3b}, R^{11b}, R^{12b}, R^{13b}, R^{14b}, R^{15b}, R^{17b}, R^{18b}, R^{23b}, and R^{24b} are independently, at each occurrence, H, D, -OH, -O(C_1-C_6alkyl), -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, -$NHS(O)_2CH_3$, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_{10}cycloalkyl, C_4-C_8cycloalkenyl, C_6aryl, 3-7-membered heterocyclyl, or 5-6-membered heteroaryl; wherein the C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_{10}cycloalkyl, C_4-C_8cycloalkenyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, -CN, halogen, C_1-C_6alkyl, -OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), -N(C_1-C_6alkyl)$_2$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl.

2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^2 is 

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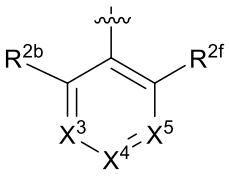
3. The compound of claim 2, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein X^2 is CR^{2a} and R^{2a} is H, halogen, -CN, -OR^{15a}, -$C(O)OR^{15a}$, or C_1-C_6alkyl; wherein the C_1-C_6alkyl is unsubstituted or substituted with one or more substituents selected from the group consisting of D, halogen, -CN, -OR^{15a}, -$C(O)R^{15b}$, -$NR^{15a}R^{16a}$, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl.

4. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^2 is 

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

X^3 is CR^{2c}; X^4 is CR^{2d}; and X^5 is CR^{2e}; and

each R^{2b}, R^{2c}, R^{2d}, R^{2e}, and R^{2f} is independently selected from the group consisting of H, D, halogen, $–OR^{17a}$, C_1-C_6alkyl, C_6aryl, and 5-6-membered heteroaryl; wherein each C_1-C_6alkyl, C_6aryl, and 5-6-membered heteroaryl is independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, halogen, $–OR^{17a}$, $–NR^{17a}R^{18a}$, $–NR^{17a}C(O)R^{18a}$, and $-NR^{17a}C(O)OR^{18a}$.

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

X^3 is CR^{2c}; X^4 is CR^{2d}; and X^5 is CR^{2e}; and

each R^{2b}, R^{2c}, R^{2d}, R^{2e}, and R^{2f} is independently selected from the group consisting of H, D, halogen, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, and -CN.

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

X^3 is CR^{2c}; X^4 is CR^{2d}; and X^5 is CR^{2e};

R^{2b} and R^{2c} together with the atoms to which they are attached form C_3-C_{10}cycloalkyl or 3-7-membered heterocyclyl; wherein the C_3-C_{10}cycloalkyl or 3-7-membered heterocyclyl is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, D, -CN, C_1-C_6alkyl, $-OR^{19a}$, and $NR^{19a}R^{20a}$; and

each R^{2d}, R^{2e}, and R^{2f} is independently H, D, halogen, $–OR^{17a}$, C_1-C_6alkyl, C_6aryl, and 5-6-membered heteroaryl; wherein each C_1-C_6alkyl, C_6aryl, and 5-6-membered heteroaryl is independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, halogen, $-OR^{17a}$, $–NR^{17a}R^{18a}$, $–NR^{17a}C(O)R^{18a}$, and $-NR^{17a}C(O)OR^{18a}$.

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

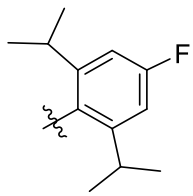
X^3 is CR^{2c}; X^4 is CR^{2d}; and X^5 is CR^{2e};

R^{2b} and R^{2c} together with the atoms to which they are attached form C_3-C_{10}cycloalkyl, wherein the C_3-C_{10}cycloalkyl is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, D, and C_1-C_6alkyl;

R^{2e} and R^{2f} together with the atoms to which they are attached form C_3-C_{10}cycloalkyl, wherein the C_3-C_{10}cycloalkyl is unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, D, and C_1-C_6alkyl; and

R^{2d} is H, D, halogen, -CN or C_1-C_6alkyl.

9. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^2 is selected from the group consisting of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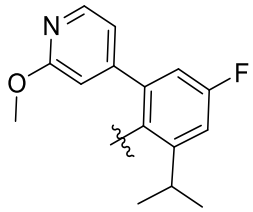
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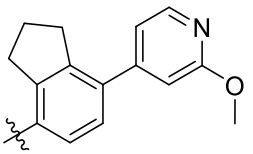
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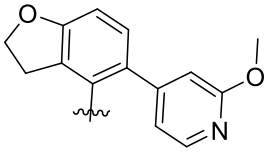
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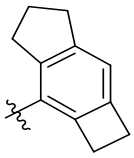
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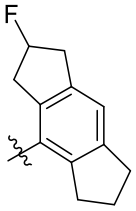
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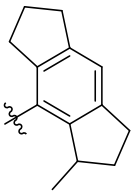
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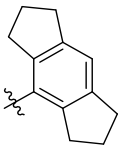
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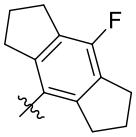
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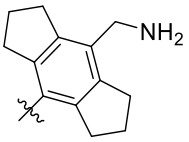
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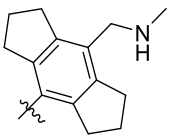
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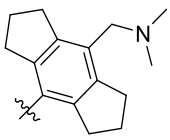
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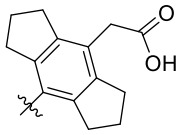
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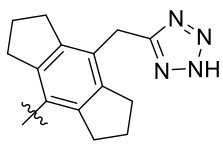
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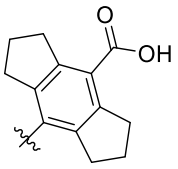
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10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein:

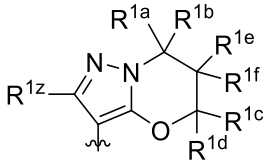
each R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f}, R^{1g}, and R^{1h}, if present, is independently selected from the group consisting of H, halogen, $–OR^{11a}$, $-C(O)R^{11b}$, $-P(O)R^{11b}R^{12b}$, $-S(O)_2R^{11b}$, $-S(O)R^{11b}$, $–NR^{11a}R^{12a}$, $-NR^{11a}C(O)R^{12a}$, $-NR^{11a}C(O)OR^{12a}$, $-NR^{11a}C(O)NR^{12a}$, $–NR^{11a}S(O)_2R^{12a}$, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_6aryl, 3-7-membered heterocyclyl, and 5-6-membered heteroaryl.

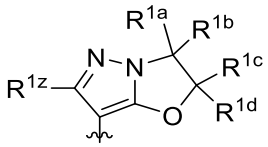
11. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein:

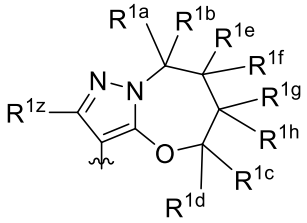
each R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f}, R^{1g}, and R^{1h}, if present, is independently selected from the group consisting of H, D, halogen, $–OR^{11a}$, $–NR^{11a}R^{12a}$, C_1-C_6alkyl, and 3-7-membered heterocyclyl;

wherein the C_1-C_6alkyl and 3-7-membered heterocyclyl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, halogen, $-OR^{11a}$, and $–NR^{11a}R^{12a}$;

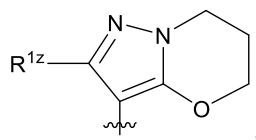
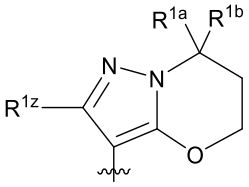
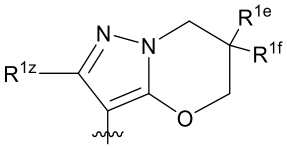
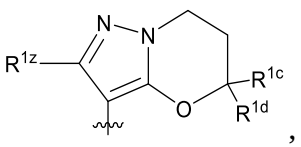
wherein R^{11a} and R^{12a} are independently, at each occurrence, H, D, or C_1-C_8alkyl, wherein the C_1-C_8alkyl is independently unsubstituted or substituted with one or more substituents selected from the group consisting of D, halogen, -OH, -O-C_1-C_6alkyl, -NH_2, -NH(C_1-C_6alkyl), and -N(C_1-C_6alkyl)$_2$.

12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^1 is  , R^{1z} is H, and R^{100} is H.

13. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^1 is  , R^{1z} is H, and R^{100} is H.

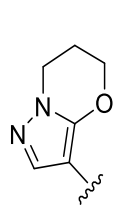
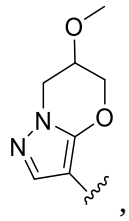
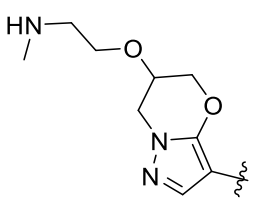
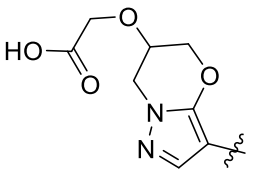
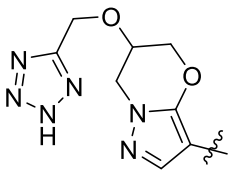
14. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^1 is  , R^{1z} is H, and R^{100} is H.

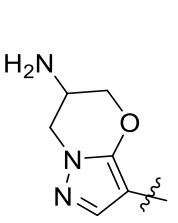
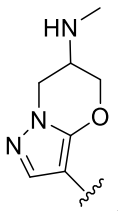
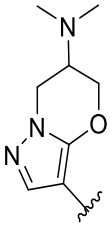
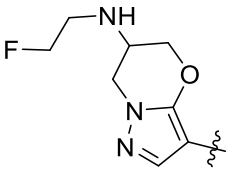
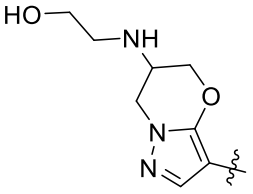
15. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^1 is selected from the group consisting

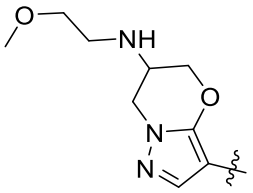
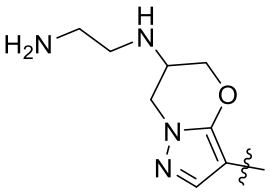
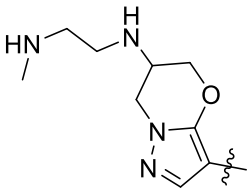
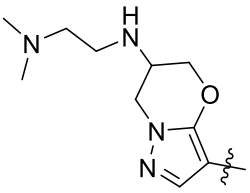
of  ,  ,  and  ,

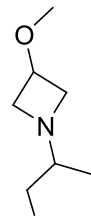
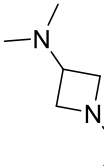
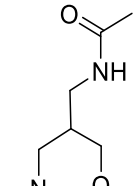
and R^{1z} is H.

16. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^1 is selected from the group consisting of:

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

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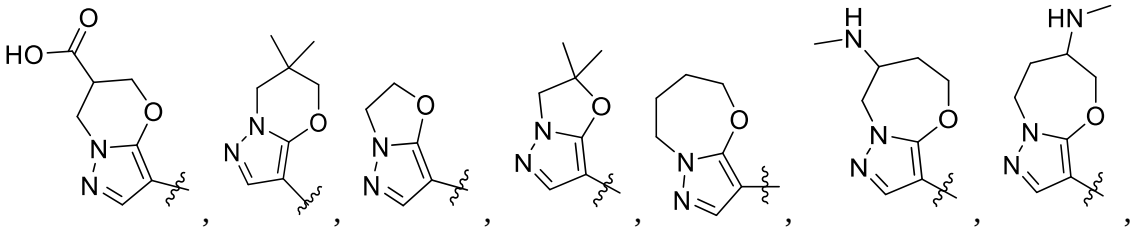
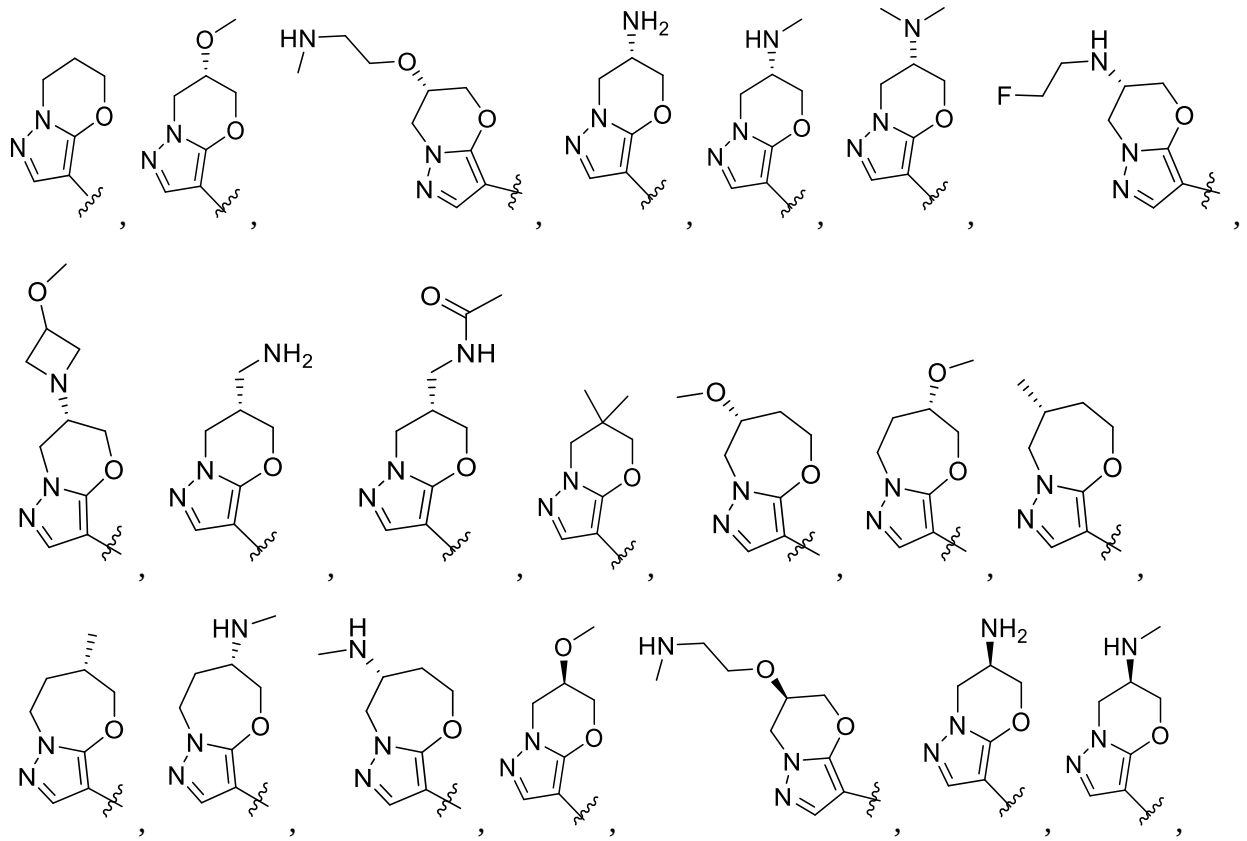
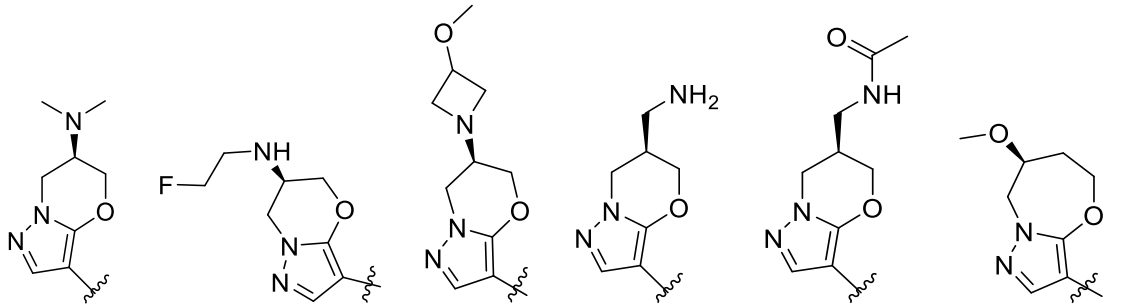

, and .

17. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein R^1 is selected from the group consisting of:

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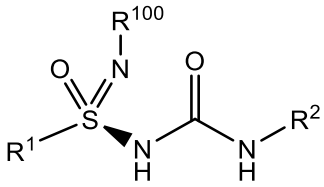
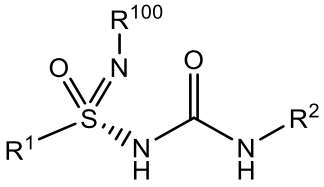
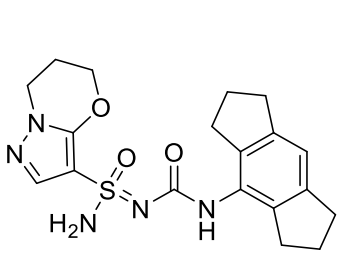
18. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein the compound is of formula:


(Ia).

19. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, wherein the compound is of formula:


(Ib).

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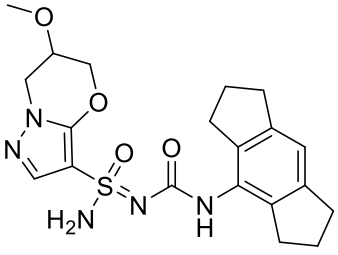
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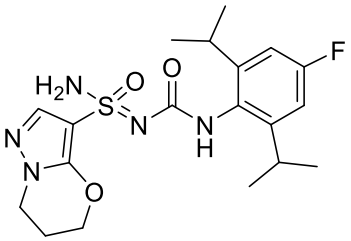
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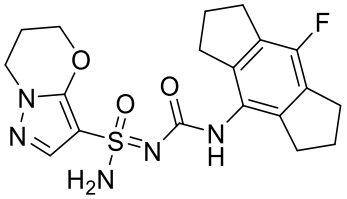
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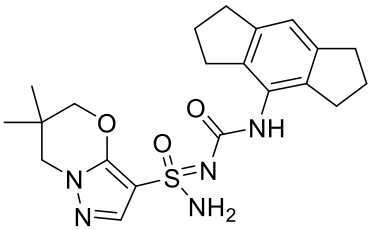
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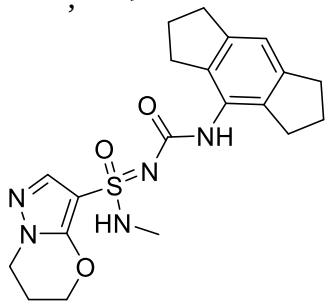
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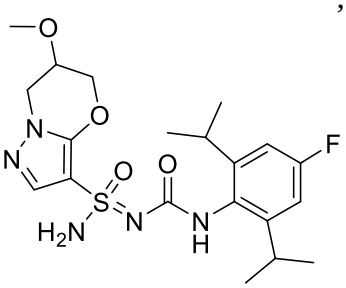
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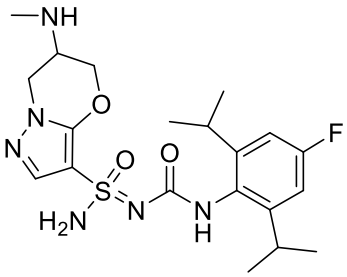
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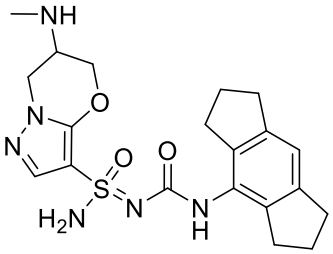
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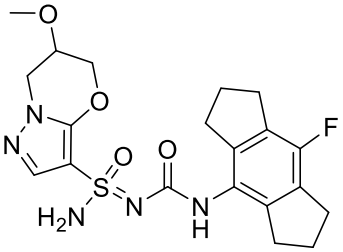
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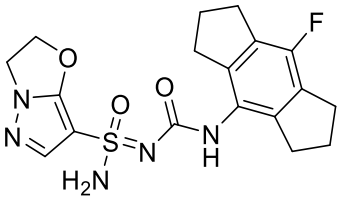
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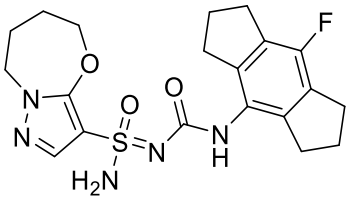
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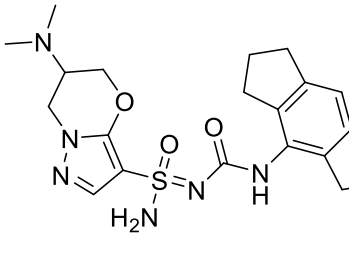
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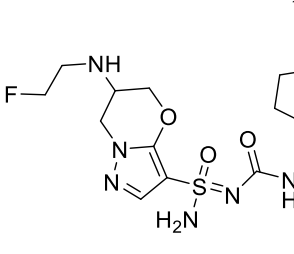
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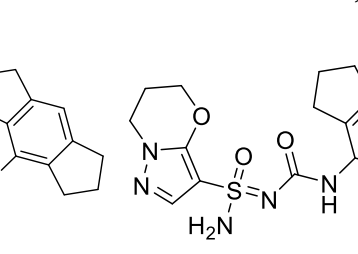
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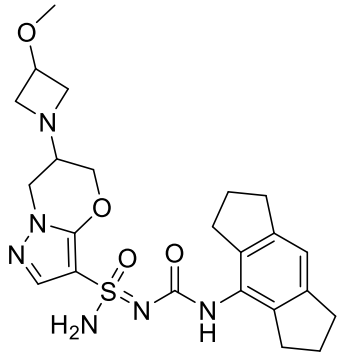
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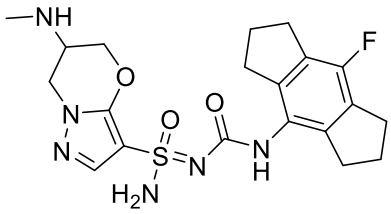
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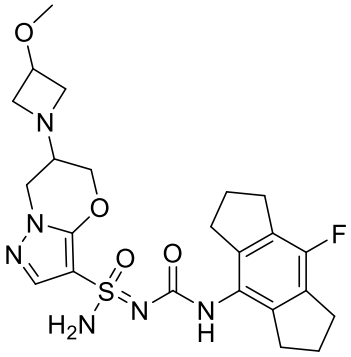
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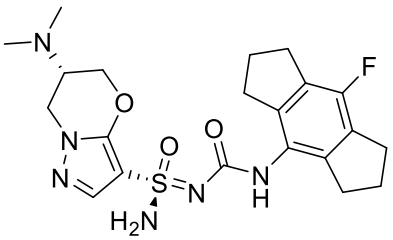
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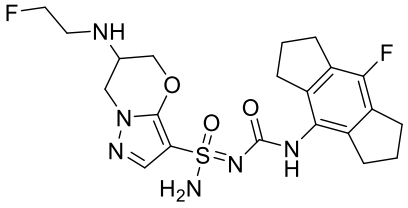
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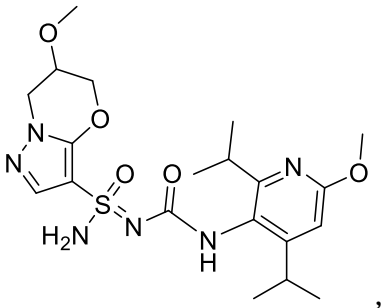
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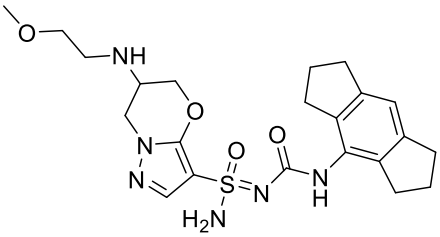
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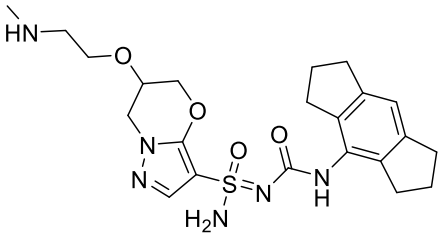
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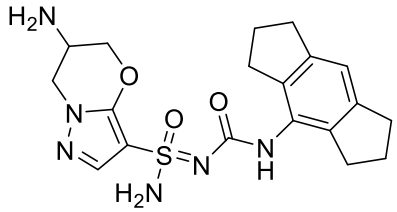
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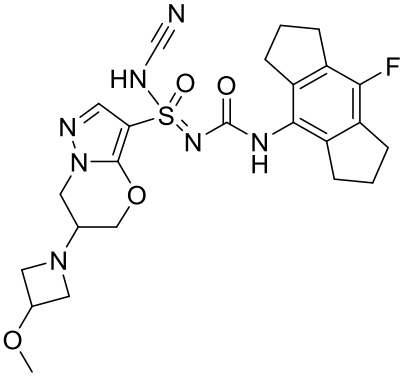
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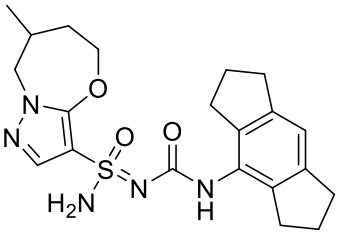
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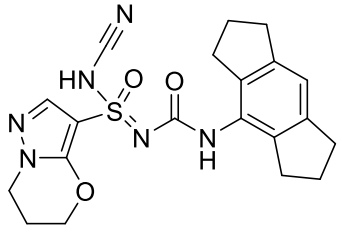
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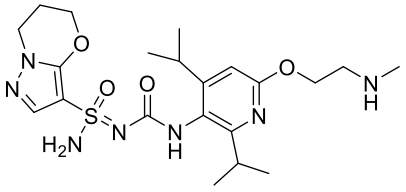
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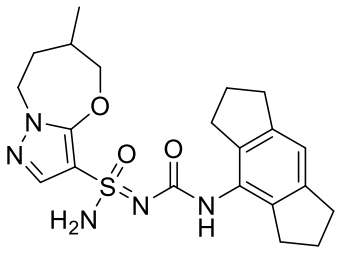
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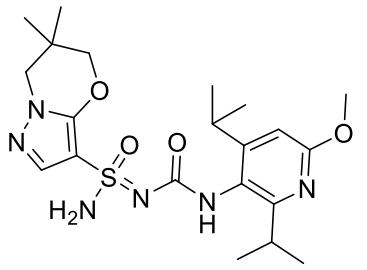
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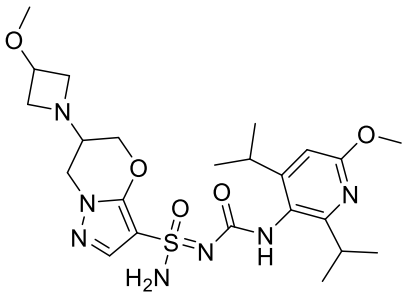
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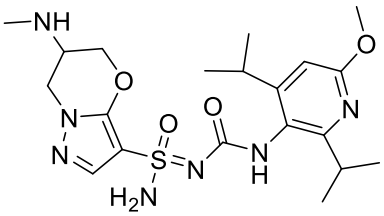
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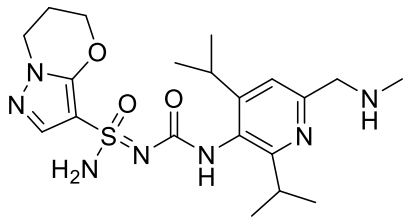
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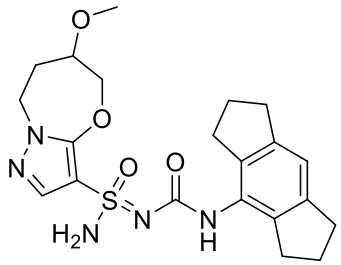
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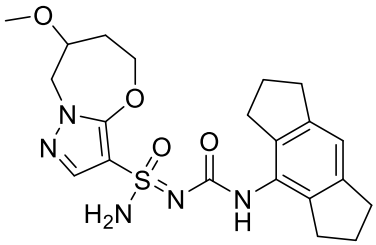
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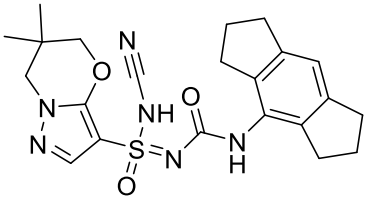
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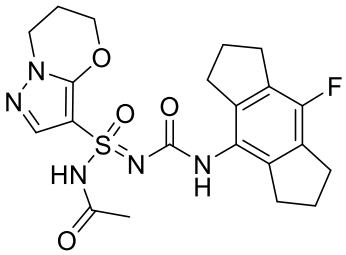
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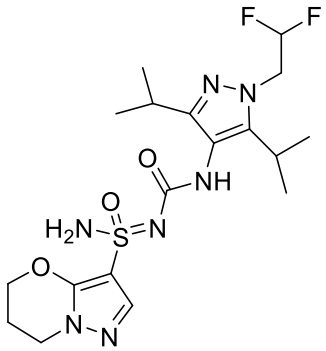
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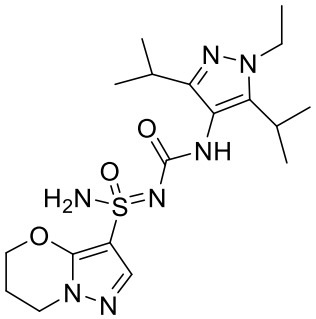
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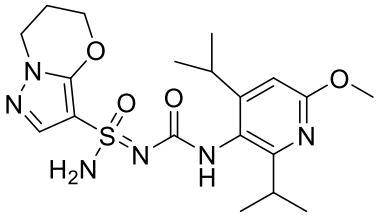
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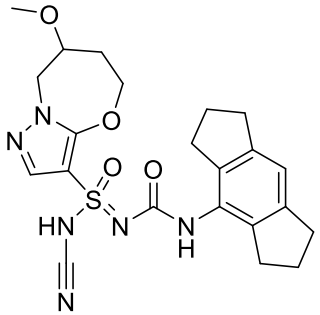
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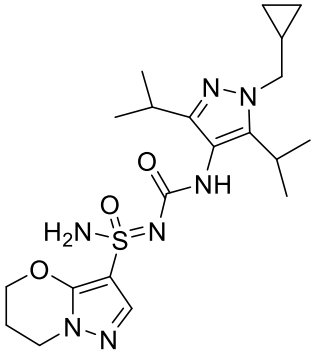
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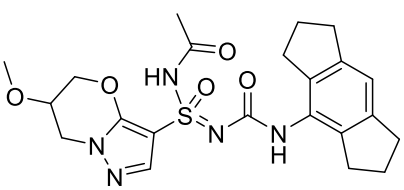
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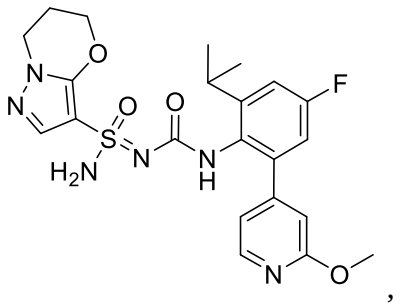
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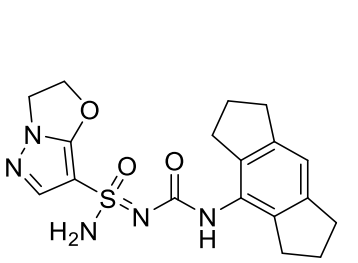
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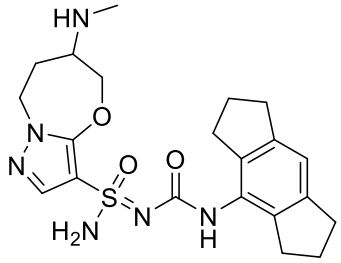
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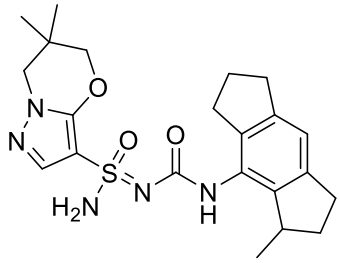
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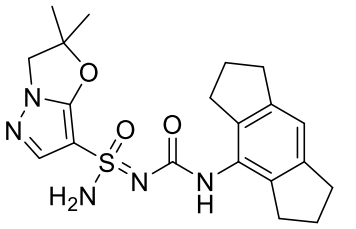
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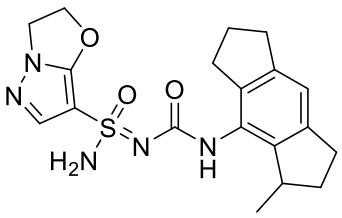
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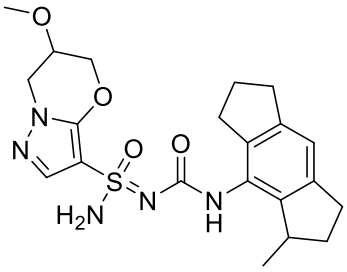
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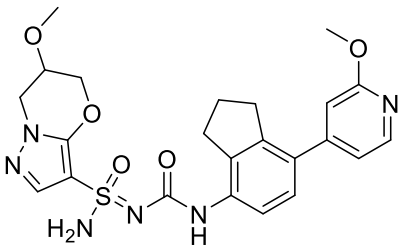
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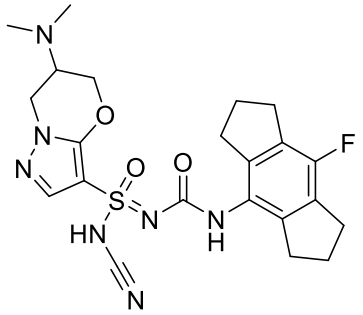
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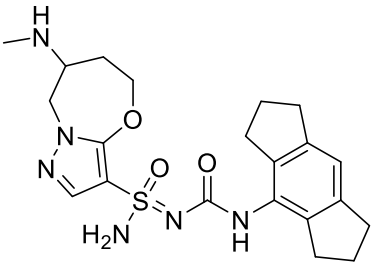
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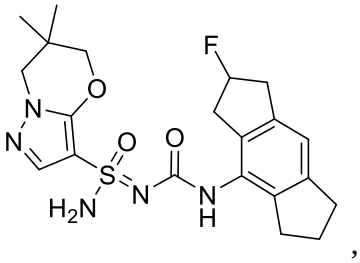
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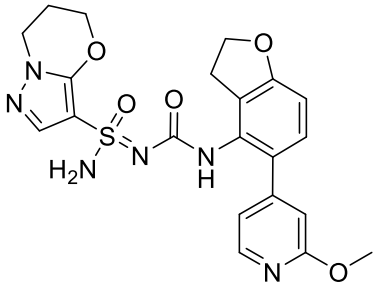
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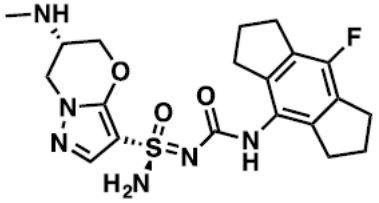
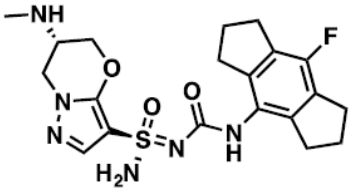
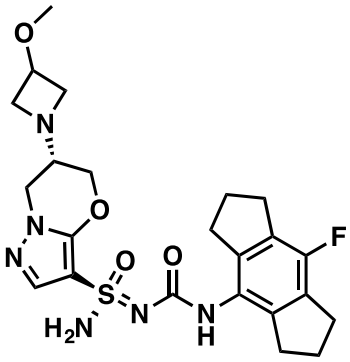
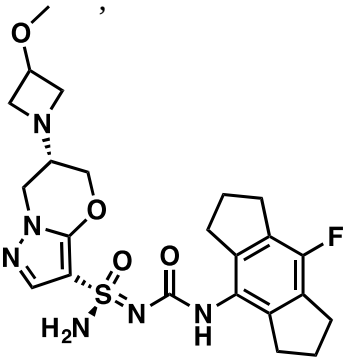
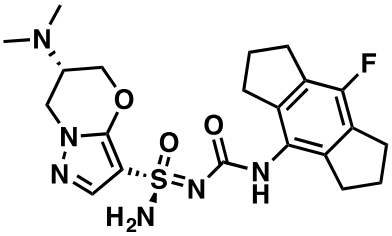
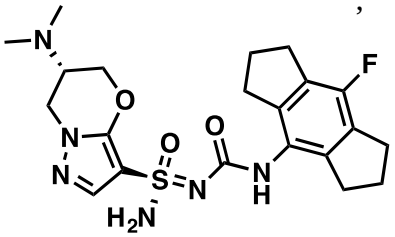
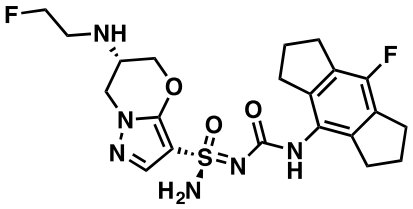
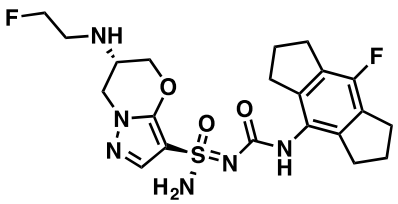
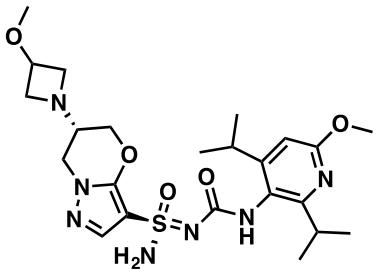
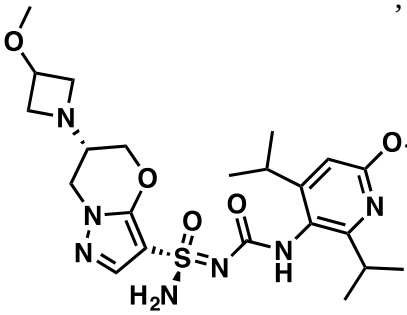
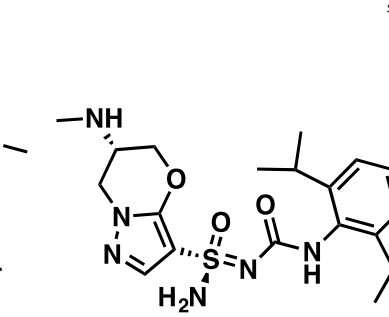
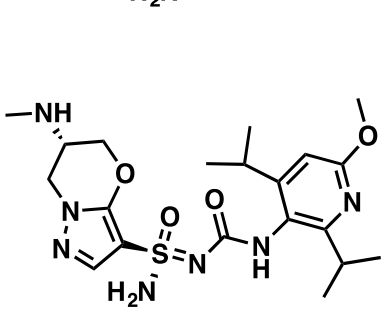
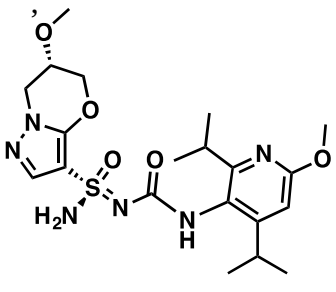
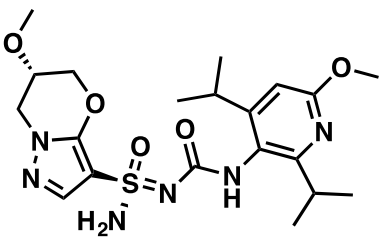
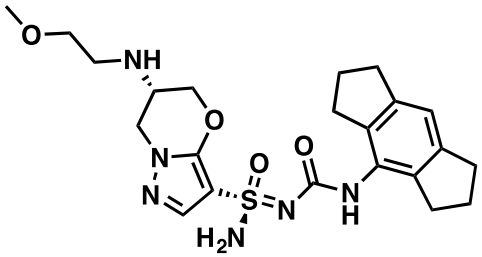
or is a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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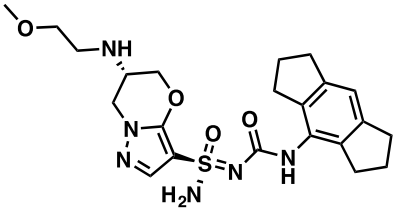
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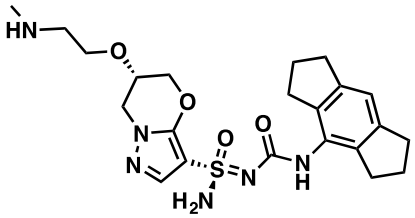
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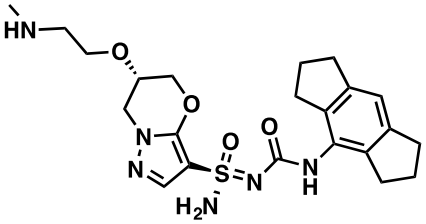
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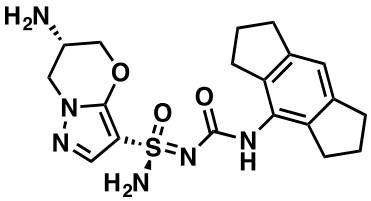
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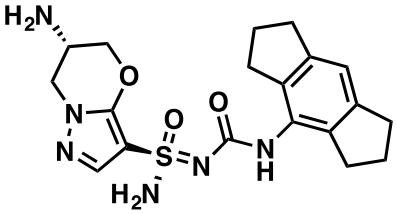
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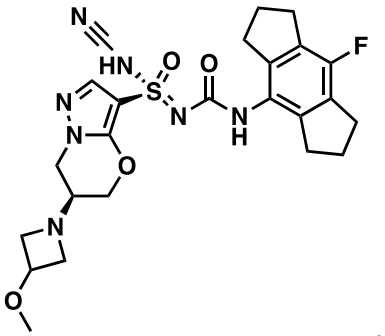
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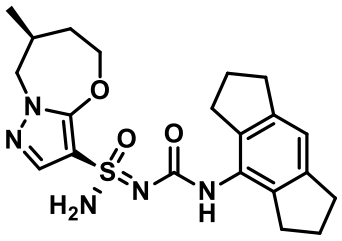
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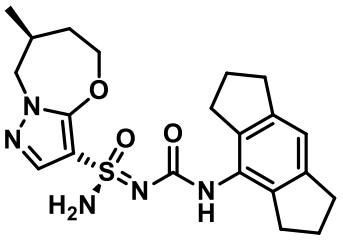
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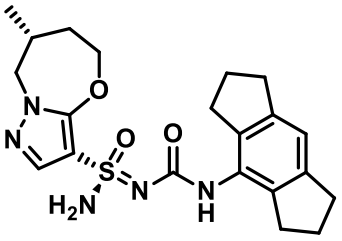
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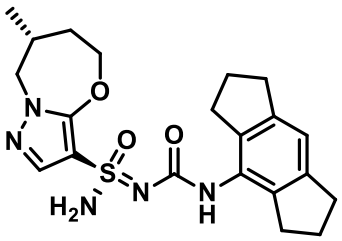
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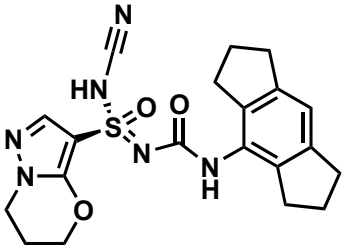
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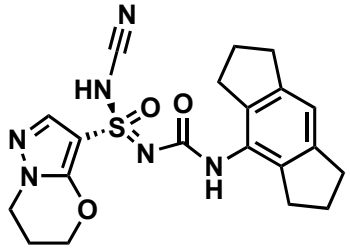
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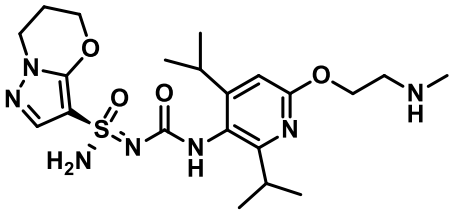
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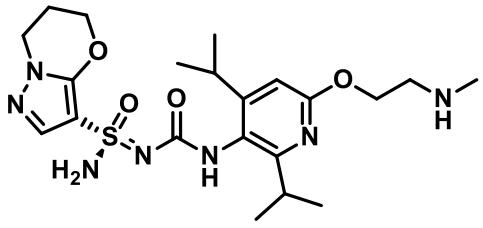
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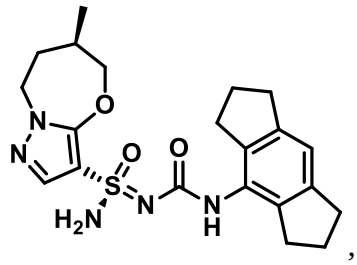
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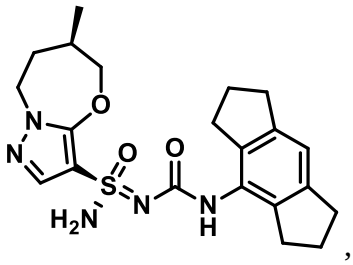
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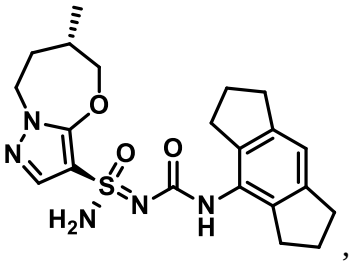
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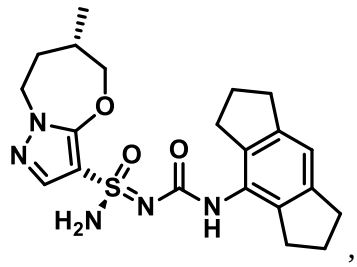
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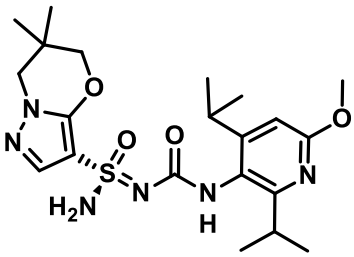
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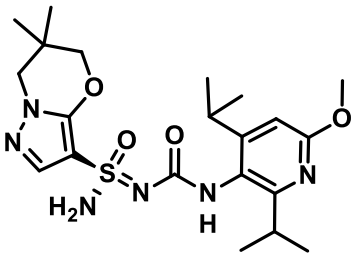
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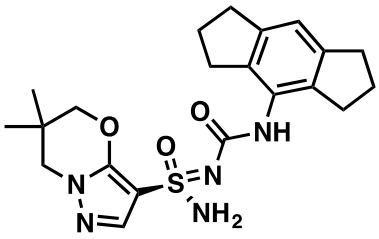
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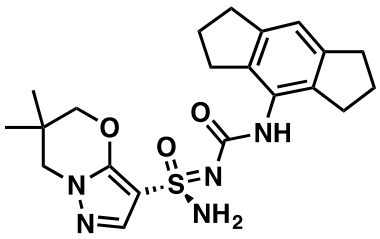
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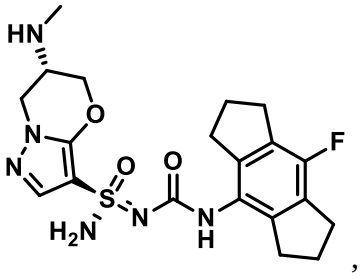
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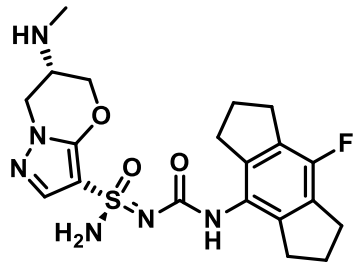
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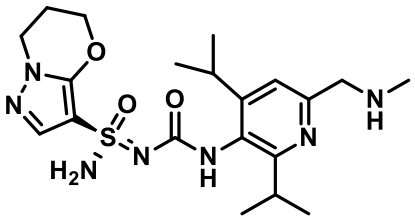
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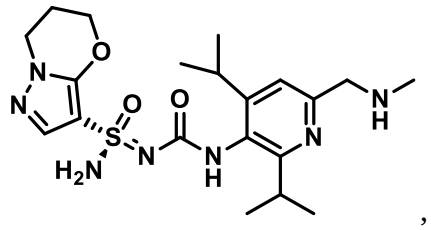
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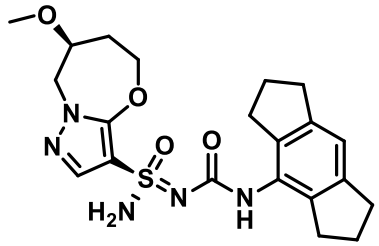
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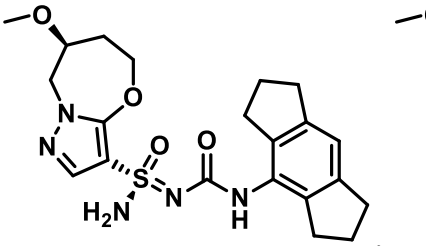
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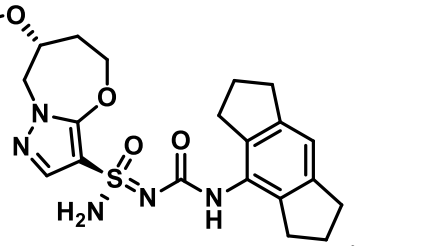
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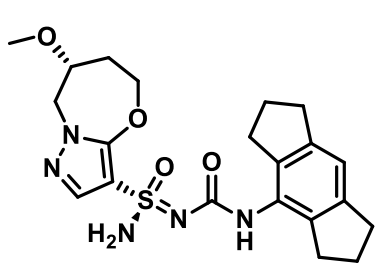
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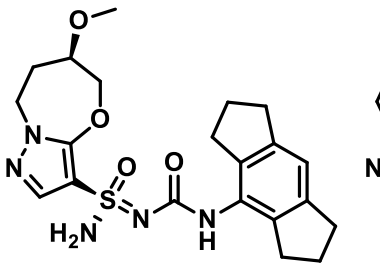
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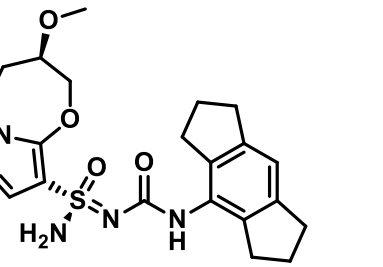
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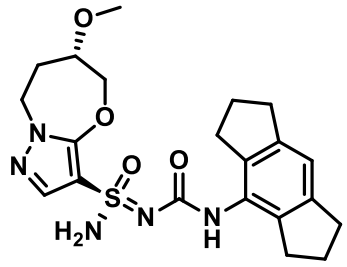
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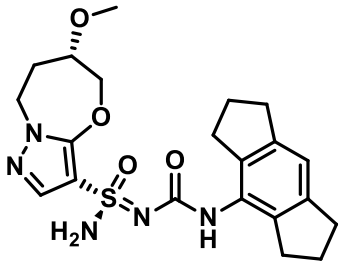
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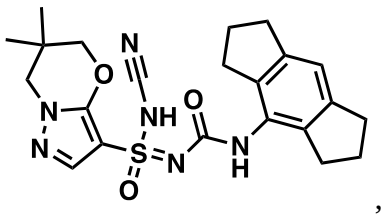
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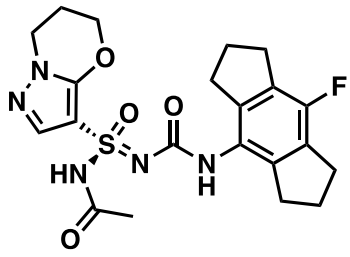
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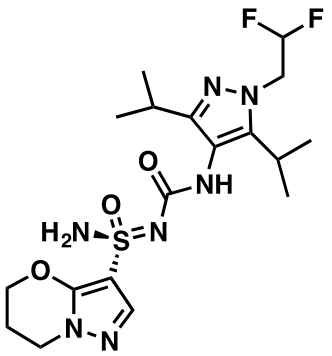
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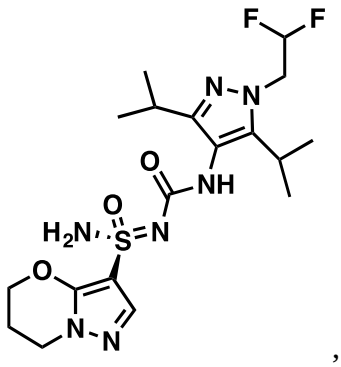
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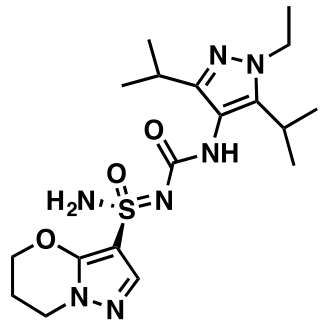
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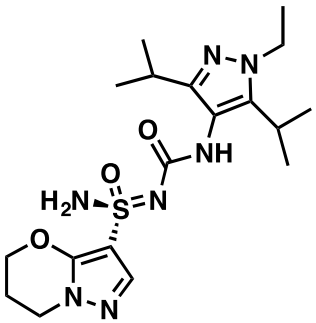
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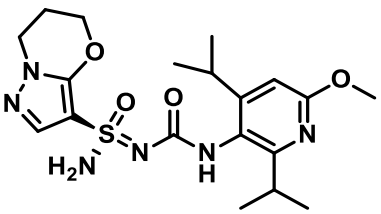
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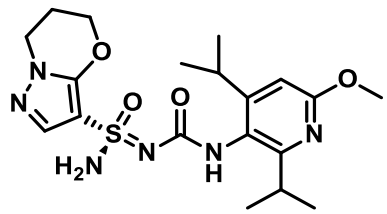
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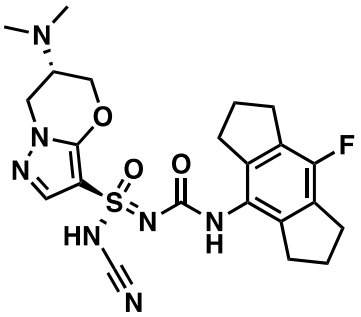
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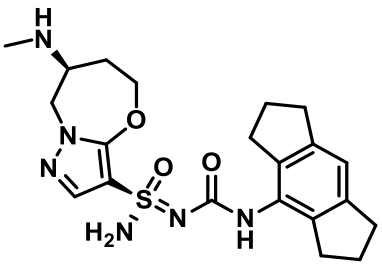
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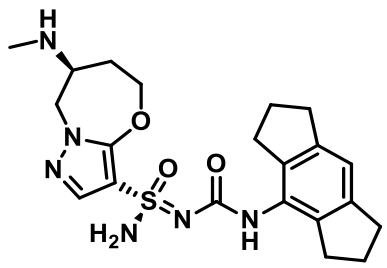
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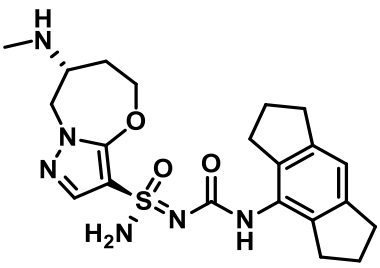
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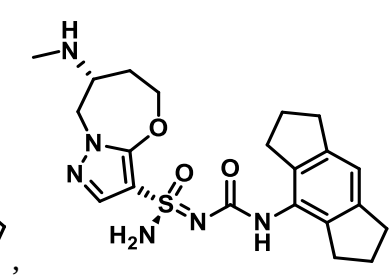
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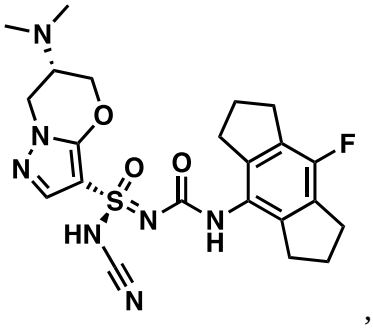
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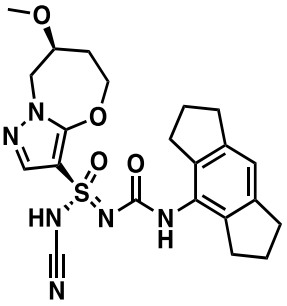
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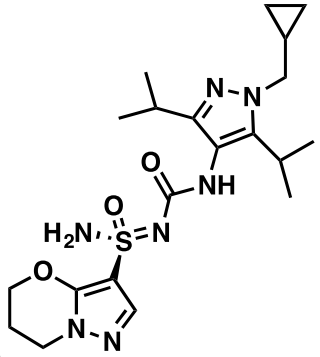
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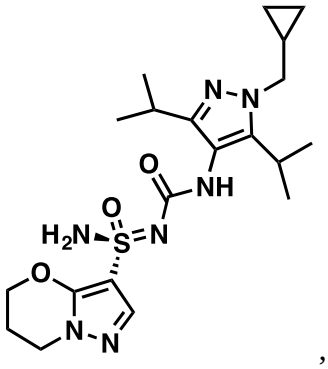
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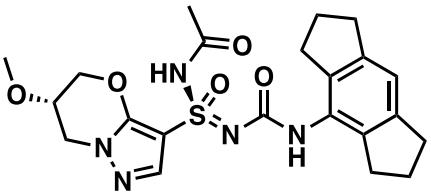
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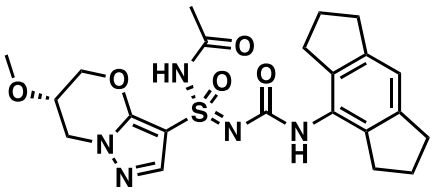
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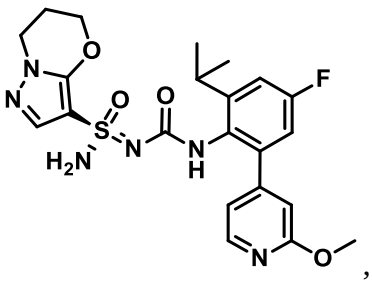
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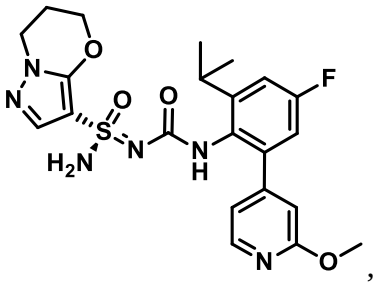
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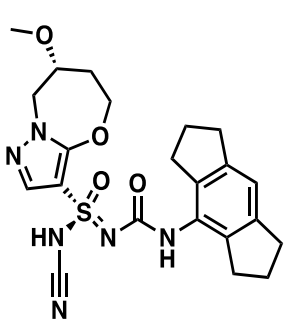
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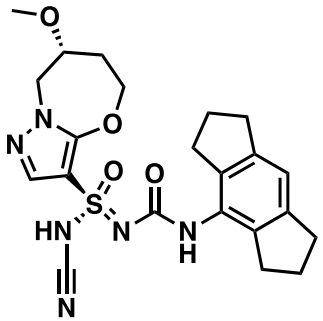
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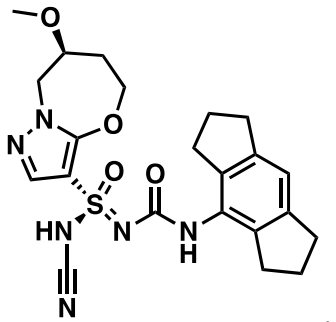
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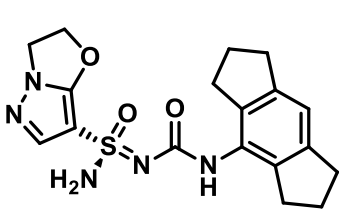
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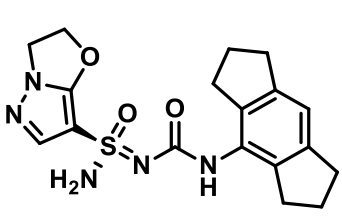
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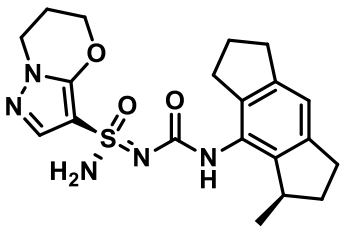
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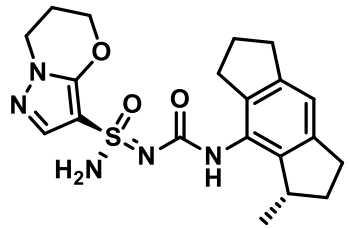
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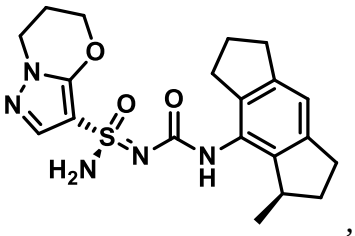
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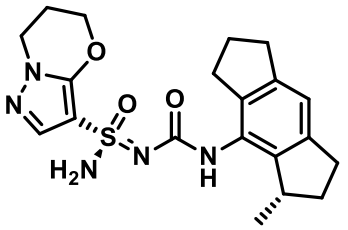
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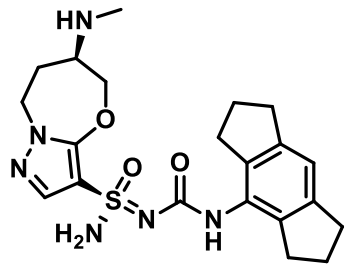
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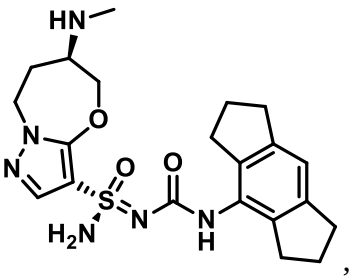
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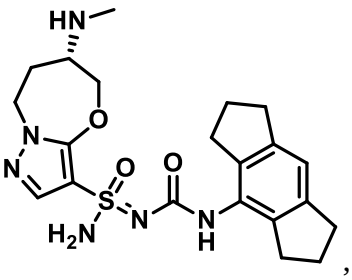
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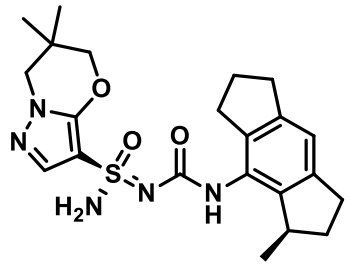
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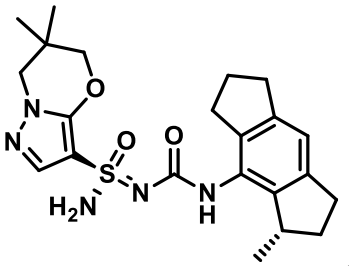
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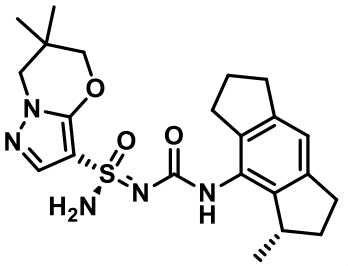
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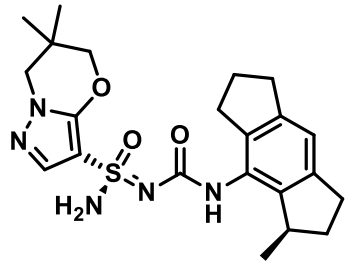
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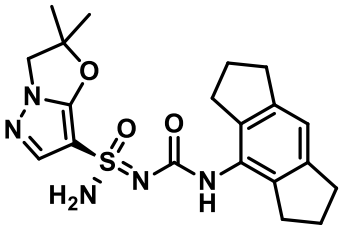
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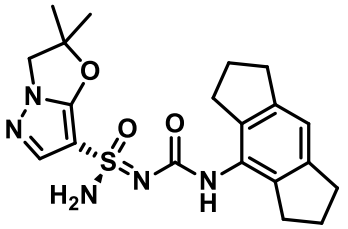
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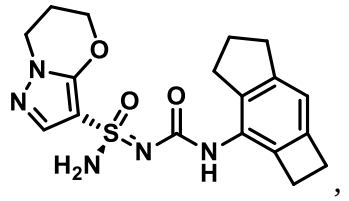
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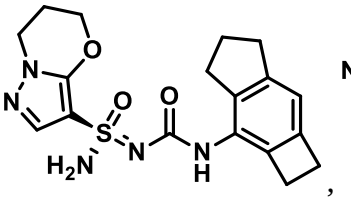
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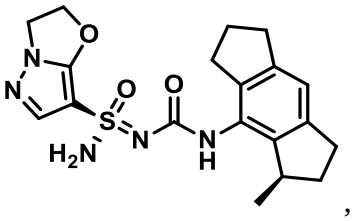
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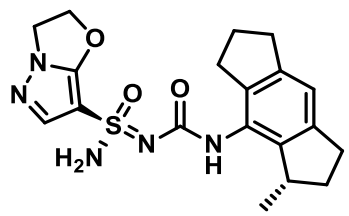
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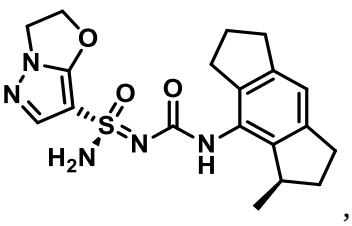
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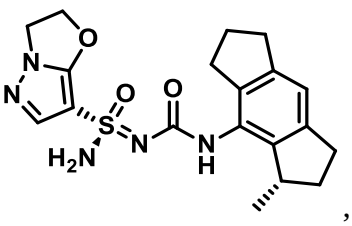
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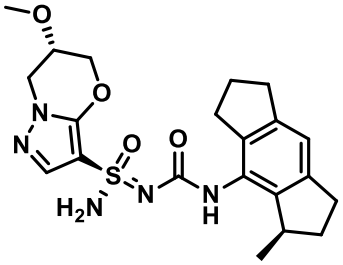
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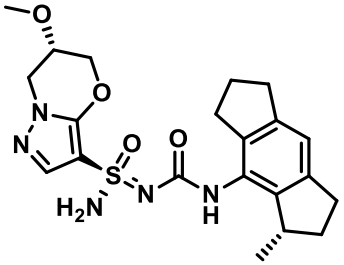
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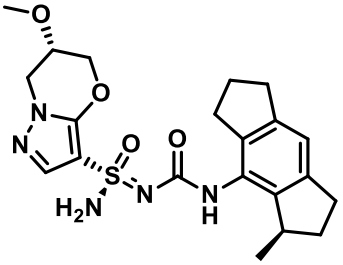
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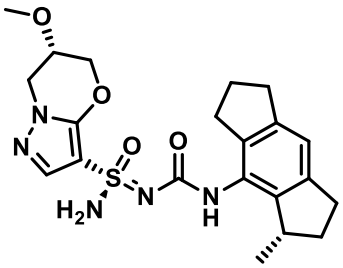
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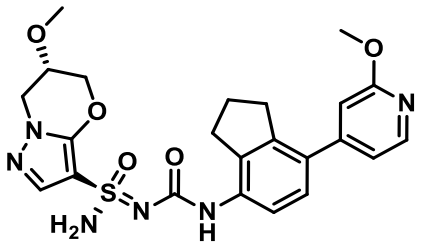
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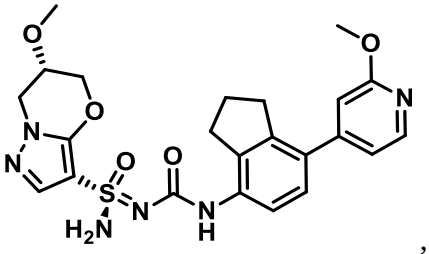
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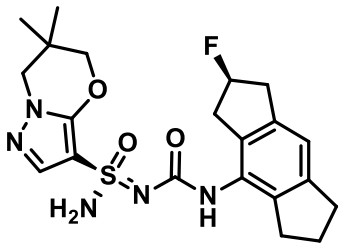
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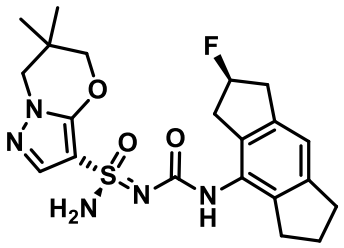
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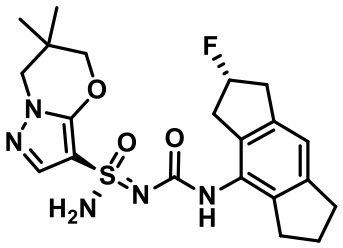
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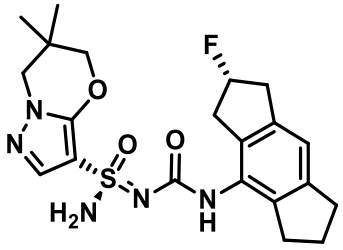
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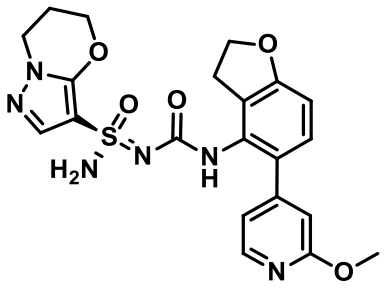
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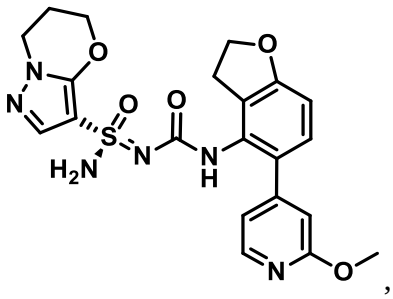
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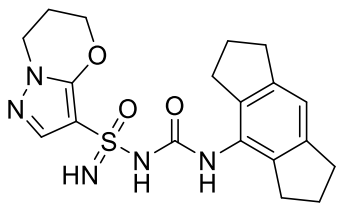
or is a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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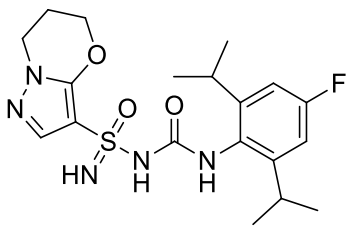
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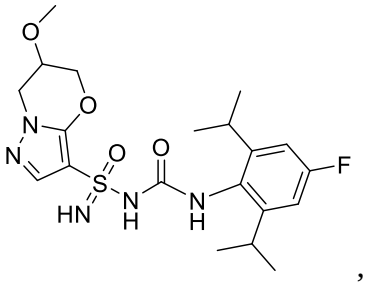
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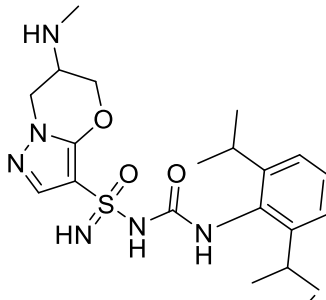
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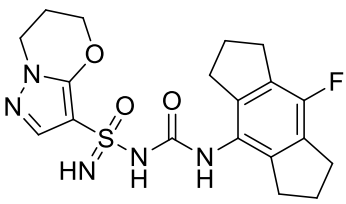
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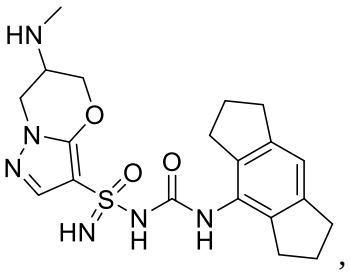
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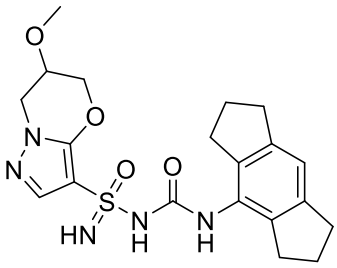
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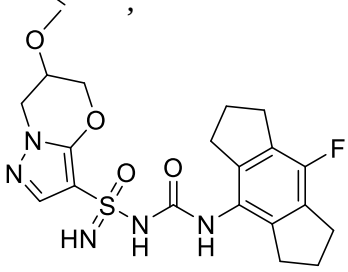
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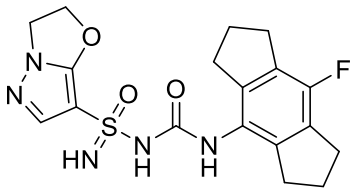
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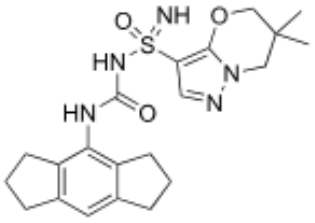
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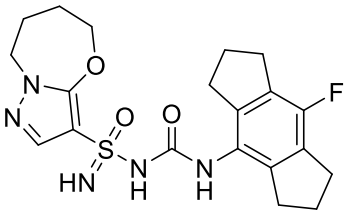
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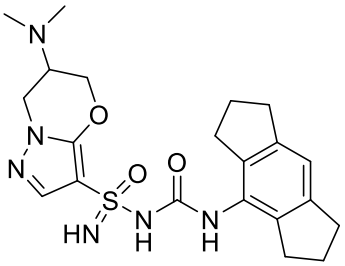
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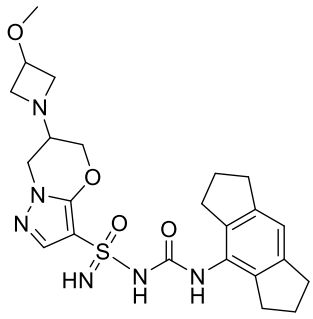
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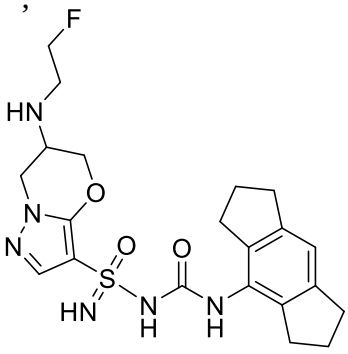
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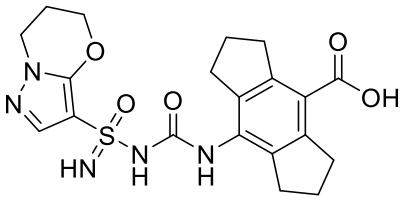
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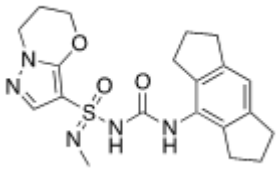
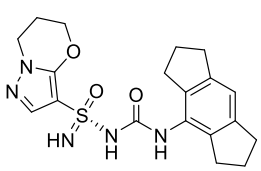

, or is a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof.

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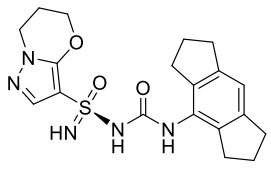
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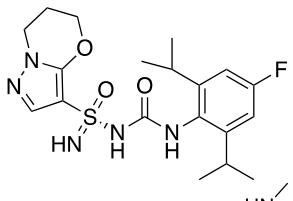
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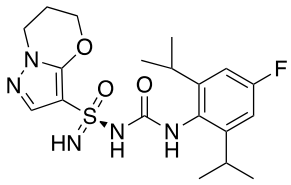
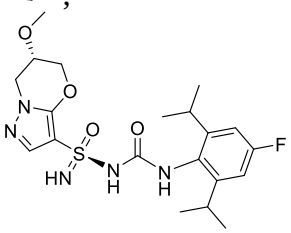
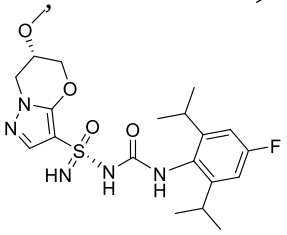
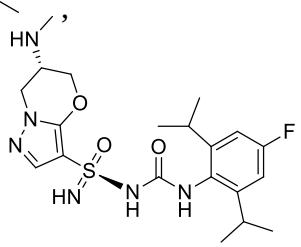
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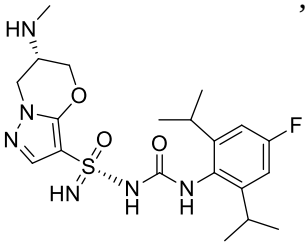
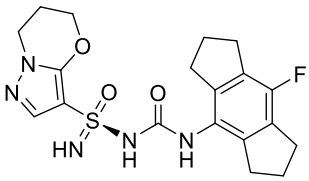
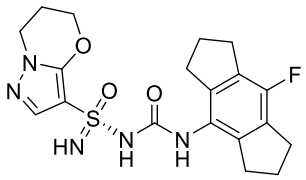
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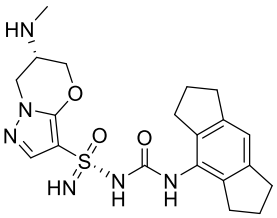
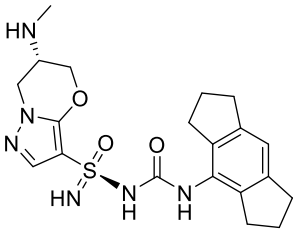
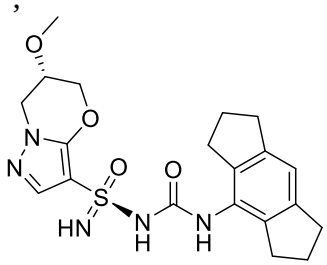
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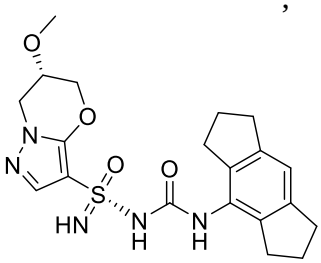
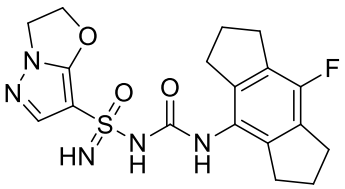
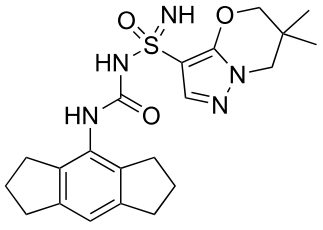
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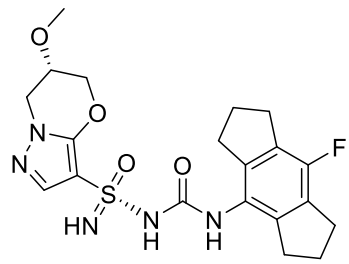
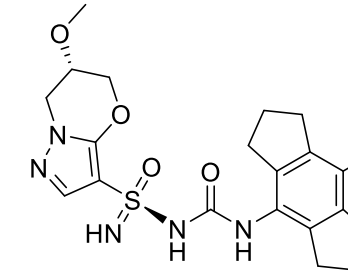
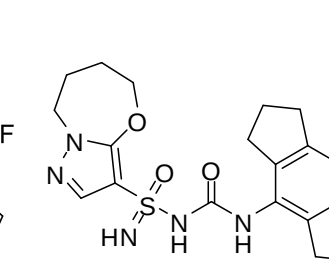
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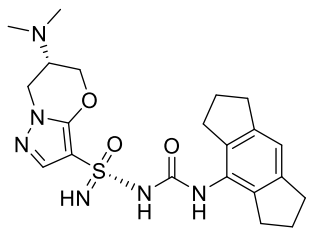
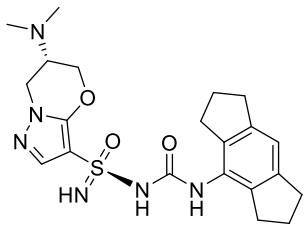
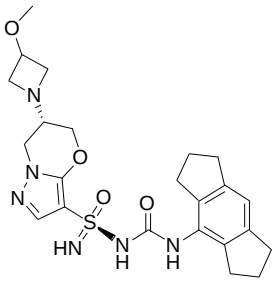
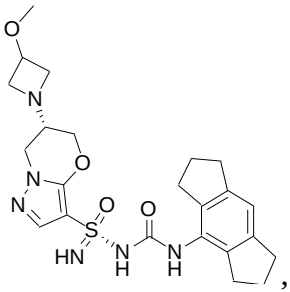
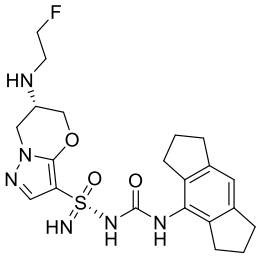
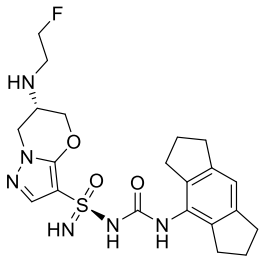
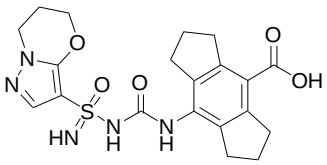
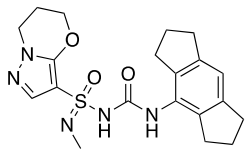
 ,  ,  ,  ,  ,  ,  , 

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

24. A pharmaceutical composition comprising a compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

25. A compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, or a pharmaceutical composition of claim 24, for use as a medicament.

26. Use of a compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, or a pharmaceutical composition of claim 24, in the manufacture of a medicament for the treatment of a disorder, wherein the disorder is a disorder of the immune system, a disorder of the liver, a disorder of the lung, a disorder of the skin, a disorder of the cardiovascular system, a disorder of the renal system, a disorder of the gastro-intestinal tract, a disorder of the respiratory system, a disorder of the endocrine system, a disorder of the central nervous system (CNS), an inflammatory disorder, an autoimmune disorder, or a cancer, tumor, or other malignancy.

27. The use of claim 26, wherein the disorder 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), 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), multiple sclerosis (MS), type-1 diabetes, psoriasis, rheumatoid arthritis, Behcet's disease, Sjogren's syndrome, Schnitzler syndrome, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disorder (COPD), steroid-resistant asthma, asbestosis, silicosis, cystic fibrosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, cerebral malaria, brain injury from pneumococcal meningitis, 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, non-alcoholic steatohepatitis, alcoholic liver disease, contact hypersensitivity, sunburn, osteoarthritis, systemic juvenile idiopathic arthritis, adult-onset Still's disease, relapsing polychondritis, hidradenitis suppurativa (HS), polymyositis, stroke, myocardial infarction, Graft versus Host Disease, hypertension, colitis, abdominal aortic aneurism, pericarditis, Dressler's syndrome, and ischaemia reperfusion injury.

28. The use of claim 26, wherein the disorder is inflammatory bowel disease, celiac disease, colitis, metabolic syndrome, rheumatoid arthritis, hepatic steatosis, fatty liver disease, liver fibrosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), lupus, lupus nephritis, gout, atherosclerosis, myocardial infarction, hypertension, Crohn’s disease, inflammatory bowel disease (IBD), Parkinson’s disease, or Alzheimer’s disease.