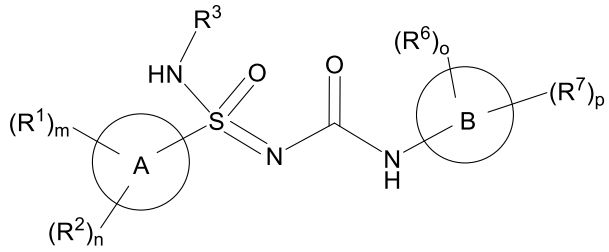
CLAIMS:

1. A compound of Formula AA



Formula AA

wherein

m = 0, 1, or 2;

n = 0, 1, or 2;

o = 1 or 2;

p = 0, 1, 2, or 3; wherein the sum of o and p is from 1 to 4;

wherein

A is a 5- to 10-membered heteroaryl or a C_6-C_{10} aryl;

B is a 6-membered heteroaromatic ring containing 1-3 N atoms, or an N-oxide thereof;

wherein at least one R^6 is *ortho* to the bond connecting the B ring to the NHC(O) group of Formula AA;

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NR^8R^9, $C(O)R^{13}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocycloalkyl are optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, R^{15}, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), and OCO(3- to 7-membered heterocycloalkyl);

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, -O(C_0-C_3 alkylene)C_6-C_{10} aryl, halo, NR^8R^9, or oxo;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl are each optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one monocyclic or bicyclic C_4-C_{12} carbocyclic ring or at least one monocyclic or bicyclic 5- to-12-membered heterocyclic ring wherein:

a) when each of the adjacent atoms is a carbon atom, then the heterocyclic ring includes from 1-3 heteroatoms and/or heteroatomic groups independently selected from O, NH, NR^{13}, S, S(O), and $S(O)_2$; and

b) when one or both of the adjacent atoms is/are a nitrogen atom(s), then the heterocyclic ring includes from 0-2 heteroatoms and/heteroatomic groups independently selected from O, NH, NR^{13}, S, S(O), and $S(O)_2$ (in addition to the aforementioned nitrogen atom(s) attached to R^1 and/or R^2), and

wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents each independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, OC_3-C_{10} cycloalkyl, NR^8R^9, $=NR^{10}$, CN, $COOC_1$-C_6 alkyl, $OS(O_2)C_6$-C_{10} aryl, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $CONR^8R^9$,

wherein the C_1-C_6 alkyl, C_1-C_6 alkoxy, $S(O_2)C_6$-C_{10} aryl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_{10} cycloalkyl, and 3- to 10-membered heterocycloalkyl are optionally substituted with one or more substituents each independently selected from hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxy, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, N(C_1-C_6

alkyl)$_2$, CONR^{8}R^9, SF$_5$, SC$_1$-C$_6$ alkyl, S(O$_2$)C$_1$-C$_6$ alkyl, C$_3$-C$_{10}$ cycloalkyl and 3- to 10-membered heterocycloalkyl, and C$_2$-C$_6$ alkenyl,

wherein R^6 and R^7 are each optionally substituted with one or more substituents independently selected from hydroxy, halo, CN, oxo, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ alkoxy, NR^{8}R^9, =NR^{10}, COOC$_1$-C$_6$ alkyl, CONR^{8}R^9, 3- to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, 5- to 10-membered heteroaryl, OCOC$_1$-C$_6$ alkyl, OCOC$_6$-C$_{10}$ aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C$_6$-C$_{10}$ aryloxy, and S(O$_2$)C$_1$-C$_6$ alkyl; and wherein the C$_1$-C$_6$ alkyl or C$_1$-C$_6$ alkoxy that R^6 or R^7 is substituted with is optionally substituted with one or more hydroxyl, C$_6$-C$_{10}$ aryl or NR^{8}R^9, or wherein R^6 or R^7 is optionally fused to a five- to –seven-membered carbocyclic ring or heterocyclic ring containing one or two heteroatoms independently selected from oxygen, sulfur and nitrogen;

wherein the 3- to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, 5- to 10-membered heteroaryl, NHCOC$_6$-C$_{10}$ aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C$_1$-C$_6$ alkyl, and OC$_1$-C$_6$ alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C$_4$-C$_8$ carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, NH, NR^{13}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ haloalkyl, C$_1$-C$_6$ alkoxy, NR^{8}R^9, CH$_2$NR^{8}R^9, =NR^{10}, COOH, COOC$_1$-C$_6$ alkyl, C$_6$-C$_{10}$ aryl, and CONR^{8}R^9;

R^{10} is C$_1$-C$_6$ alkyl;

each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_3$-C$_7$ cycloalkyl, C$_1$-C$_6$ haloalkyl, (C=NR^{13})NR^{11}R^{12}, S(O$_2$)C$_1$-C$_6$ alkyl, S(O$_2$)NR^{11}R^{12}, COR^{13}, CO$_2$R^{13} and CONR^{11}R^{12}; wherein the C$_1$-C$_6$ alkyl is optionally substituted with one or more hydroxy, halo, C$_1$-C$_6$ alkoxy, C$_6$-C$_{10}$ aryl, 5- to 10-membered heteroaryl, C$_3$-C$_7$ cycloalkyl, 3- to 7-membered heterocycloalkyl, or NR^{11}R^{12};

or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 10-membered monocyclic or bicyclic ring optionally containing one or more heteroatoms in addition to the nitrogen they are attached to, wherein the ring is optionally substituted with one or more

substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, oxo, N(C_1-C_6 alkyl)$_2$, NH_2, NH(C_1-C_6 alkyl), and hydroxy;

R^{13} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, or –$(Z^1$-$Z^2)_{a1}$-Z^3;

each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, and –$(Z^1$-$Z^2)_{a1}$-Z^3;

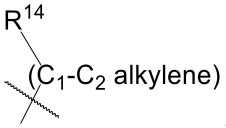
a1 is an integer selected from 0-10 (e.g., 0-5);

each Z^1 is independently C_1-C_6 alkylene optionally substituted with one or more substituents independently selected from oxo, halo, and hydroxy;

each Z^2 is independently a bond, NH, N(C_1-C_6 alkyl), -O-, -S-, or 5-10 membered heteroarylene;

Z^3 is independently C_6-C_{10} aryl, C_2-C_6 alkyenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocycloalkyl, each of which is optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, C_{1-6} haloalkyl, C_1-C_6 alkoxy, oxo, N(C_1-C_6 alkyl)$_2$, NH_2, NH(C_1-C_6 alkyl), and hydroxy;

R^3 is selected from hydrogen, cyano, hydroxy, CO_2C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkyl,

and 

, wherein the C_1-C_2 alkylene group is optionally substituted with oxo;

R^{14} is hydrogen, C_1-C_6 alkyl, 5- to 10-membered monocyclic or bicyclic heteroaryl or C_6-C_{10} monocyclic or bicyclic aryl, wherein each C_1-C_6 alkyl, aryl or heteroaryl is optionally independently substituted with 1 or 2 R^6;

R^{15} is –$(Z^4$-$Z^5)_{a2}$-Z^6;

a2 is an integer selected from 1-10 (e.g., 1-5 (e.g., 2-5));

each Z^4 is independently selected from –O-, -S-, -NH-, and –N(C_1-C_3 alkyl)-;

provided that the Z^4 group directly attached to R^1 or R^2 is –O- or –S-;

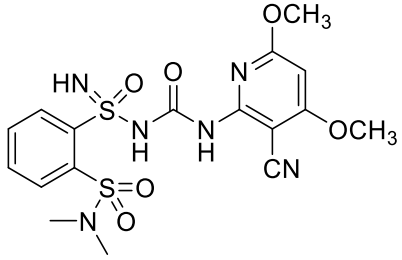
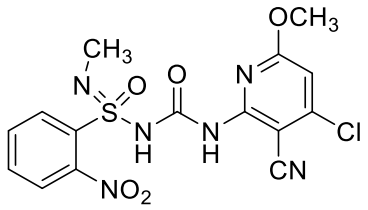
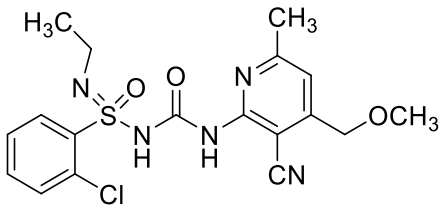
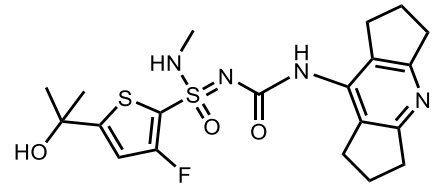
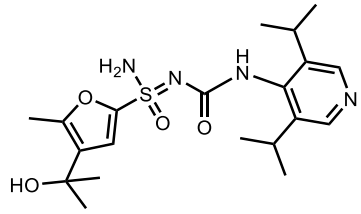
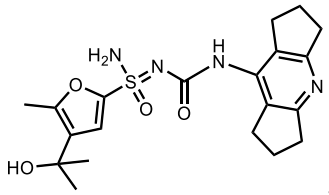
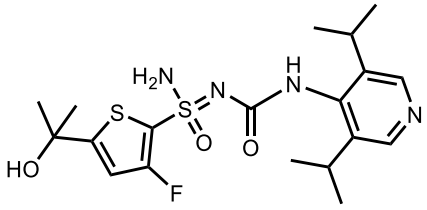
each Z^5 is independently C_1-C_6 alkylene optionally substituted with one or more substituents independently selected from oxo, halo, and hydroxy; and

Z^6 is OH, OC_1-C_6 alkyl, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, NHC(O)(C_1-C_6 alkyl), NHC(O)(C_1-C_6 alkoxy), or an optionally substituted group selected from the group consisting of:

C_6-C_{10} aryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocycloalkyl, each of which is optionally substituted with

one or more substituents independently selected from halo, C_1-C_6 alkyl, C_{1-6} haloalkyl, C_1-C_6 alkoxy, oxo, N(C_1-C_6 alkyl)$_2$, NH_2, NH(C_1-C_6 alkyl), and hydroxy;

with the proviso that the compound of Formula AA is not a compound selected from the group consisting of:


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, and

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or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein

A is a 5-membered heteroaryl, or

A is a 6- to 10-membered heteroaryl, or

A is a C_6-C_{10} aryl.

3. The compound of claim 1, wherein

A is a 5-membered heteroaryl comprising 1 heteroatom or heteroatomic group selected from N, NH, and NR^1, or

A is a 5-membered heteroaryl comprising 1 heteroatom selected from O and S, wherein the heteroatom is not bonded to the position of the heteroaryl that is bonded to the S(O)(NHR^3)=N moiety.

4. The compound of claim 1 or 2, wherein

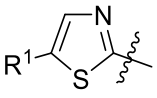
   A is thiophenyl, or

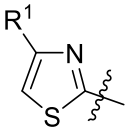
   A is thiazolyl, or

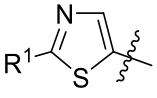
   A is pyrazolyl, or

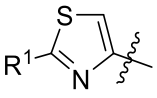
   A is phenyl.

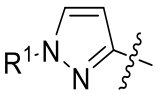
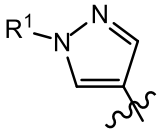
5. The compound of any one of claims 1-4, wherein m=1 and n=0, and

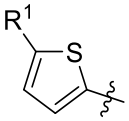
   wherein the optionally substituted ring A is , or

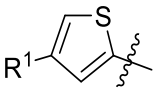
   wherein the optionally substituted ring A is , or

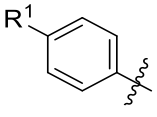
   wherein the optionally substituted ring A is , or

   wherein the optionally substituted ring A is , or

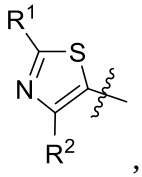
   wherein the optionally substituted ring A is  or , or

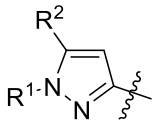
   wherein the optionally substituted ring A is , or

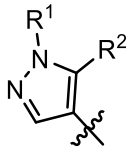
   wherein the optionally substituted ring A is , or

   wherein the optionally substituted ring A is .

6. The compound of any one of claims 1-4, wherein m=1 and n=1, and

wherein the optionally substituted ring A is , or

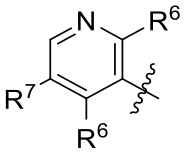
wherein the optionally substituted ring A is , or

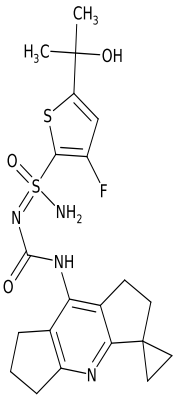
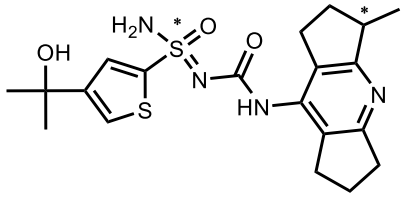
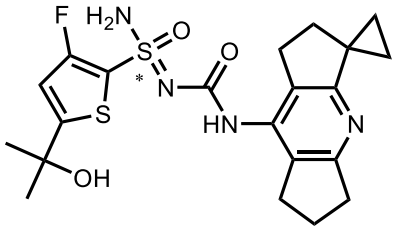
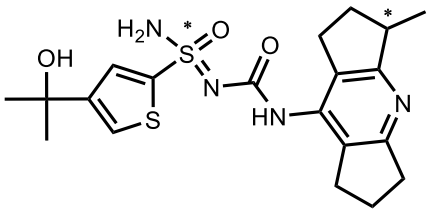
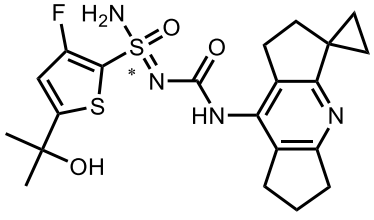
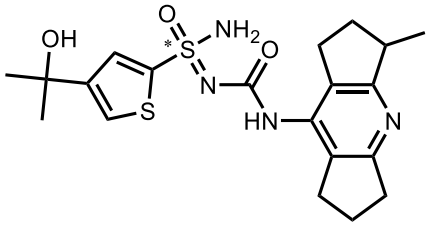
wherein the optionally substituted ring A is .

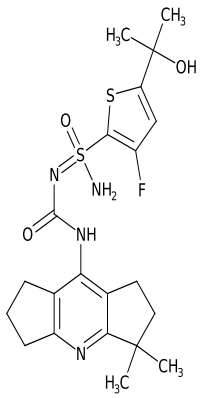
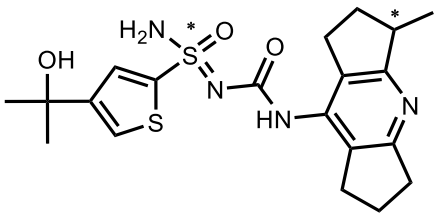
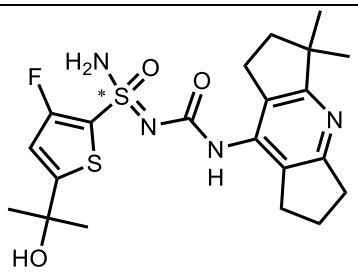
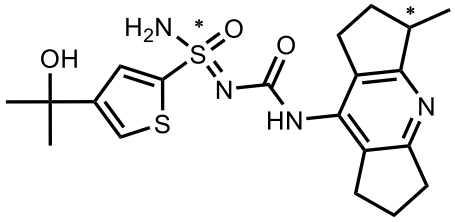
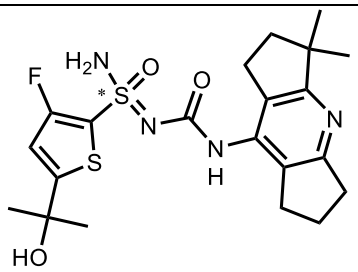
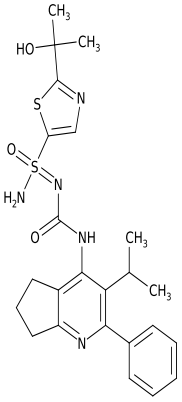
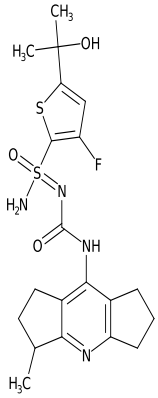
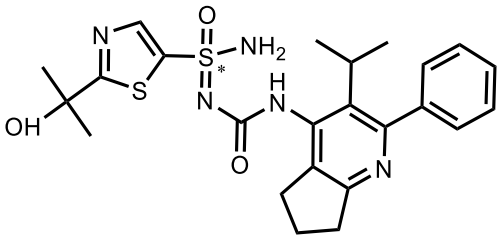
7. The compound of any one of claims 1-6, wherein R^1, when present, is independently selected from the group consisting of C_1-C_6 alkyl optionally substituted with one or more hydroxy, C_1-C_6 alkyl optionally substituted with one or more halo, oxo, C_1-C_6 alkoxy, or NR^8R^9; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, halo, oxo, C_1-C_6 alkoxy, C_1-C_6 alkyl, or NR^8R^9 wherein the C_1-C_6 alkoxy or C_1-C_6 alkyl is further optionally substituted with one to three hydroxy, halo, NR^8R^9, or oxo; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, halo, oxo, C_1-C_6 alkyl, or NR^8R^9 wherein the C_1-C_6 alkoxy or C_1-C_6 alkyl is further optionally substituted with one to three hydroxy, halo, NR^8R^9, or oxo; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; CO-C_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; $S(O_2)NR^{11}R^{12}$; $S(O)C_1$-C_6 alkyl; and $S(O_2)C_1$-C_6 alkyl.

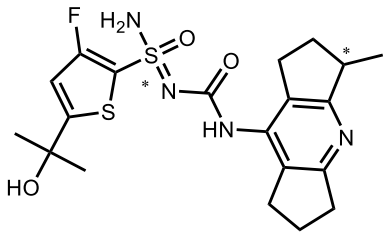
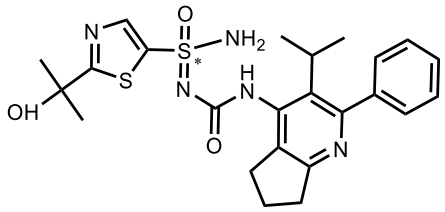
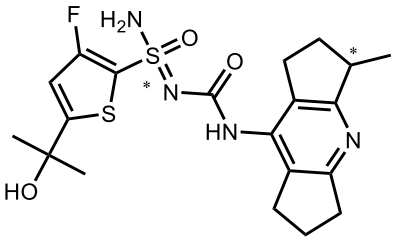
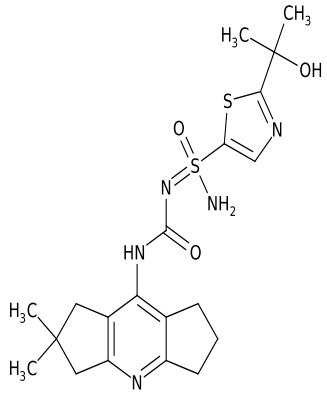
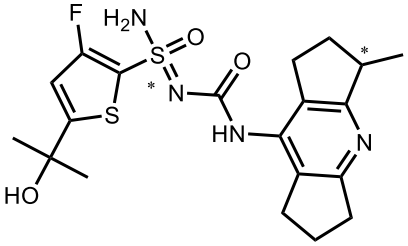
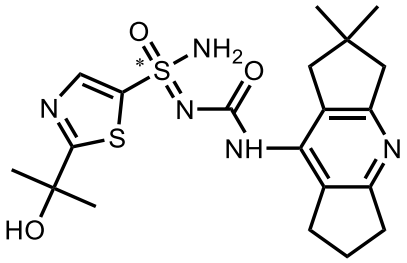
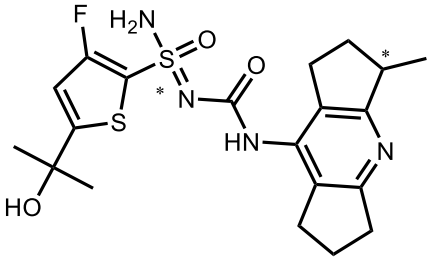
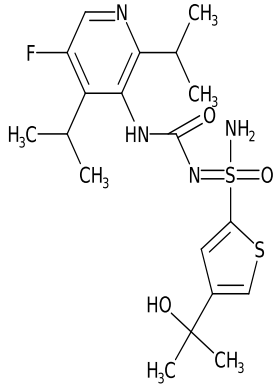
8. The compound of any one of claims 1-7, wherein R^1 is selected from the group consisting of 1-hydroxy-2-methylpropan-2-yl; 1,2-dihydroxy-2-propyl; methyl; ethyl; difluoromethyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl;

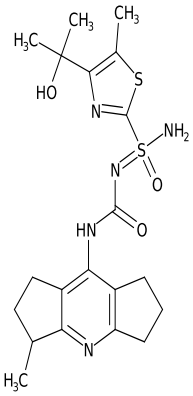
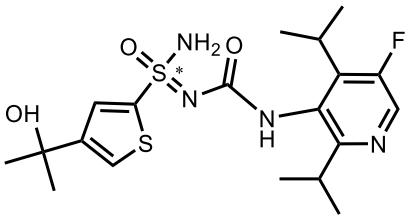
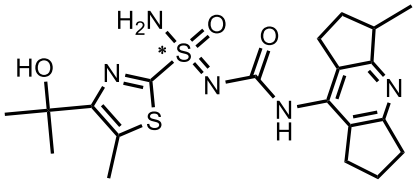
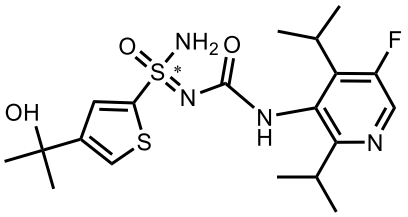
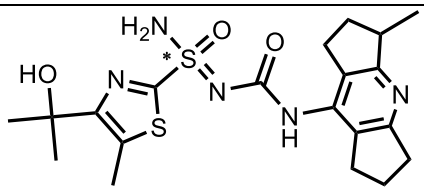
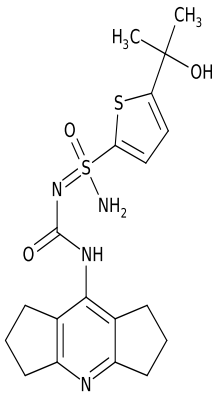
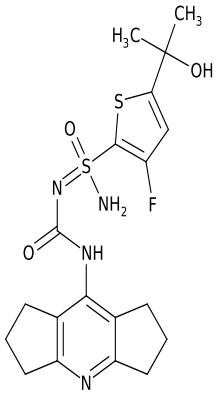
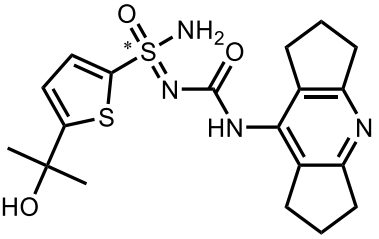
(methylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; $S(O_2)CH_3$; and $S(O_2)NR^{11}R^{12}$.

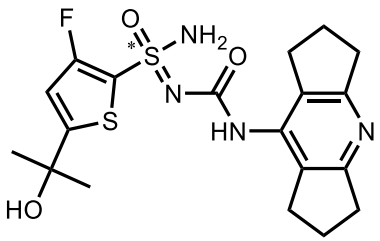
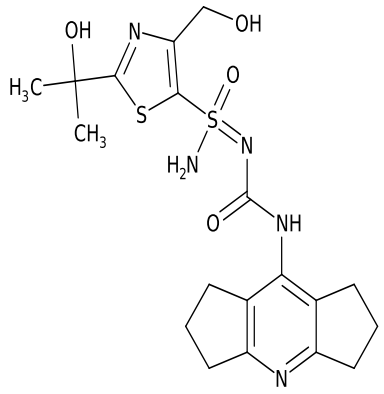
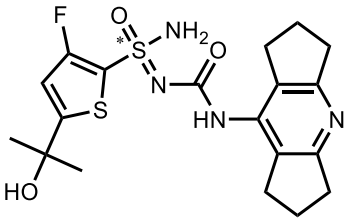
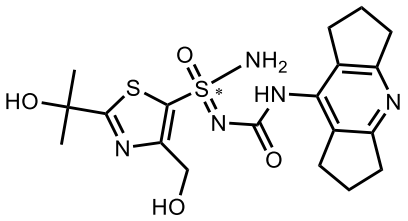
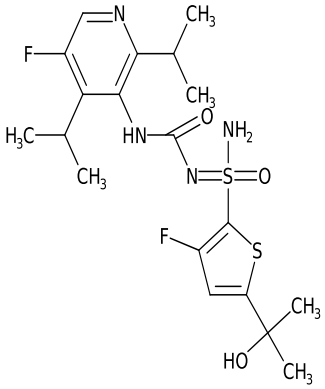
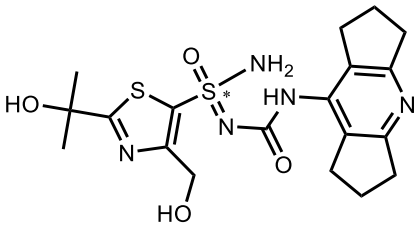
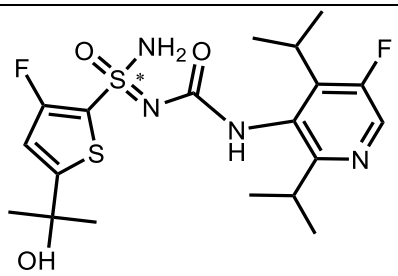
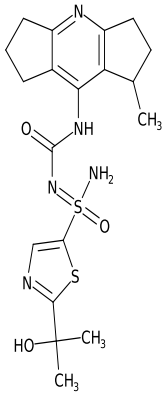
9. The compound of any one of claims 1-8, wherein B is pyridyl, or an N-oxide thereof.
10. The compound of any one of claims 1-9, wherein the B is 3-pyridyl.
11. The compound of any one of claims 1-10, wherein o=2 and p=1.
12. The compound of any one of claims 1-11, wherein the substituted ring B is .
13. A compound selected from the group consisting of the compounds below:

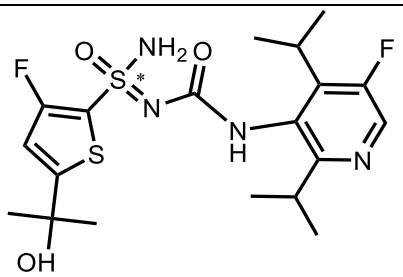
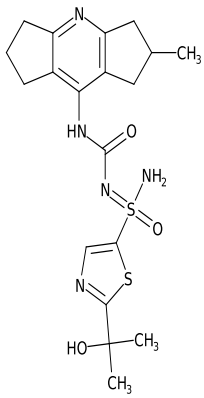
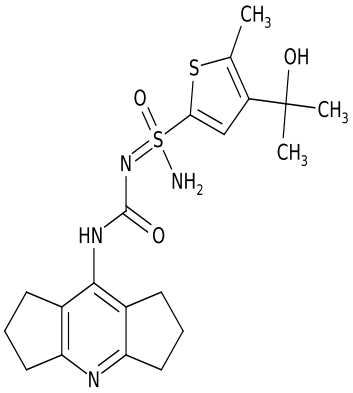
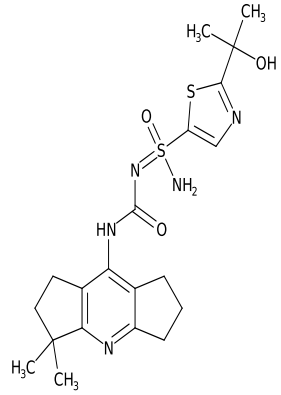
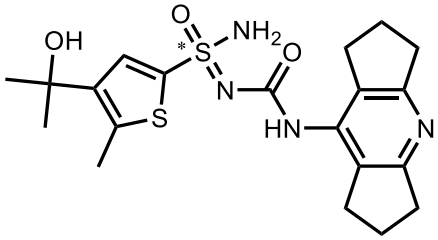
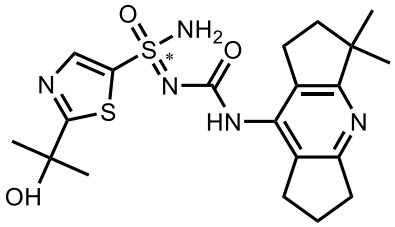
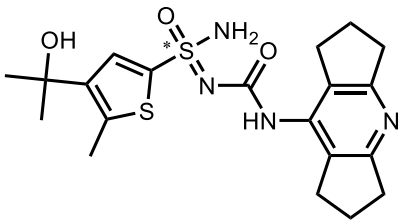
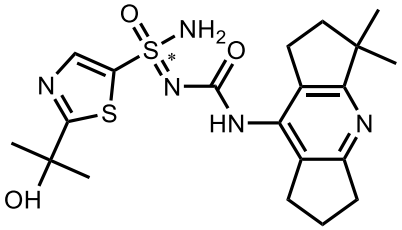
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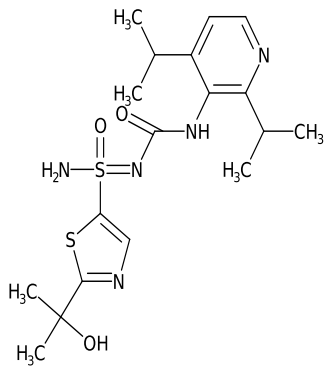
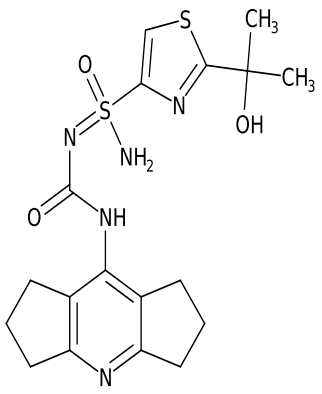
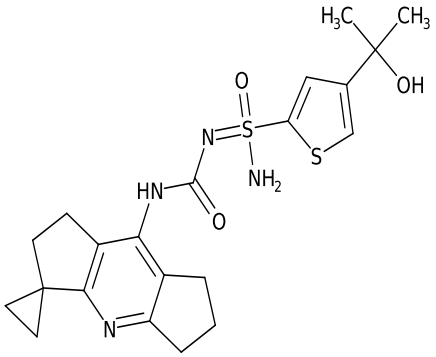
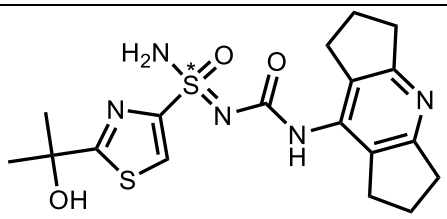
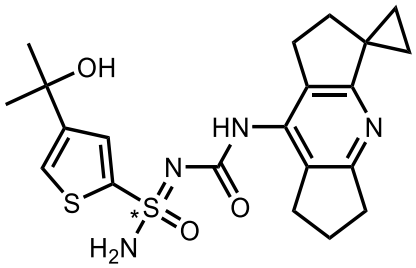
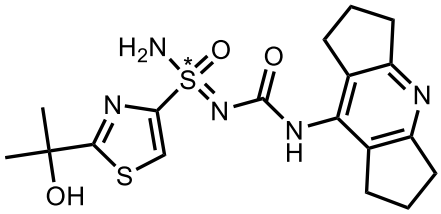
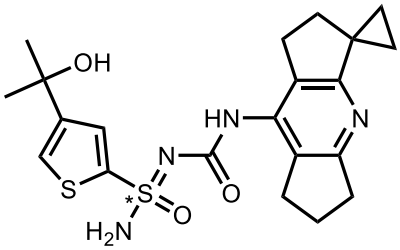
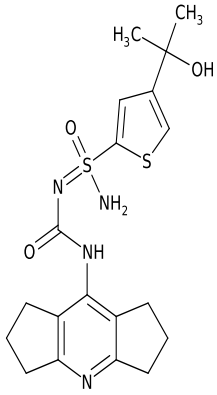
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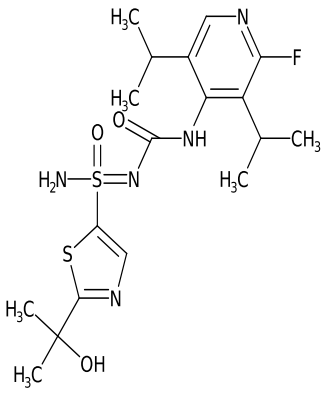
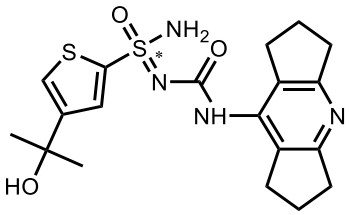
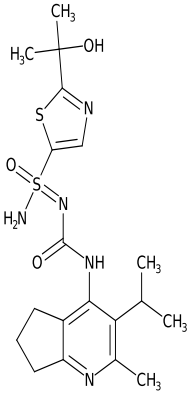
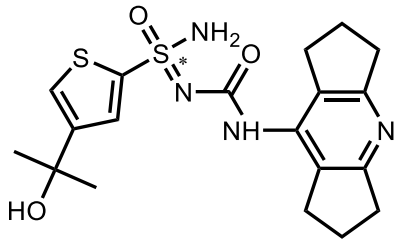
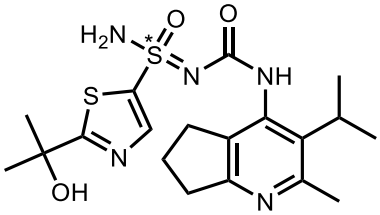
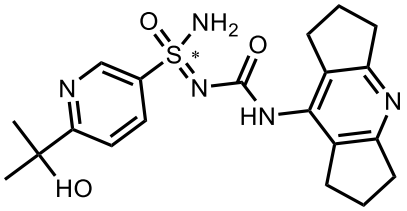
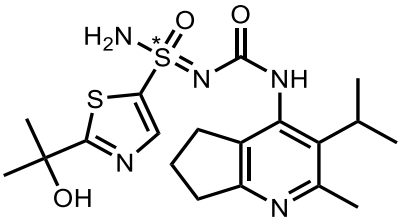
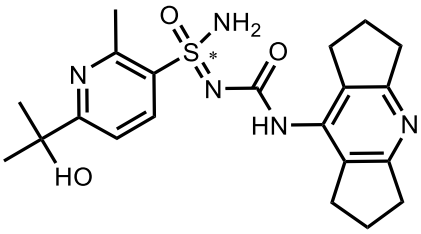
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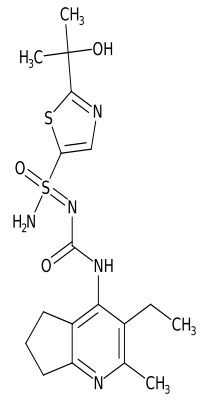
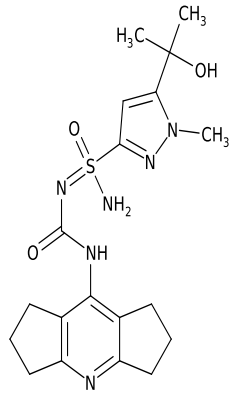
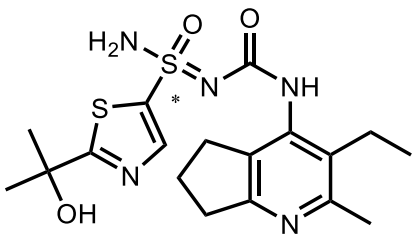
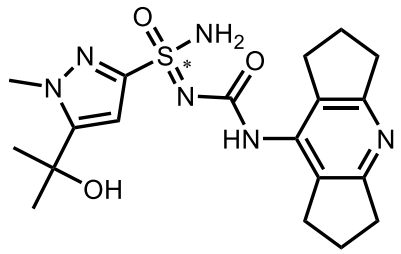
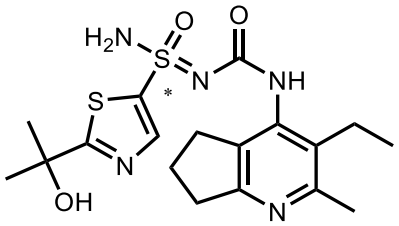
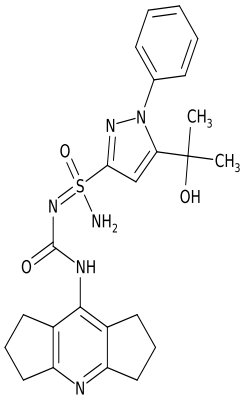
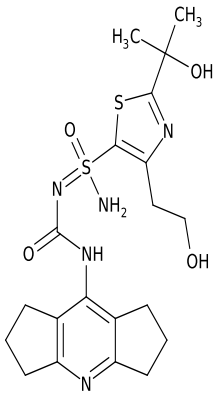
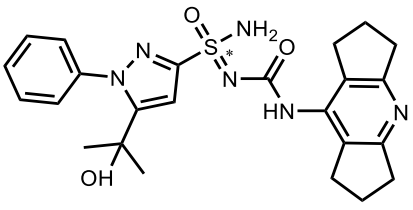
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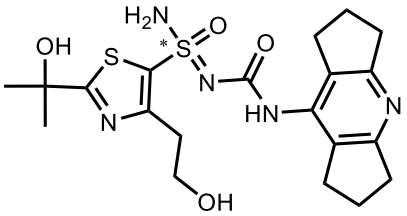
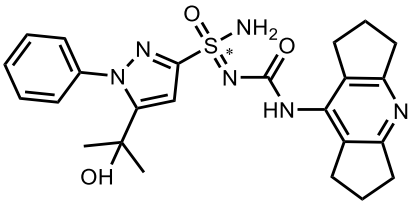
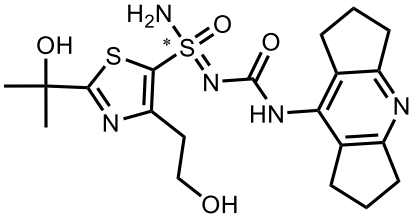
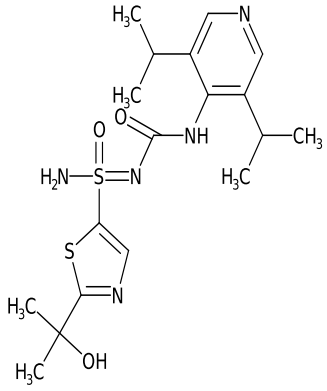
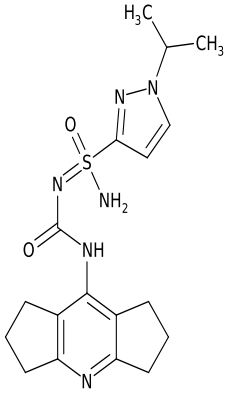
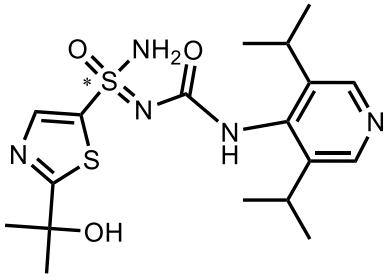
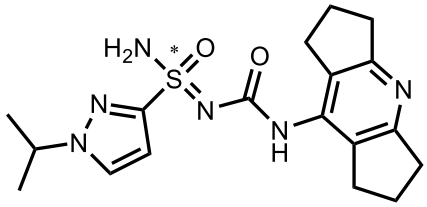
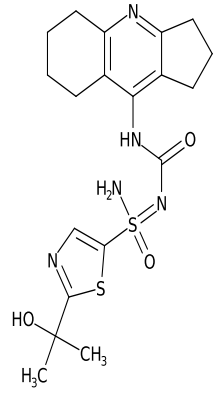
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106a		**151**	

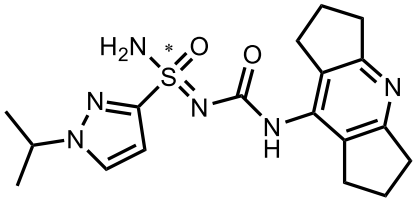
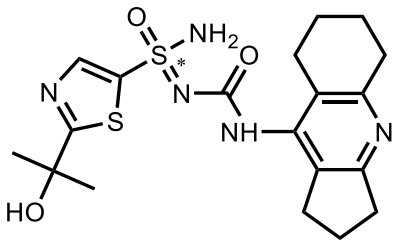
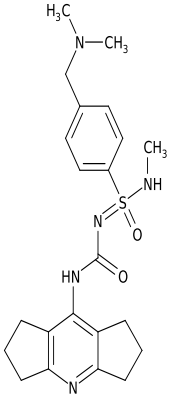
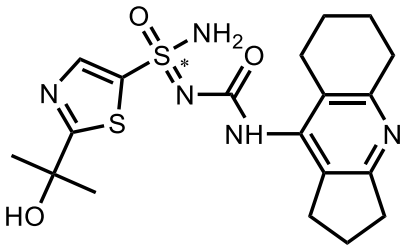
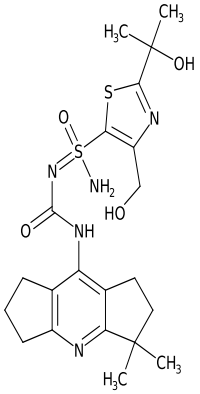
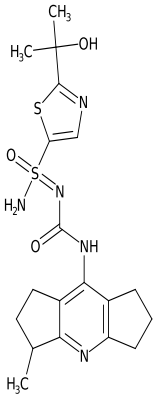
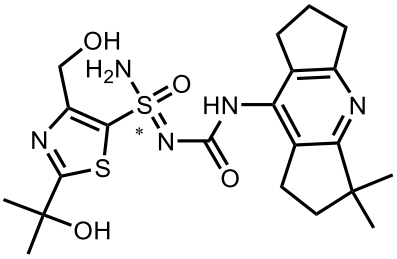
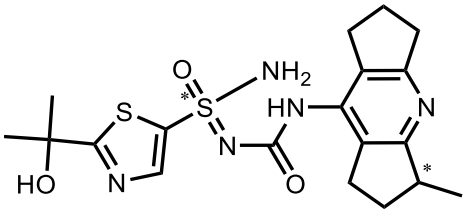
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107b		**153b**	

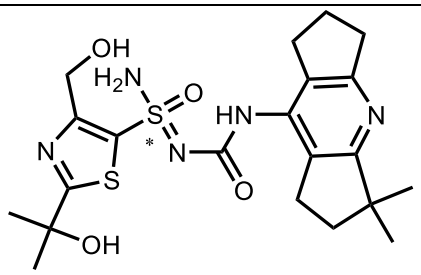
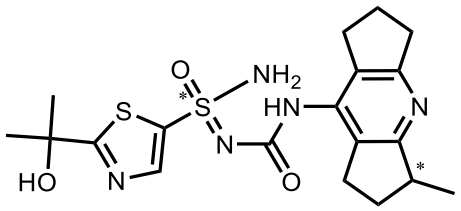
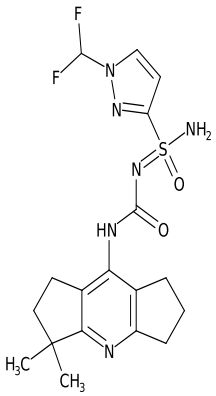
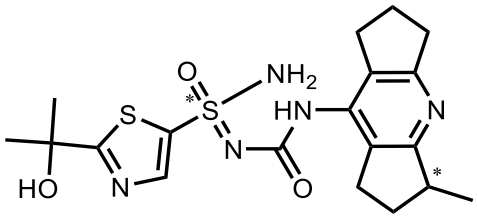
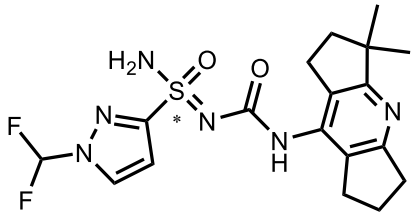
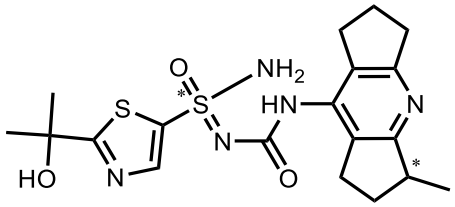
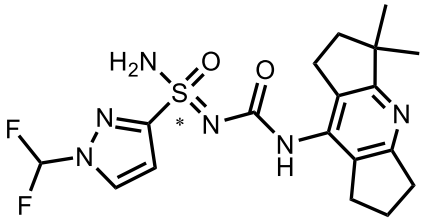
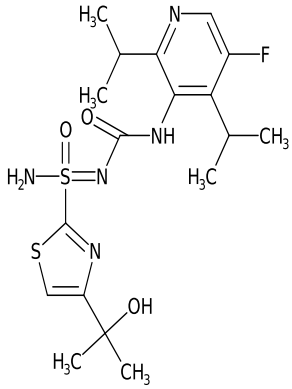
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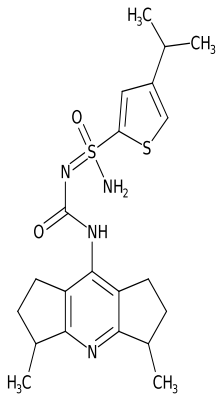
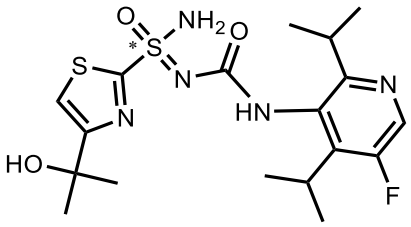
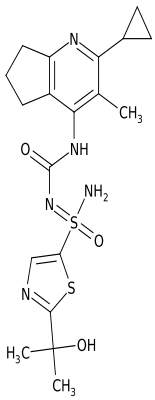
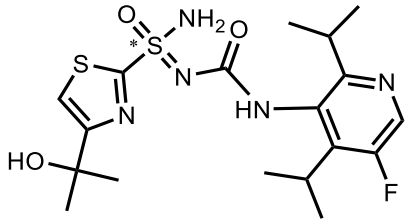
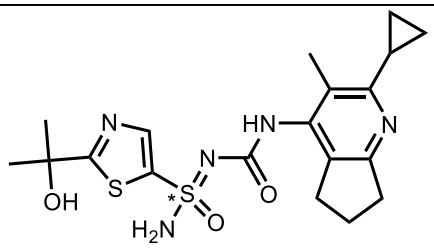
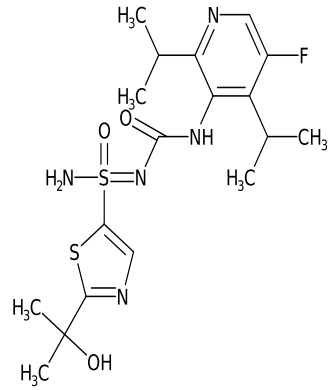
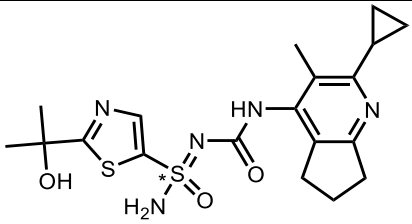
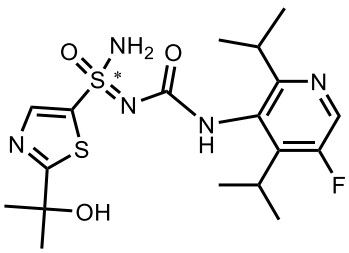
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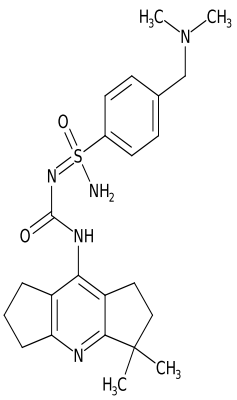
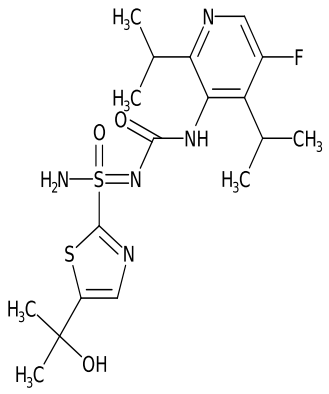
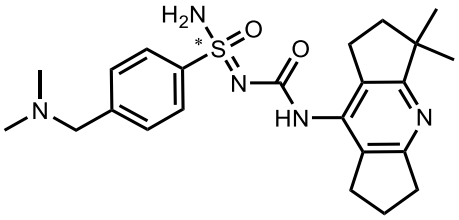
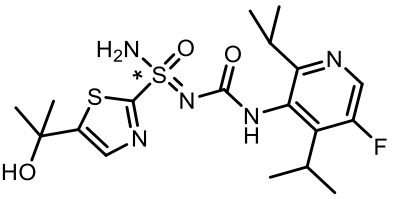
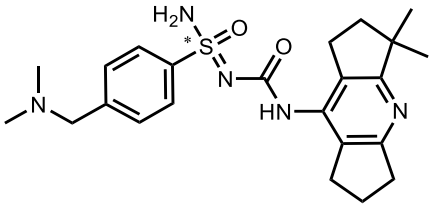
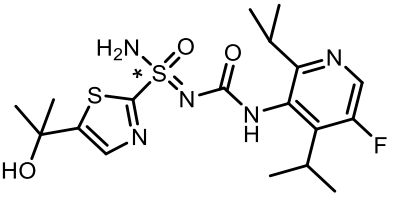
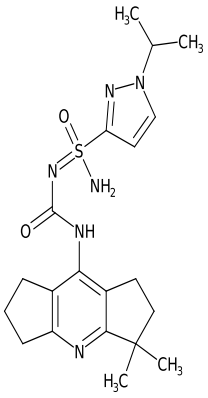
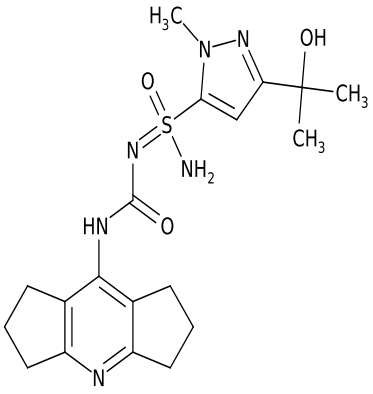
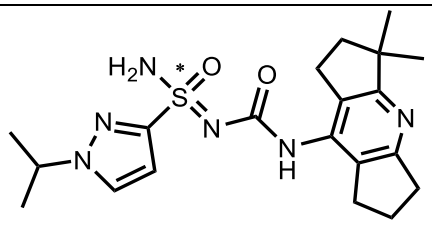
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118		**159a**	

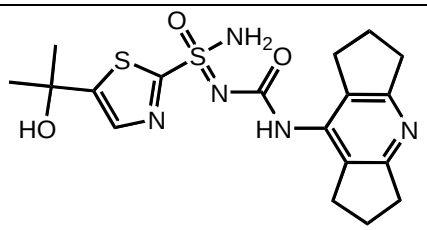
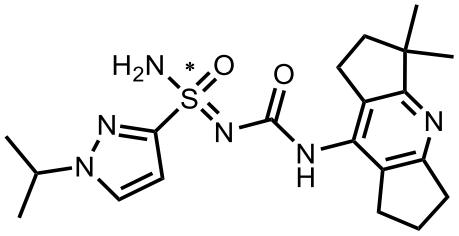
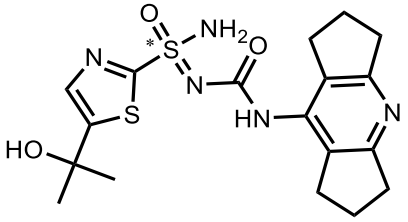
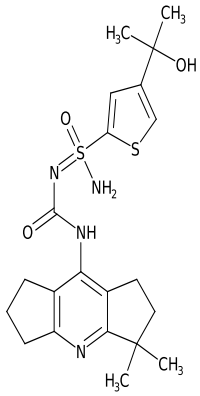
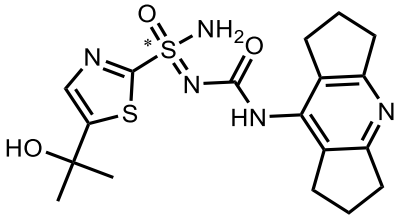
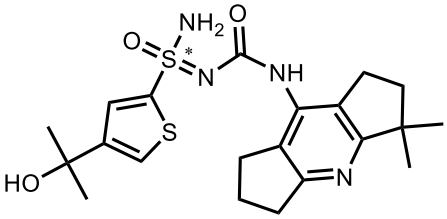
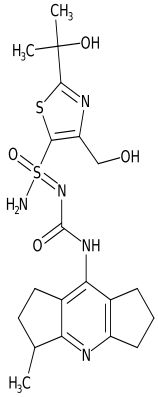
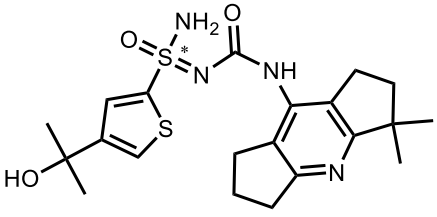
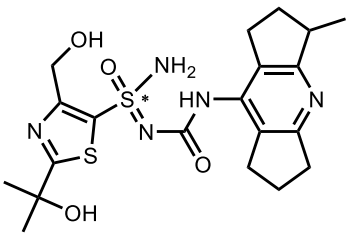
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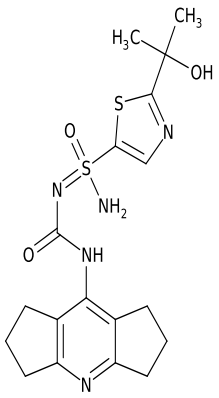
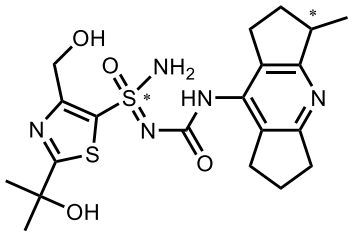
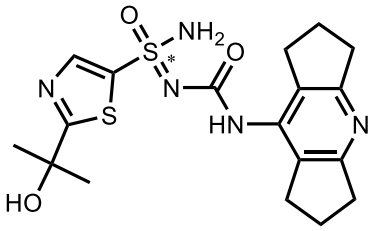
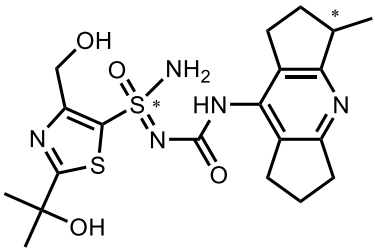
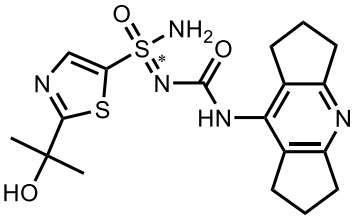
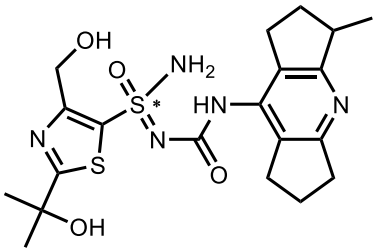
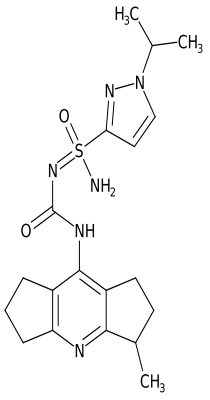
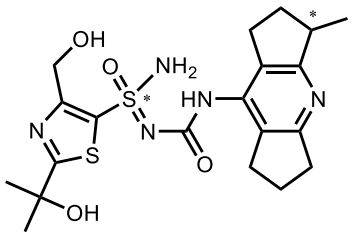
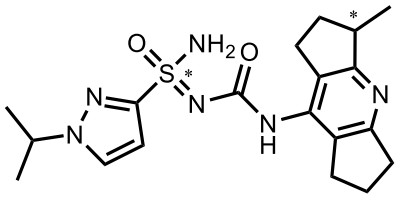
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121a		**162aa**	

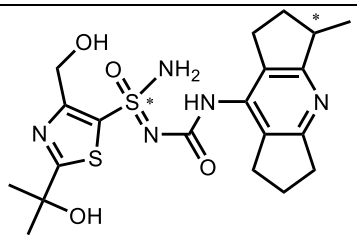
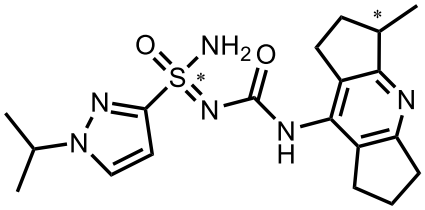
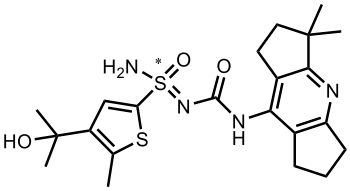
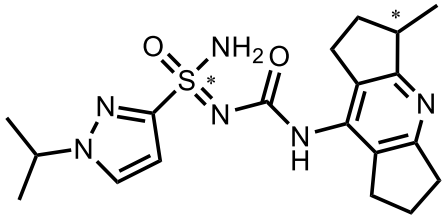
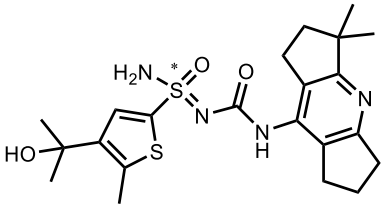
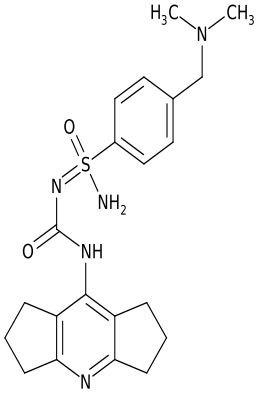
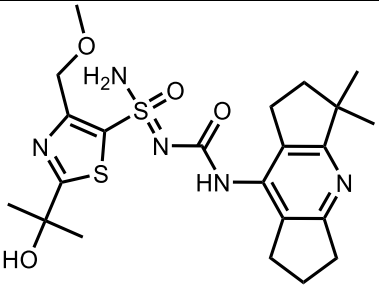
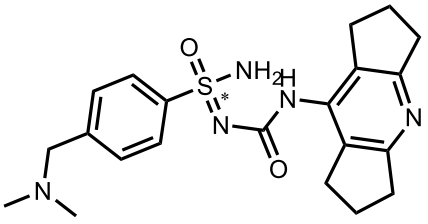
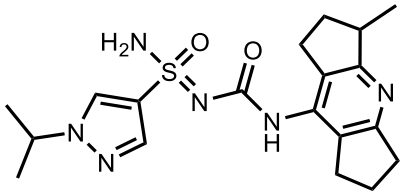
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122		**162ba**	
122a		**162bb**	 (R,R)
122b		**163**	

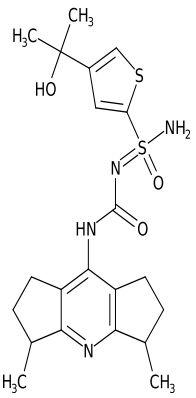
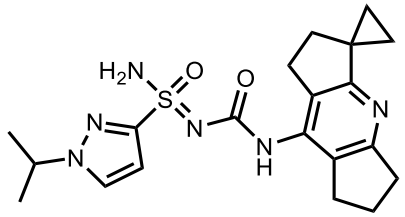
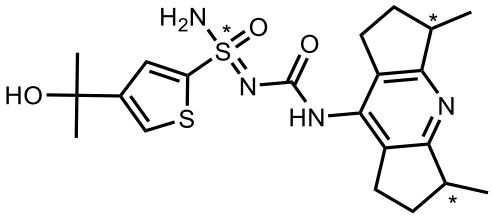
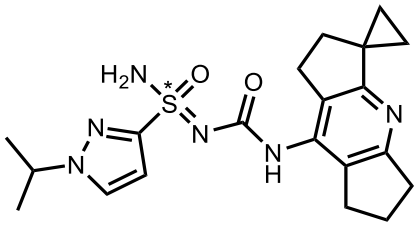
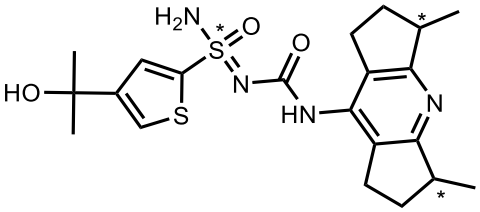
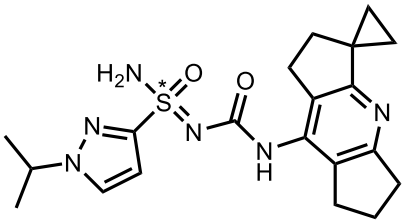
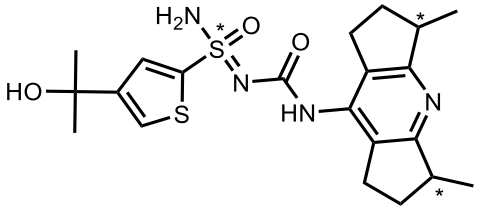
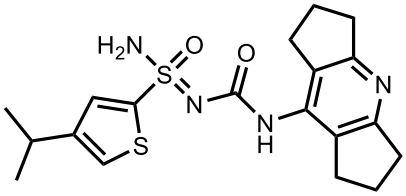
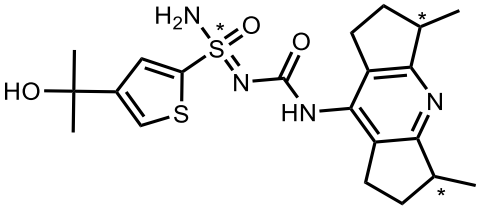
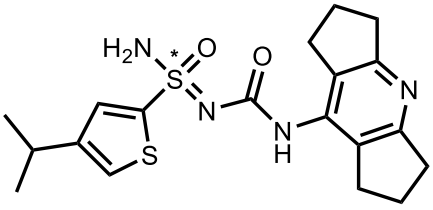
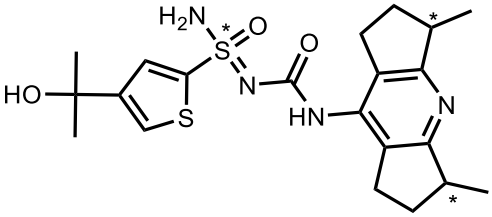
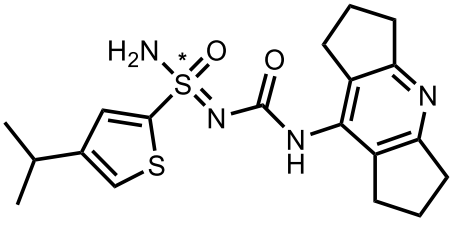
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124		**163b**	
124a		**164**	
124b		**164a**	

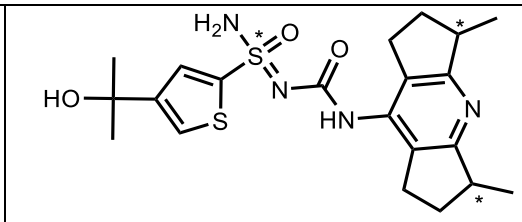
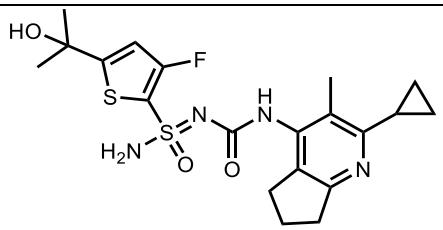
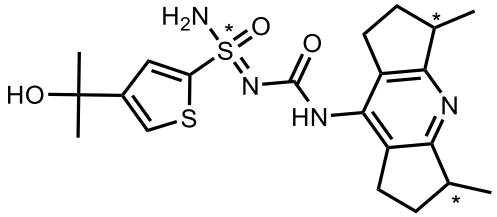
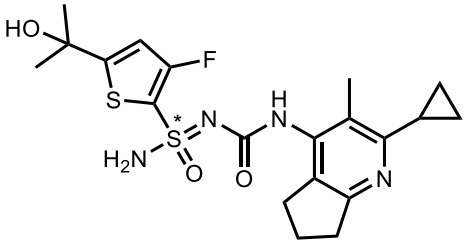
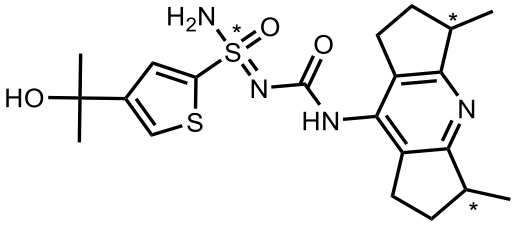
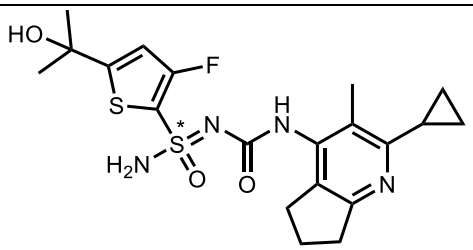
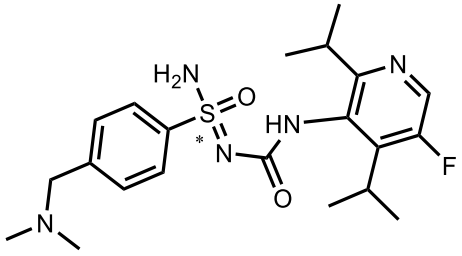
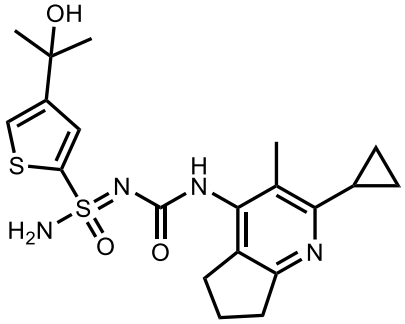
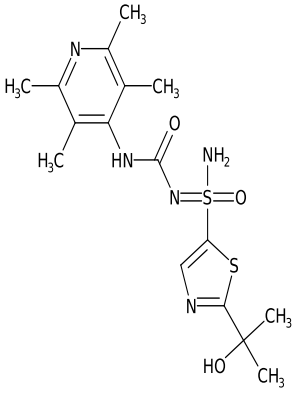
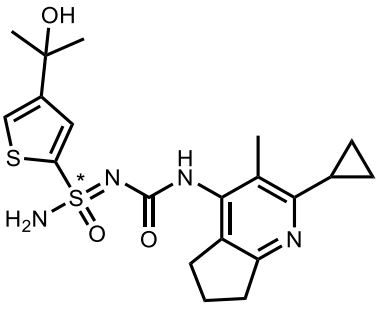
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125b		**165b**	
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126a		**167**	

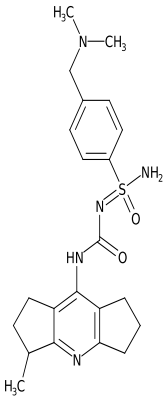
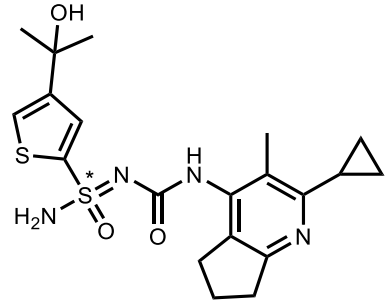
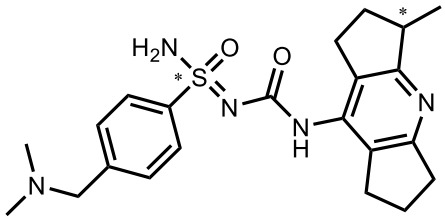
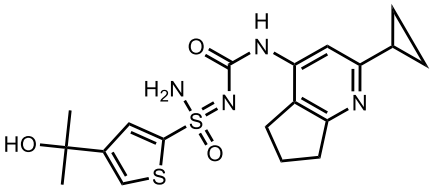
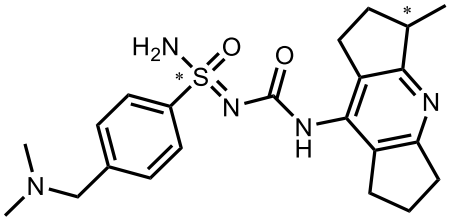
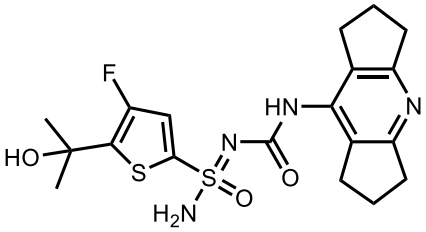
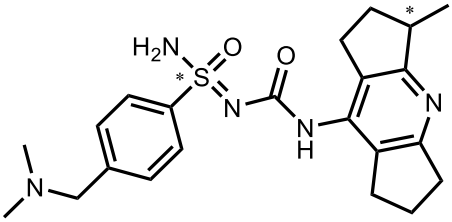
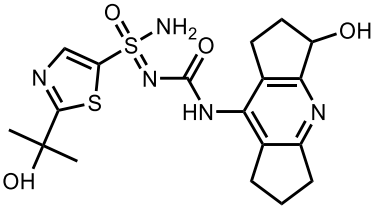
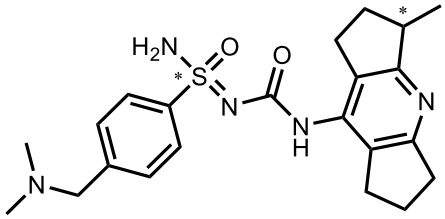
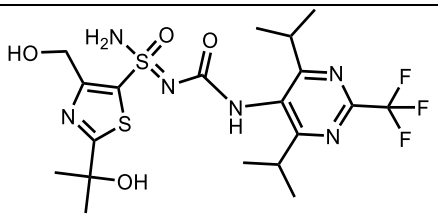
			
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127		**167b**	
127a		**168**	
127b		**168a**	

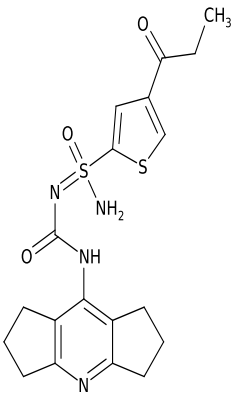
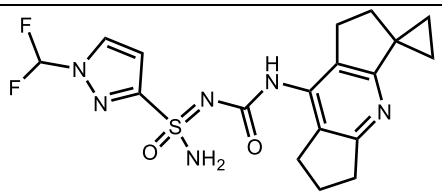
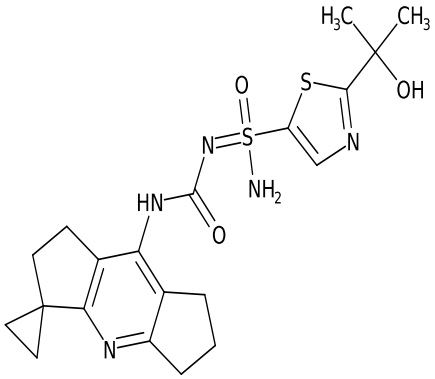
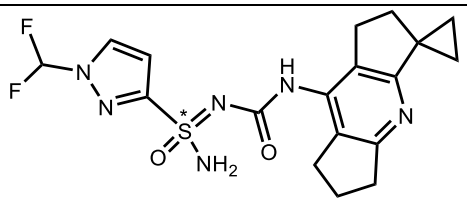
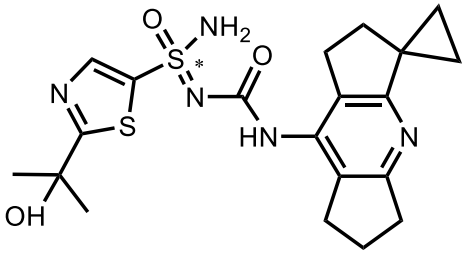
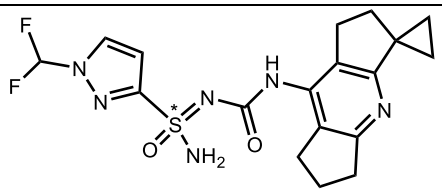
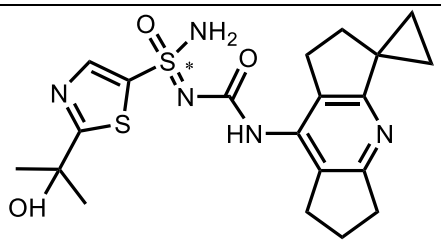
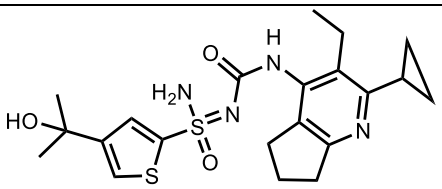
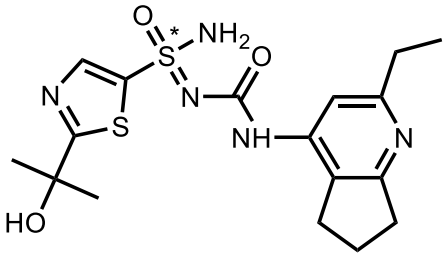
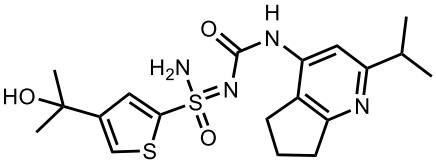
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128b		**168b**	
129		**168ba**	
129aa		**168bb**	

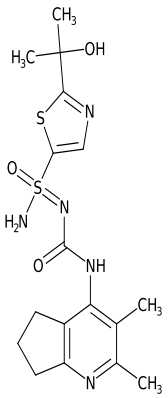
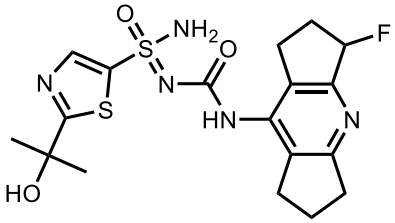
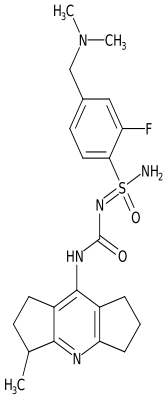
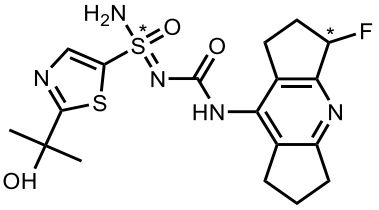
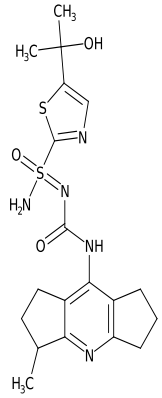
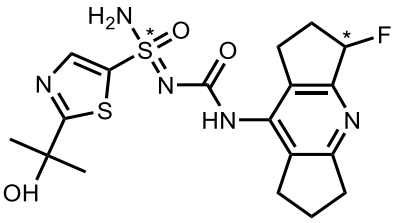
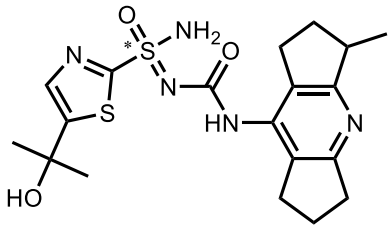
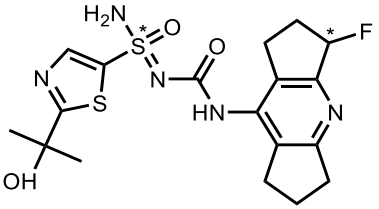
			
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129bb		**169b**	
130		**170**	
130b		**171**	

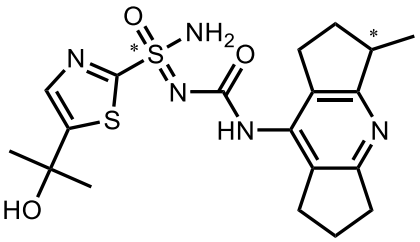
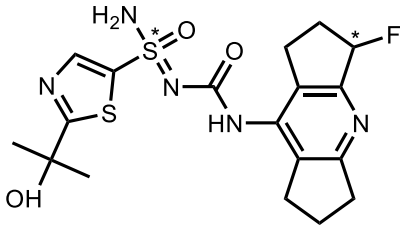
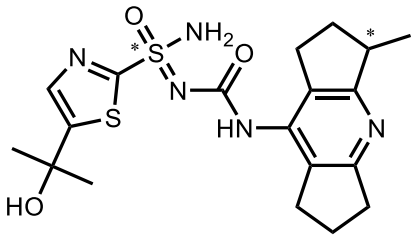
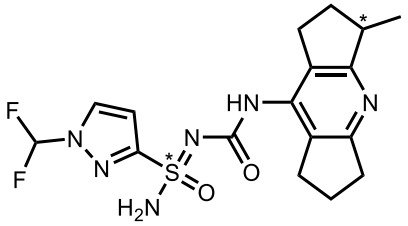
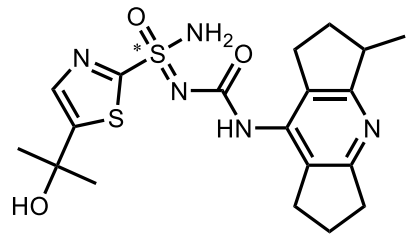
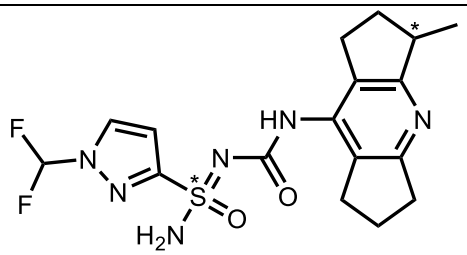
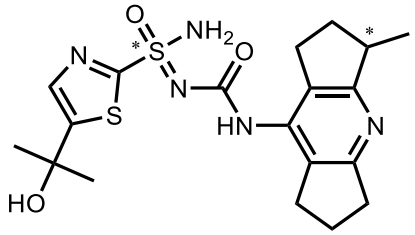
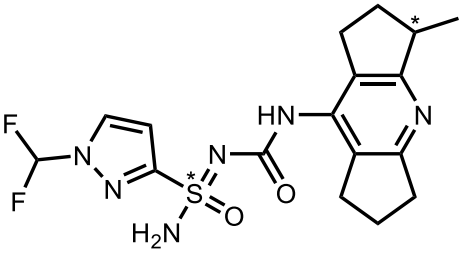
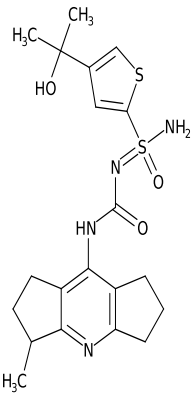
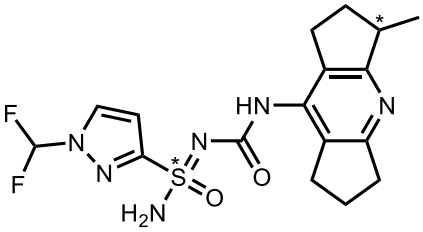
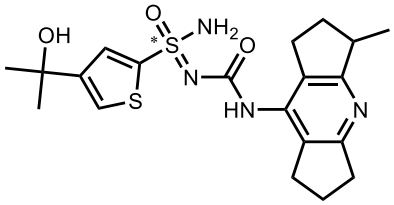
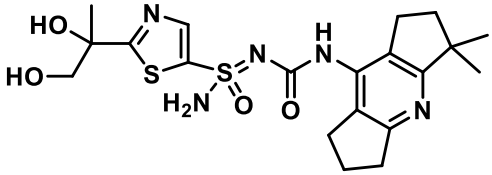
131		**172**	
131a		**172a**	
131aab		**172b**	
131b		**173**	
131c		**173a**	
131d		**173b**	

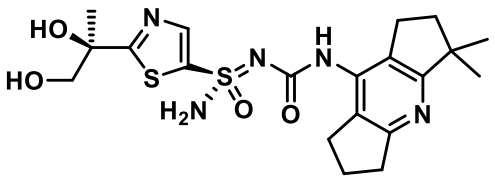
131e		**174**	
131f		**174a**	
131g		**174b**	
132b		**175**	
133		**175a**	

134		**175b**	
134aa		**176**	
134ab		**177**	
134ba		**178**	
134bb		**179**	

135		**180**	
136		**180a**	
136a		**180b**	
136b		**181**	
137a		**182**	

138		**183**	
139		**183a**	
140		**183b**	
140a		**183c**	

140aa		**183d**	
140ab		**184a**	
140b		**184b**	
140ba		**184c**	
141		**184d**	
141a		**201**	

		201a	

and pharmaceutically acceptable salts thereof.

14. The compound of any one of claims 1-13, wherein the sulfur in the moiety $S(=O)(NHR^3)=N-$ has (S) stereochemistry.
15. The compound of any one of claims 1-13, wherein the sulfur in the moiety $S(=O)(NHR^3)=N-$ has (R) stereochemistry.
16. A pharmaceutical composition comprising a compound or salt as claimed in any one of claims 1-15 and one or more pharmaceutically acceptable excipients.
17. Use of the compound of any one of claims 1-16 in the manufacture of a medicament for the treatment of a subject having a disease in which NLRP3 signaling contributes to the pathology and/or symptoms and/or progression of the disease.
18. The use according to claim 17, wherein the disease, disorder or condition that is any one of:

    a metabolic disorder, optionally wherein the metabolic disorder is Type 2 diabetes, atherosclerosis, obesity or gout;

    a disease of the central nervous system, optionally wherein the disease of the central nervous system is Alzheimer's disease, multiple sclerosis, Amyotrophic Lateral Sclerosis or Parkinson's disease;

    lung disease, optionally wherein the lung disease is asthma, COPD or pulmonary idiopathic fibrosis;

    liver disease, optionally wherein the liver disease is NASH syndrome, viral hepatitis or cirrhosis;

    pancreatic disease, optionally wherein the pancreatic disease is acute pancreatitis or chronic pancreatitis;

    kidney disease, optionally wherein the kidney disease is acute kidney injury or chronic kidney injury;

intestinal disease, optionally wherein the intestinal disease is Crohn's disease or Ulcerative Colitis;

skin disease, optionally wherein the skin disease is psoriasis;

musculoskeletal disease, optionally wherein the musculoskeletal disease is scleroderma;

a vessel disorder, optionally wherein the vessel disorder is giant cell arteritis;

a disorder of the bones, optionally wherein the disorder of the bones is osteoarthritis, osteoporosis or osteopetrosis disorders;

eye disease, optionally wherein the eye disease is glaucoma or macular degeneration a disease caused by viral infection, optionally wherein the diseases caused by viral infection is HIV or AIDS;

an autoimmune disease, optionally wherein the autoimmune disease is Rheumatoid Arthritis, Systemic Lupus Erythematosus, Autoimmune Thyroiditis cancer or aging, optionally wherein the disorder or condition that is cancer is selected from: myelodysplastic syndromes (MDS); non-small cell lung cancer, such as non-small cell lung cancer in patients carrying mutation or overexpression of NLRP3; acute lymphoblastic leukemia (ALL), such as ALL in patients resistant to glucocorticoids treatment; Langerhan's cell histiocytosis (LCH); multiple myeloma; promyelocytic leukemia; acute myeloid leukemia (AML); chronic myeloid leukemia (CML); gastric cancer; and lung cancer metastasis.

19. The use according to claim 17 or claim 18, wherein a therapeutically effective amount of an anti-TNFα agent is to be administered to the subject; optionally wherein:

the medicament is to be administered to the subject prior to administration of the anti-TNFα agent to the subject; or

wherein the anti-TNFα agent is to be administered to the subject prior to the administration of the medicament to the subject; or

wherein the medicament and the anti-TNFα agent are to be administered to the subject at substantially the same time.

20. The compound of any one of claims 1-16 for use in the treatment of a subject having a disease in which NLRP3 signaling contributes to the pathology and/or symptoms and/or progression of the disease.