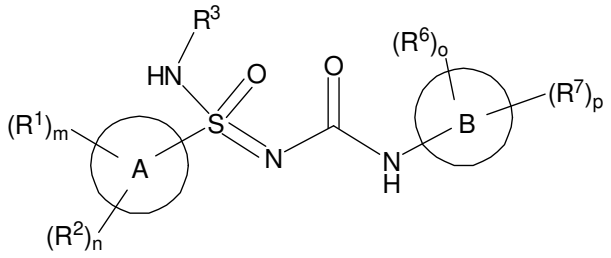
CLAIMS:

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

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

B is a 5-membered heteroaryl, a 7-10 membered monocyclic or bicyclic heteroaryl, or a C_6-C_{10} monocyclic or bicyclic aryl;

wherein

at least one R^6 is *ortho* to the bond connecting the B ring to the NH(CO) 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, COC_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$)_2$, $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, $NHCOOCC_1$-C_6 alkyl, NH-$(C{=}NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is 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, 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), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

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, halo, NR^8R^9, or oxo;

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^1 and R^2 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, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$ wherein the C_1-C_6 alkyl and C_1-C_6 alkoxy are optionally substituted with hydroxy, halo, 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$)_2$, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_{10} cycloalkyl and 3- to 10-membered heterocycloalkyl, and a 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^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), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, 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^8R^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, N, 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 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

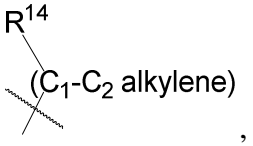
each of R^4 and R^5 is independently selected from hydrogen and C_1-C_6 alkyl;

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, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{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 or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms in addition to the nitrogen they are attached to;

R^{13} is C_1-C_6 alkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

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

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

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,

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein A is a 5- to 6-membered monocyclic heteroaryl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2;

optionally wherein A is any one of:

furanyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2;

thiophenyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2;

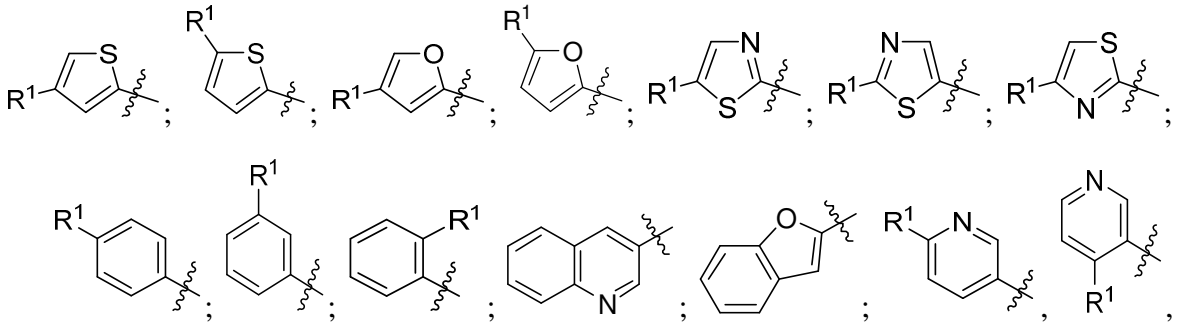
oxazolyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2;

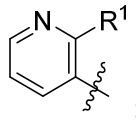
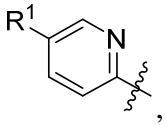
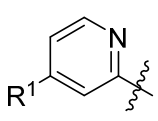
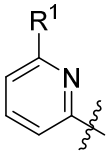
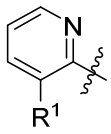
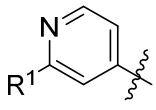
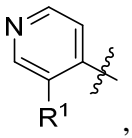
thiazolyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2;

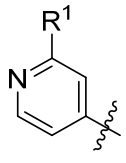
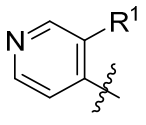
phenyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2.

3. The compound of claim 1 or 2, wherein m=1 and n=0;

optionally wherein A is any one of:

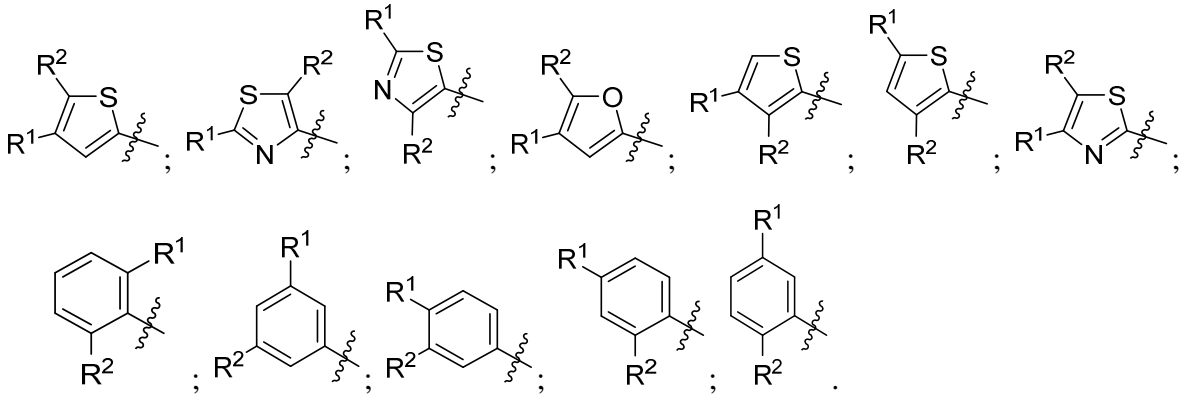


or  ; , , , or  ; , ,

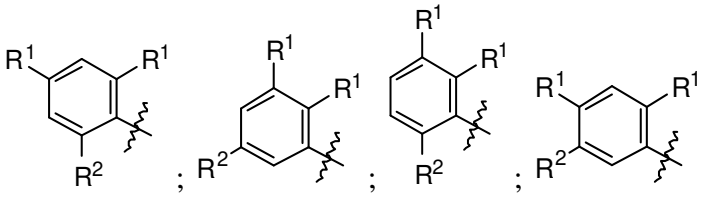
, or .

4. The compound of any one of claims 1 to 3, wherein m=1 and n=1;

optionally wherein A is any one of:



5. The compound of any one of claims 1 to 3, wherein m=2 and n=1;

optionally wherein A is any one of: .

6. The compound of any one of claims 1 to 5, wherein each of R^1 and R^2, when present, is independently selected from the group consisting of C_1-C_6 alkyl optionally substituted with one or more hydroxy, 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 salkoxy 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-

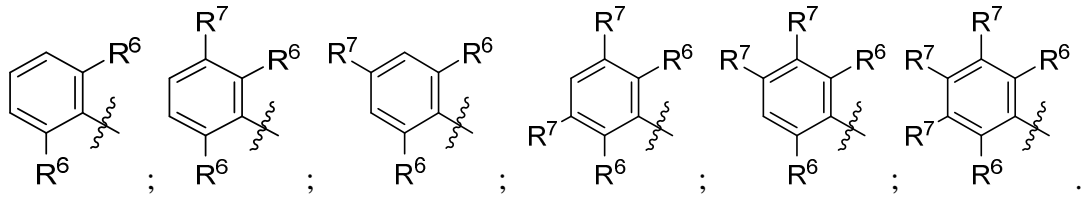
C_6 alkoxy or C_1-C_6 alkyl is further optionally substituted with one to three hydroxy, halo, NR^8R^9, or oxo; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; CO-C_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 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.

7. The compound of any one of claims 1 to 5, wherein R^1 is selected from the group consisting of 1-hydroxy-2-methylpropan-2-yl; methyl; 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; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; $S(O_2)CH_3$, and $S(O_2)NR^{11}R^{12}$.

8. The compound of claim 6 or 7, wherein R^2 is selected from the group consisting of fluoro, chloro, cyano, methyl; methoxy; ethoxy; isopropyl; 1-hydroxy-2-methylpropan-2-yl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; $COCH_3$; COPh; 2-methoxy-2-propyl; (dimethylamino)methyl; $S(O_2)CH_3$, and $S(O_2)NR^{11}R^{12}$.

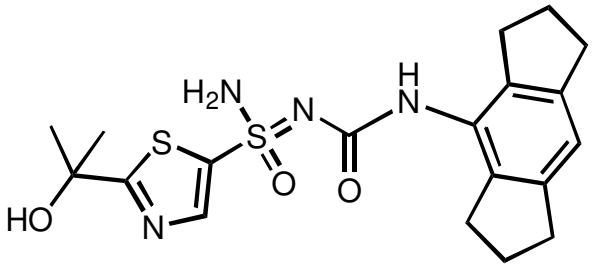
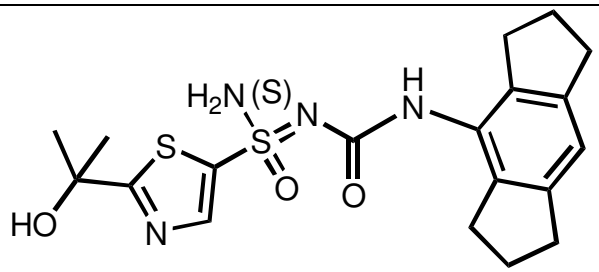
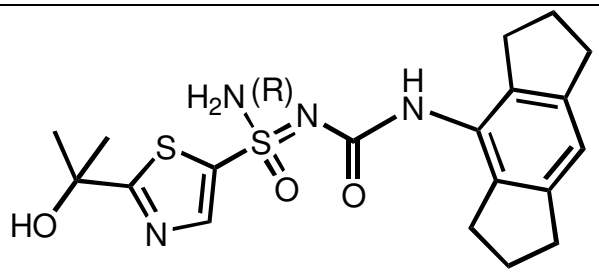
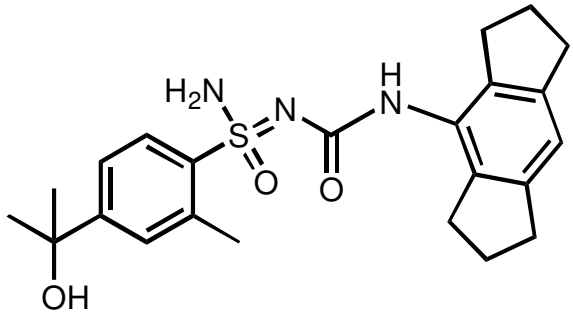
9. The compound of any one of the preceding claims, wherein B is phenyl substituted with 1 or 2 R^6 and optionally substituted with 1, 2, or 3 R^7.

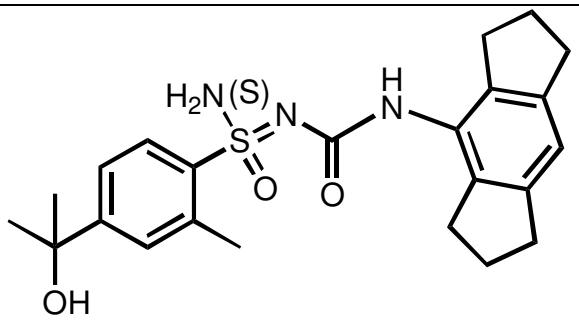
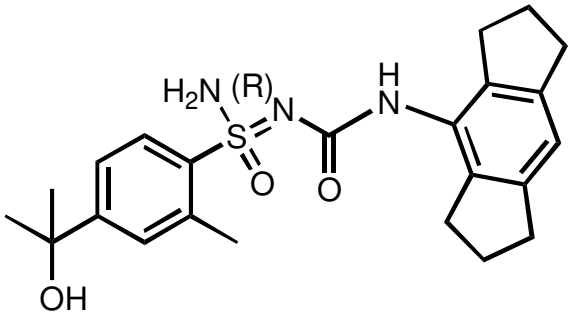
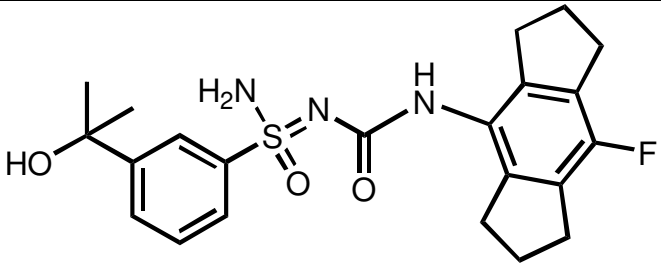
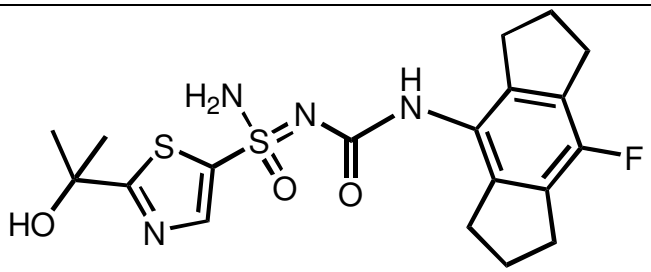
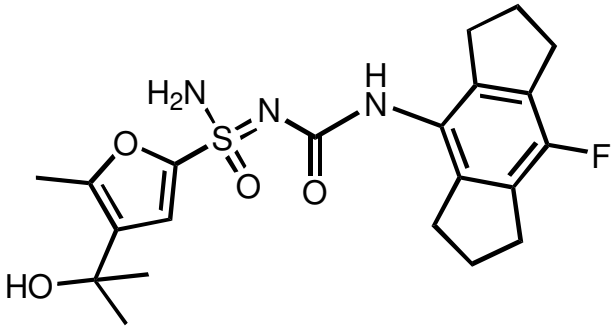
10. The compound of any one of claim 9, wherein B is any one of:

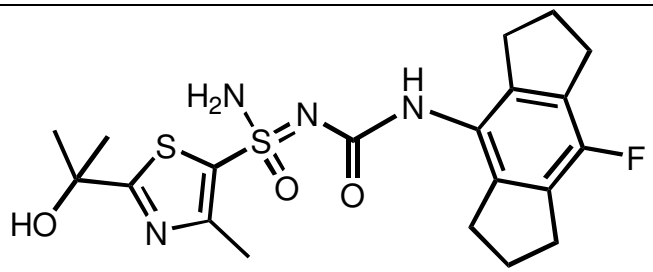
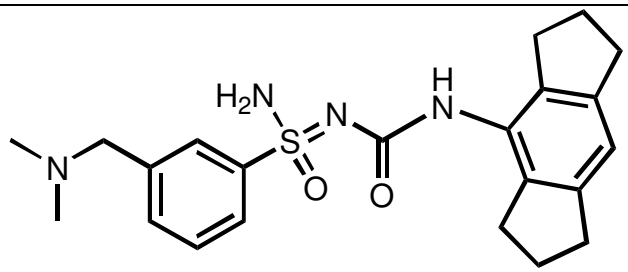
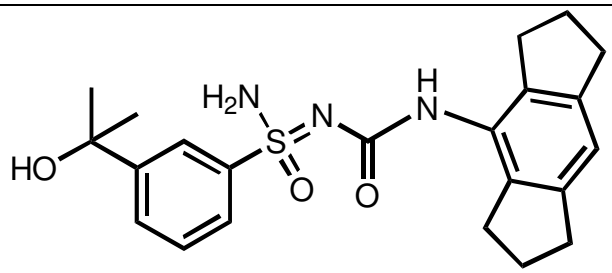
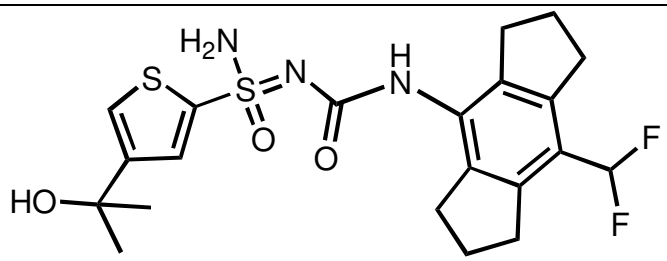
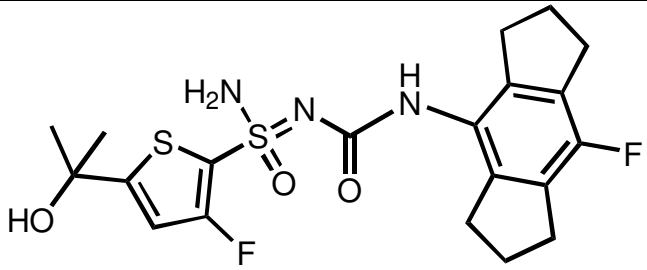


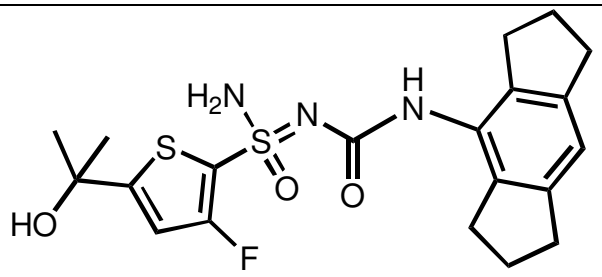
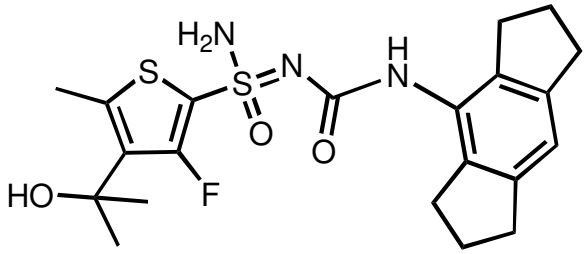
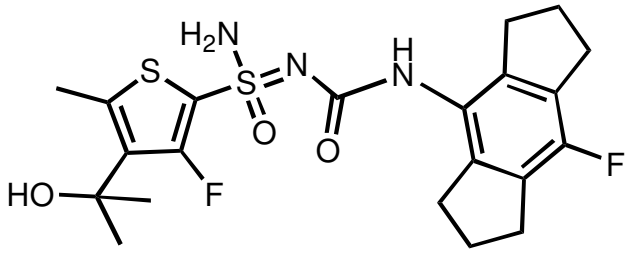
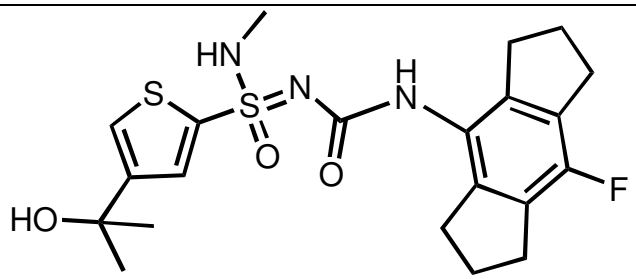
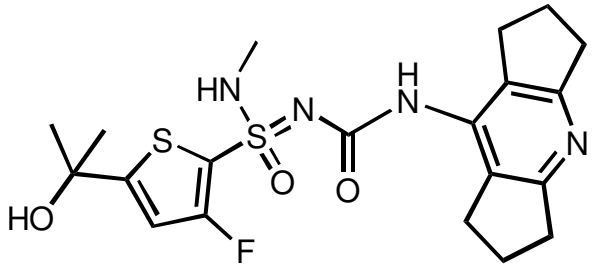
11. The compound of any one of the preceding claims, wherein R^3 is hydrogen.

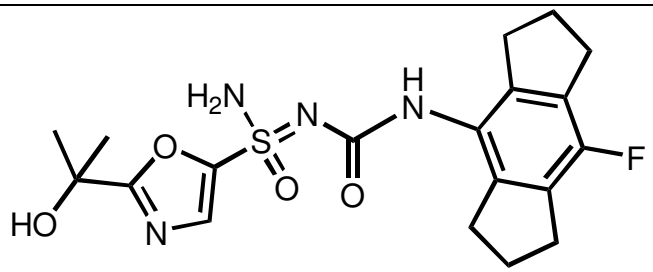
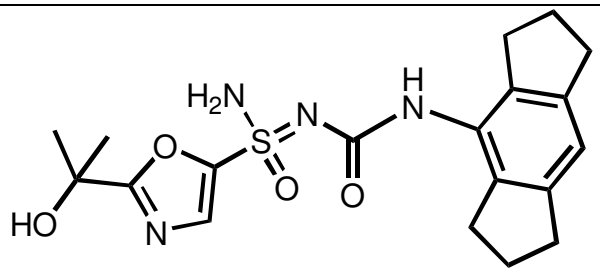
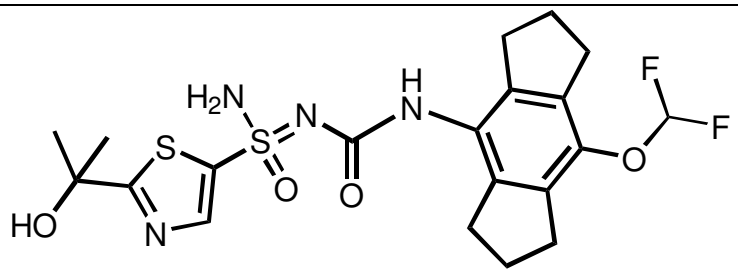
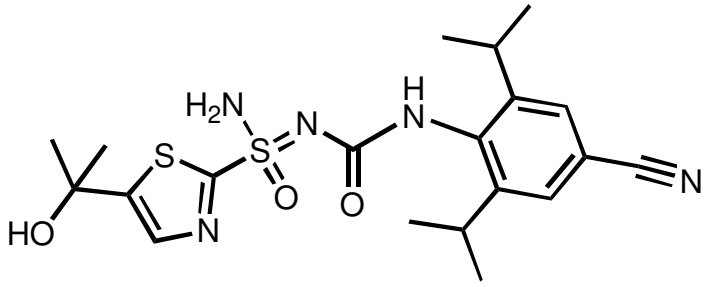
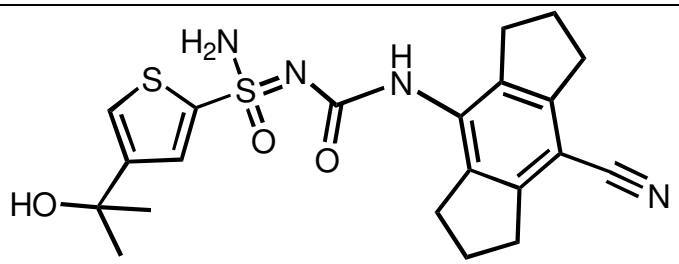
12. A compound selected from the group consisting of the compounds below:

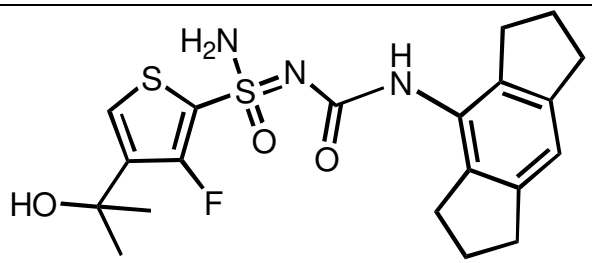
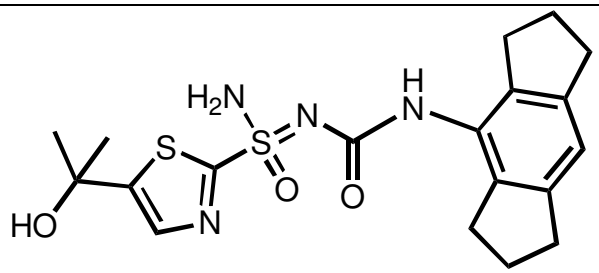
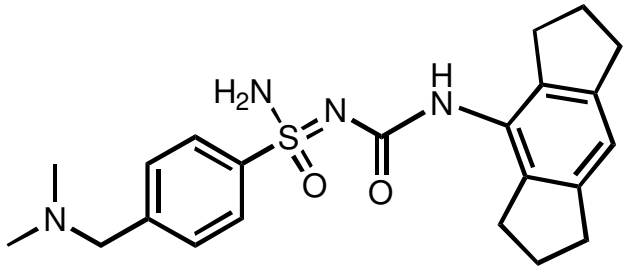
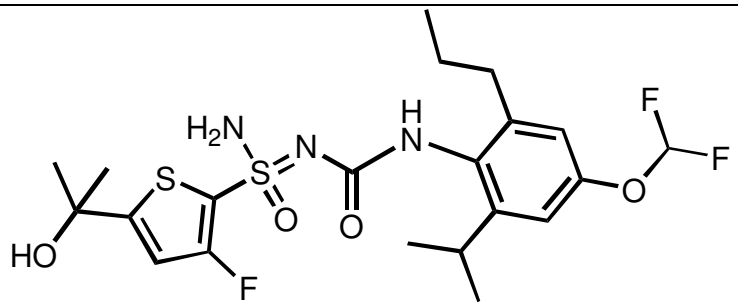
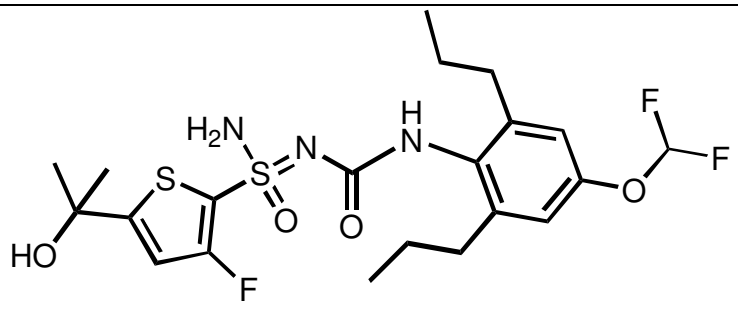
Compound	Structure
101'	
101	
102	
103'	

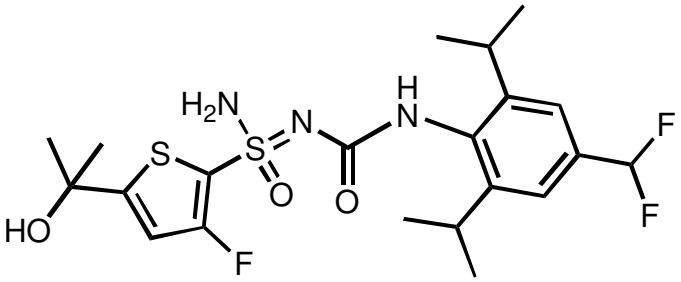
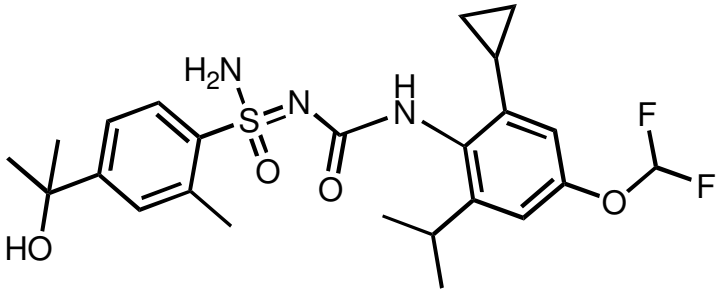
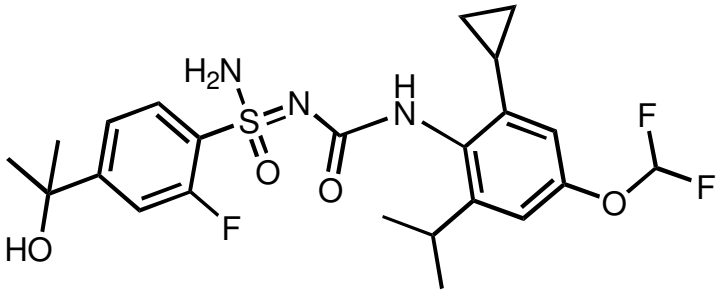
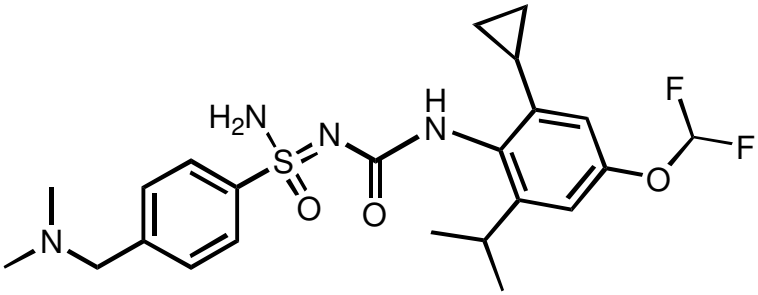
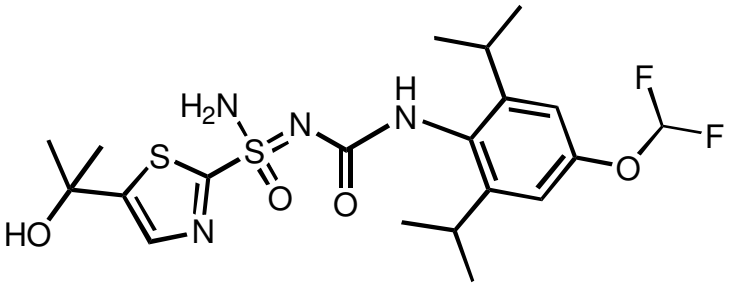
103	
104	
105	
106	
107	

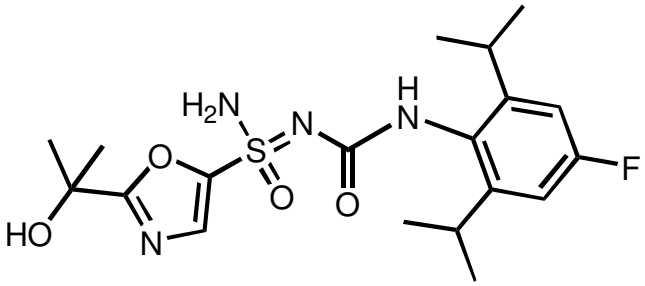
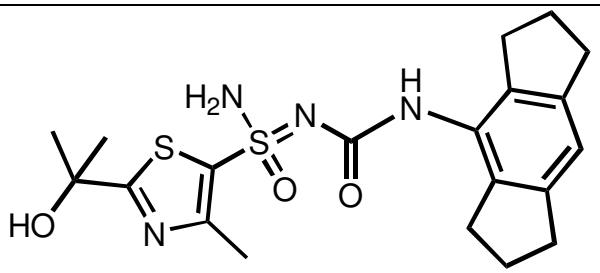
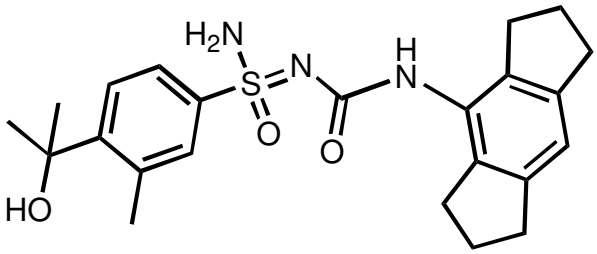
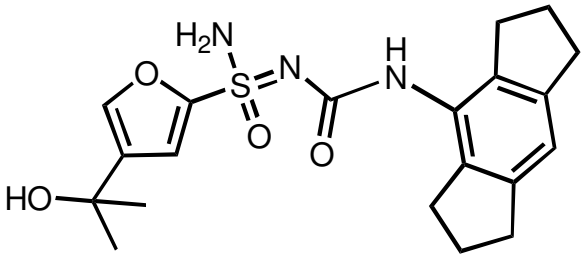
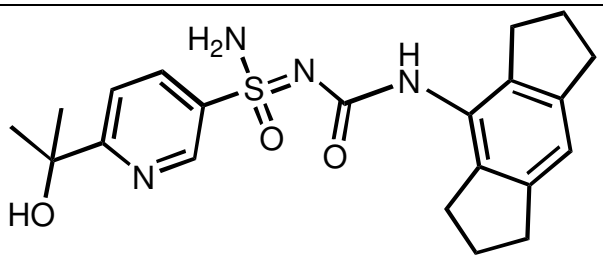
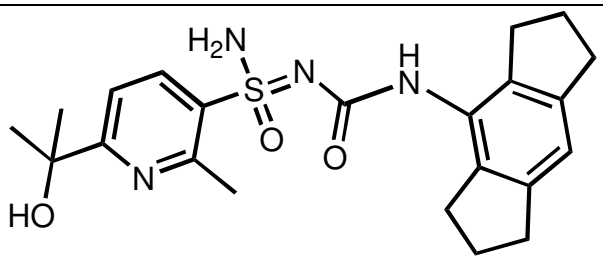
108	
109	
110	
111	
112	

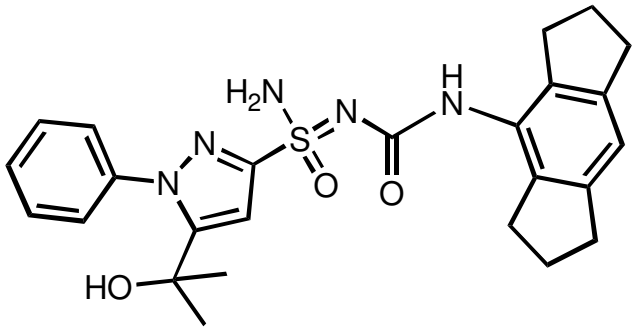
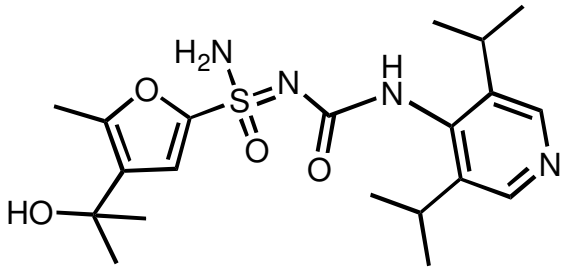
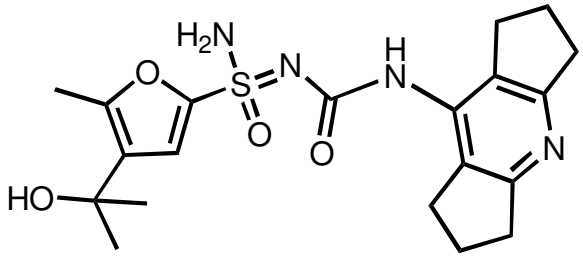
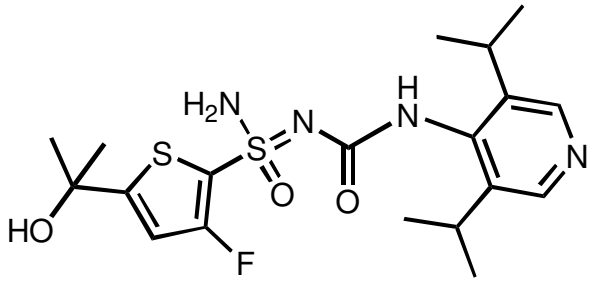
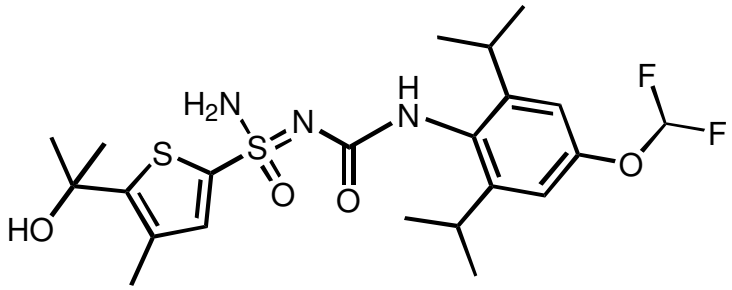
113	
114	
115	
116	
117	

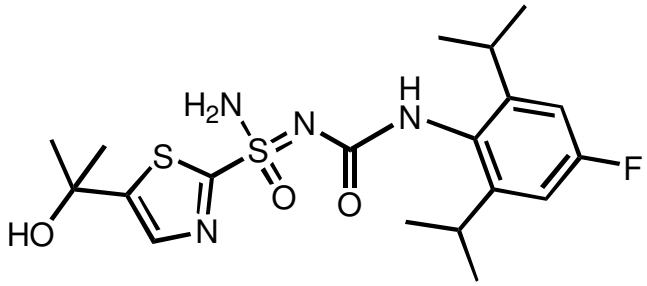
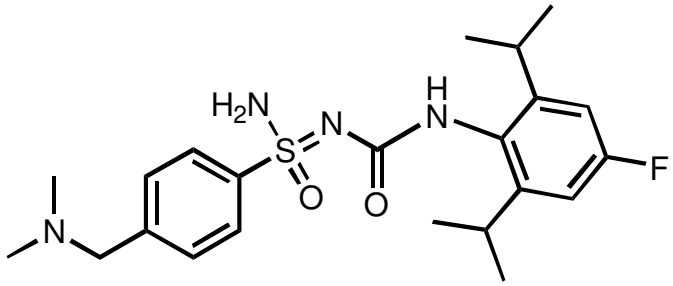
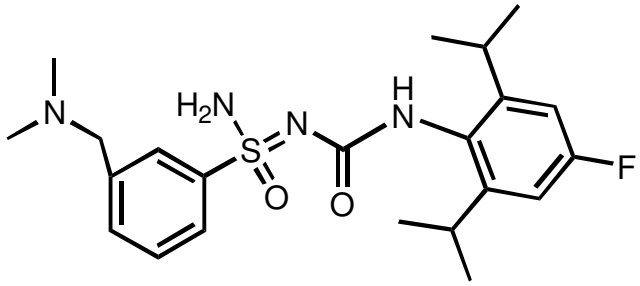
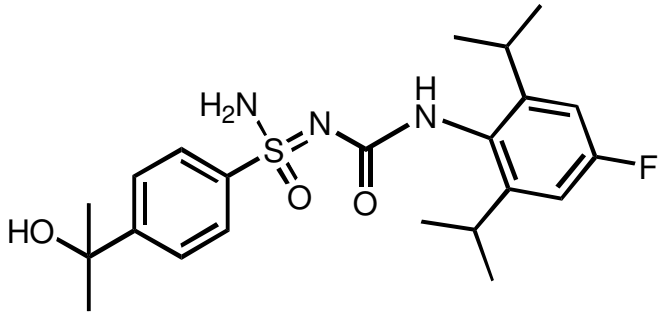
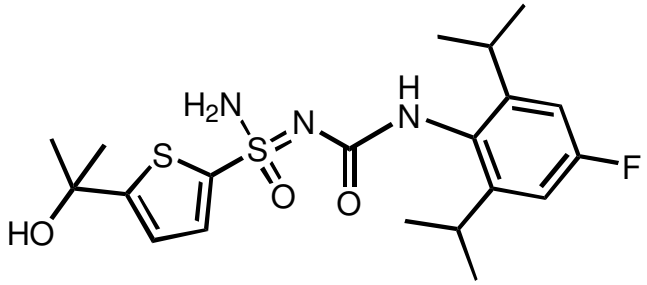
118	
119	
120	
121	
122	

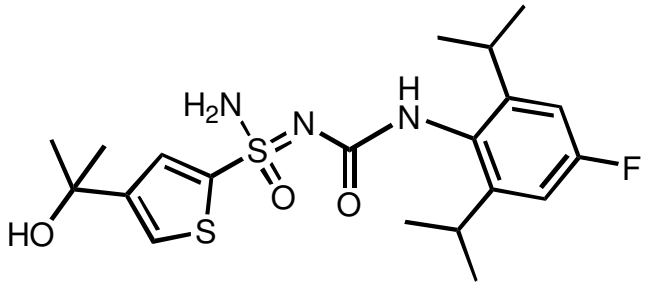
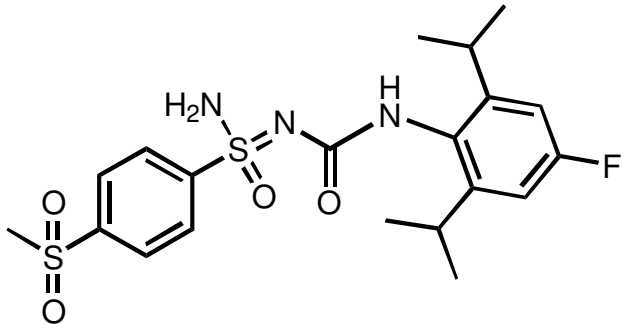
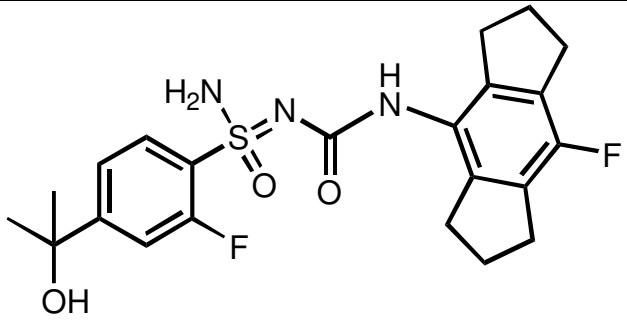
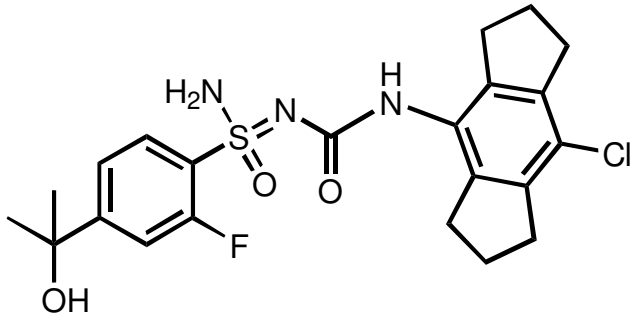
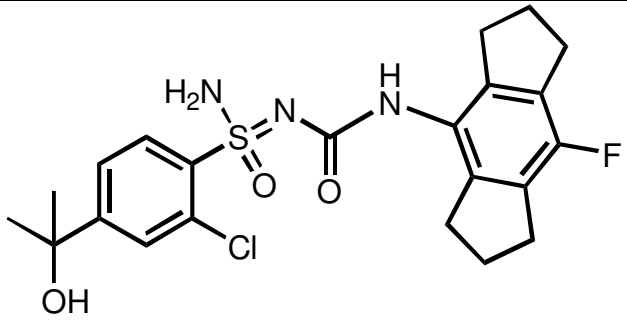
123	
124	
125	
126	
127	

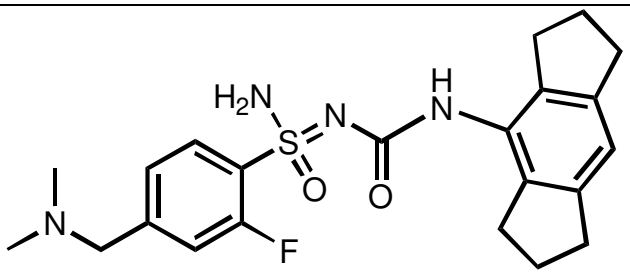
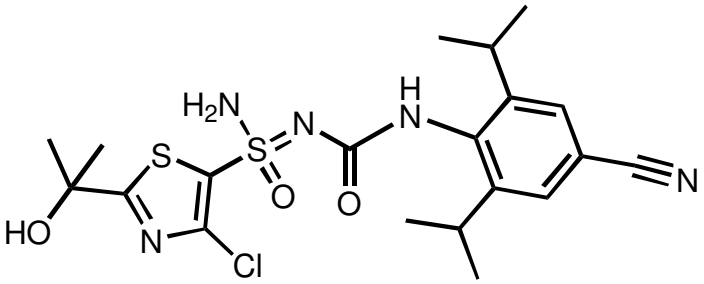
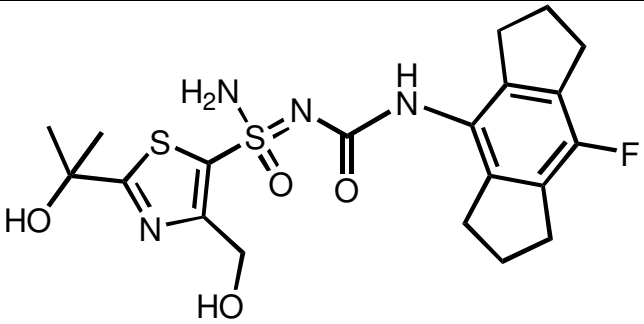
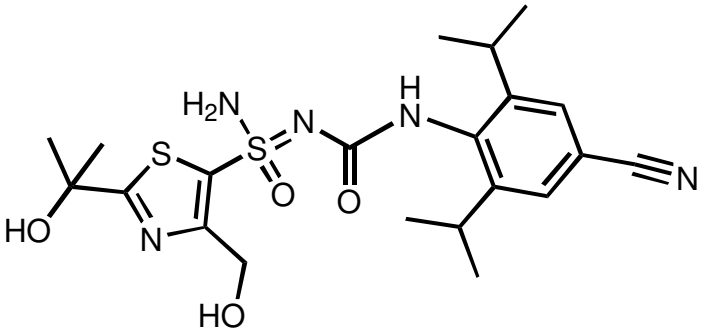
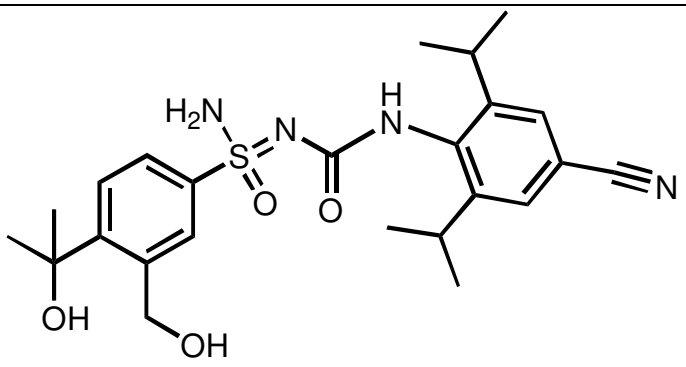
128	
129	
130	
131	
132	

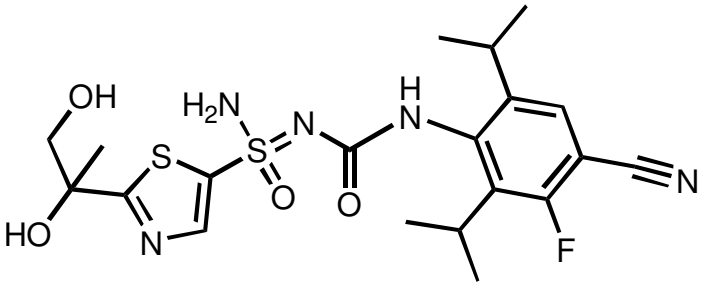
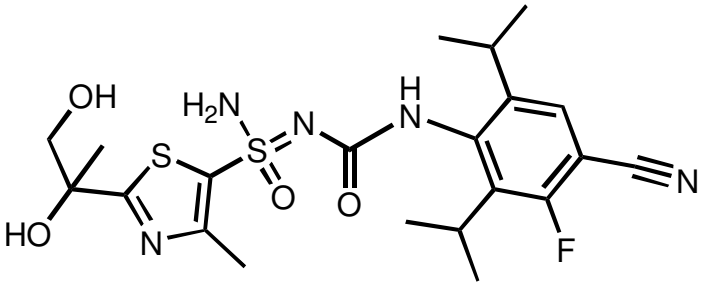
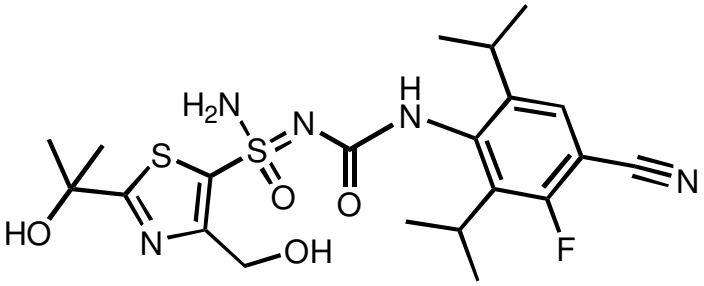
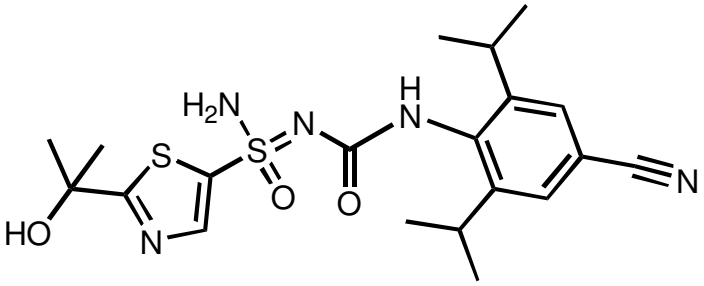
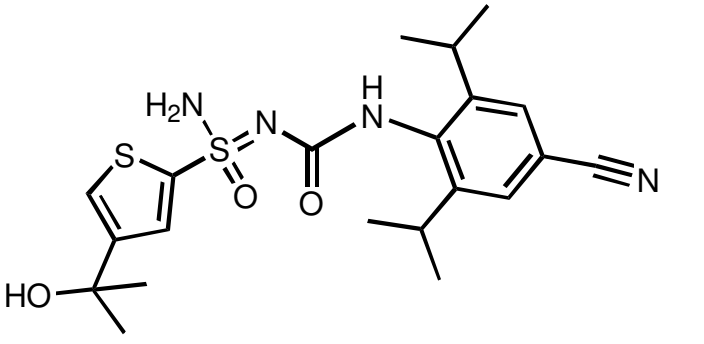
133	
134	
135	
136	
137	
138	

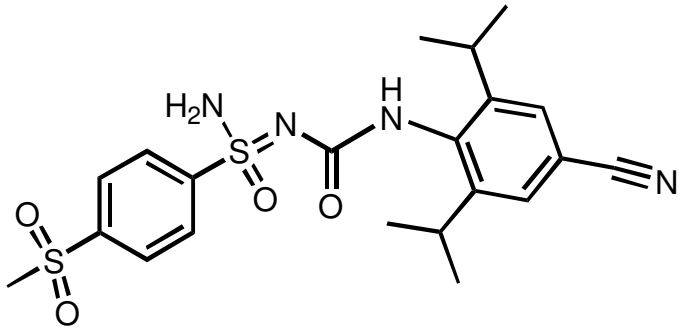
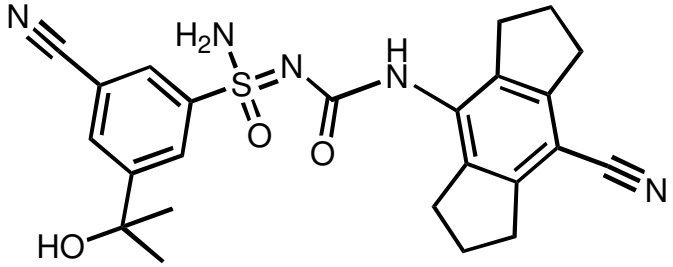
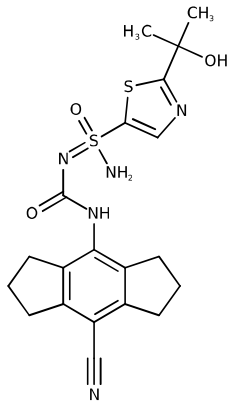
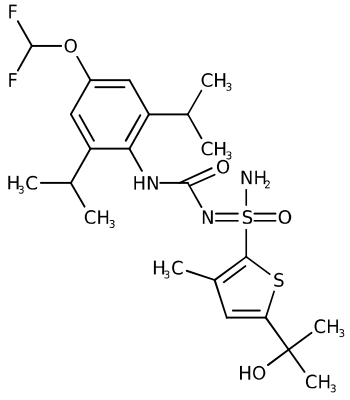
139	
140	
141	
142	
143	

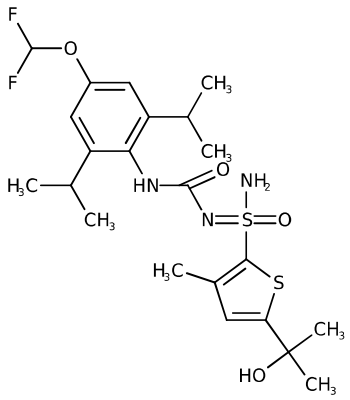
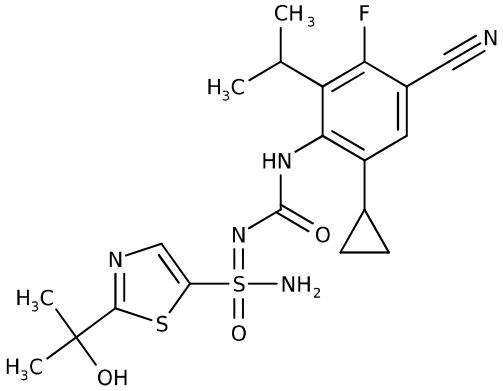
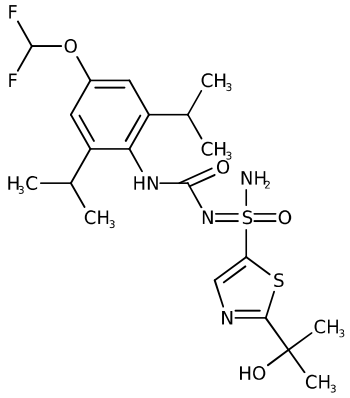
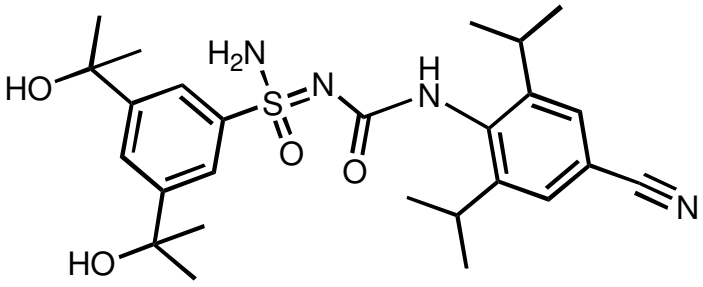
144	
145	
146	
147	
148	

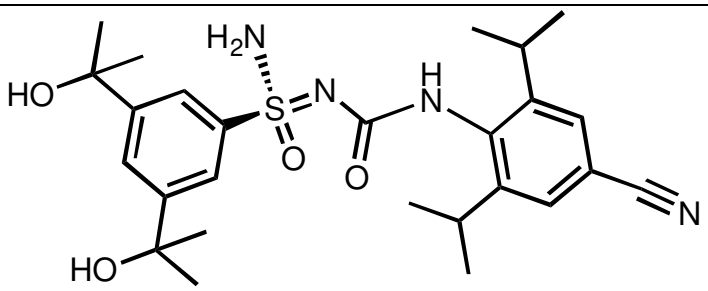
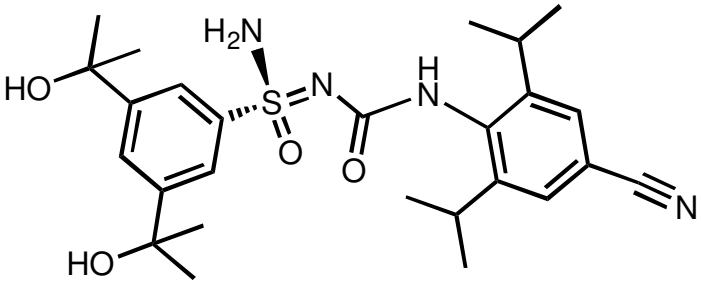
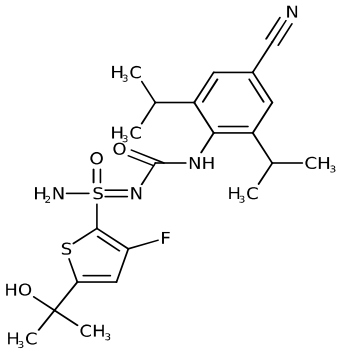
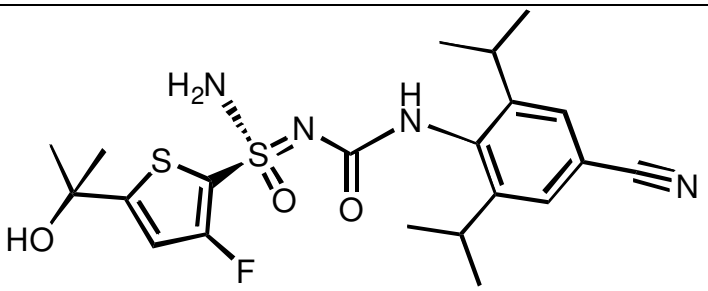
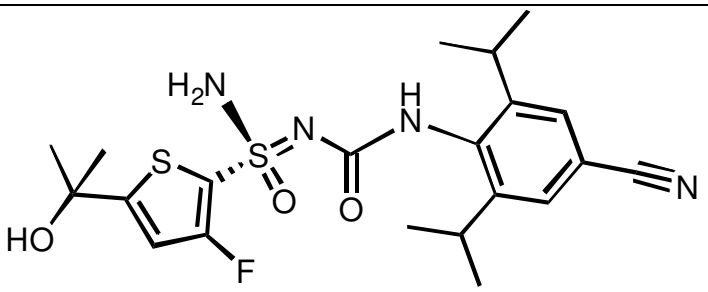
149	
150	
151	
152	
153	

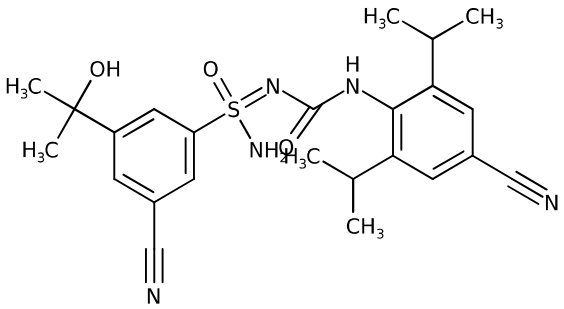
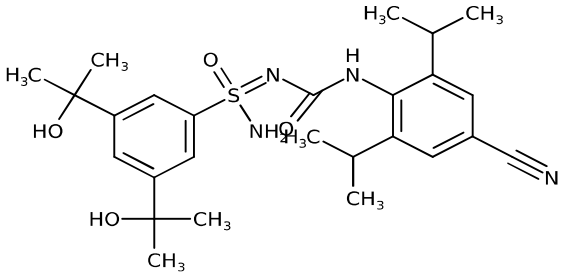
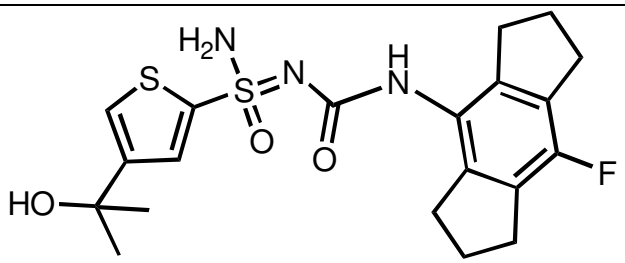
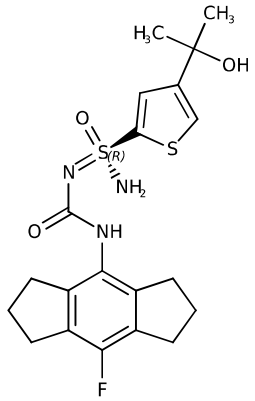
154	
155	
156	
157	
158	

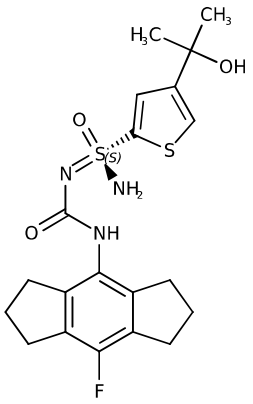
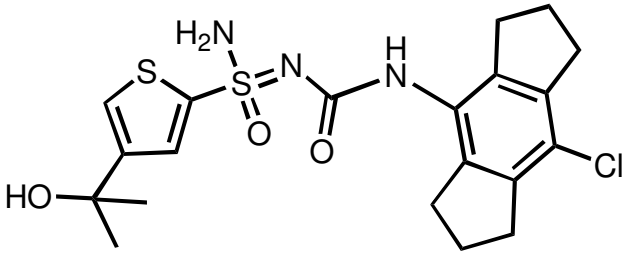
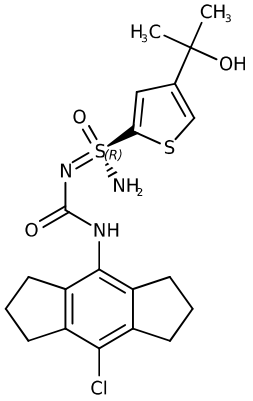
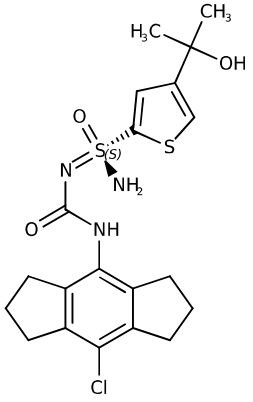
159	
160	
161	
163	
164	

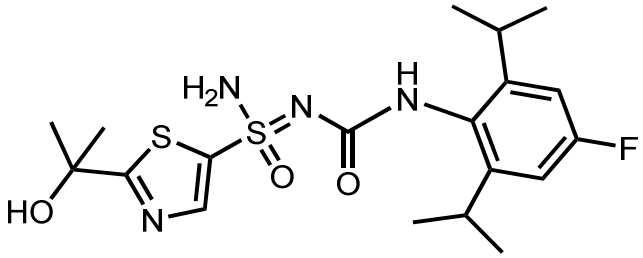
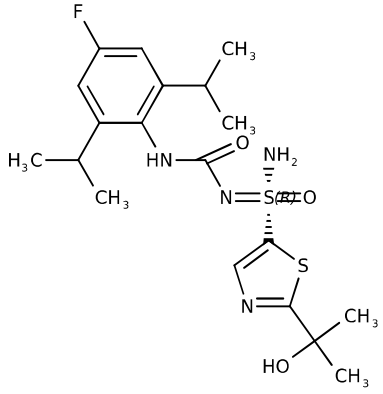
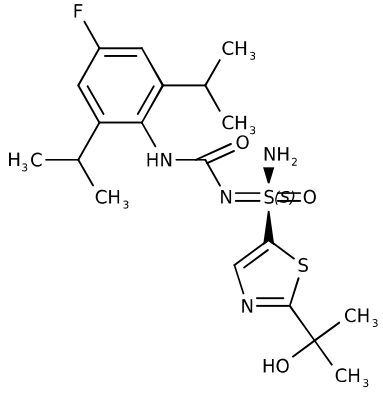
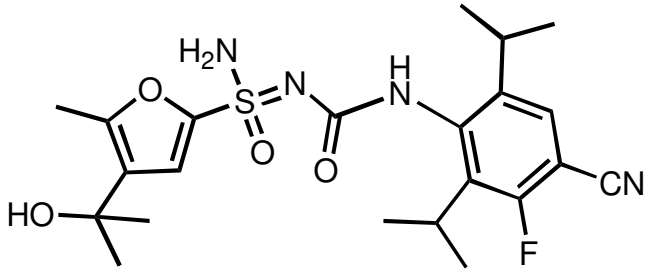
165	
166	
167	
168	

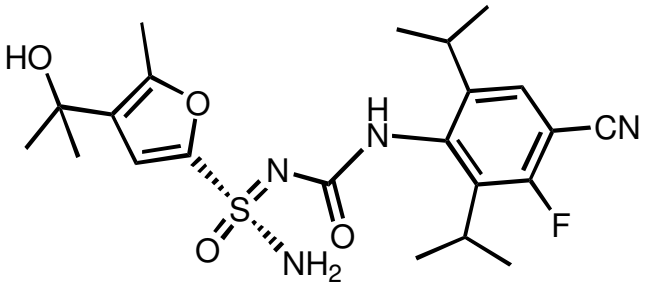
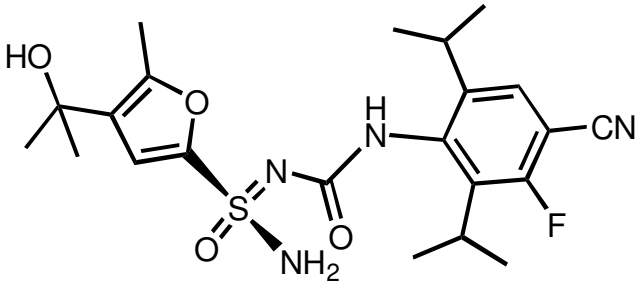
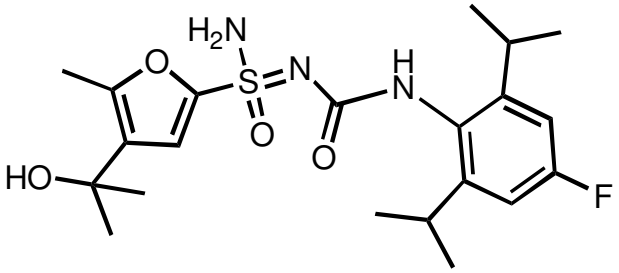
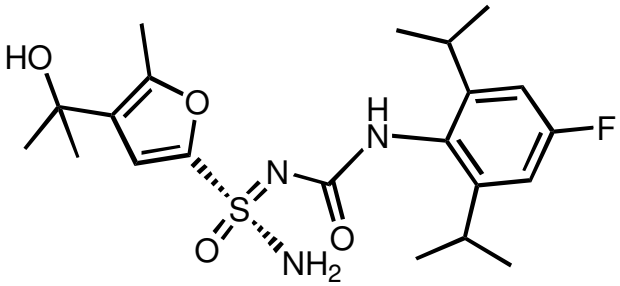
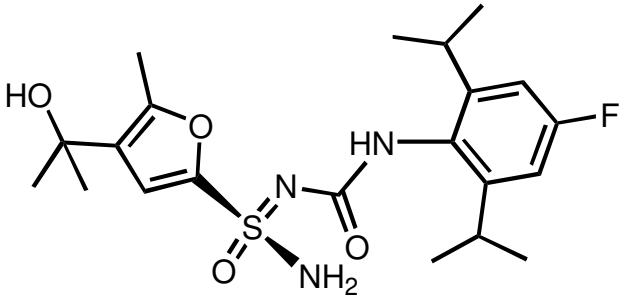
169	
170	
171	
172	

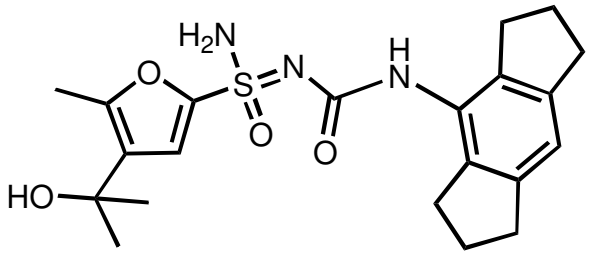
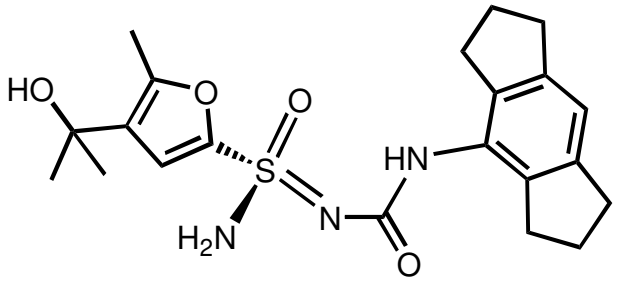
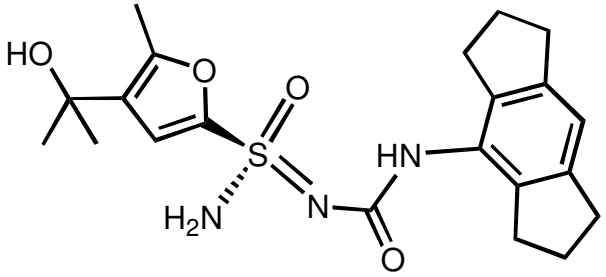
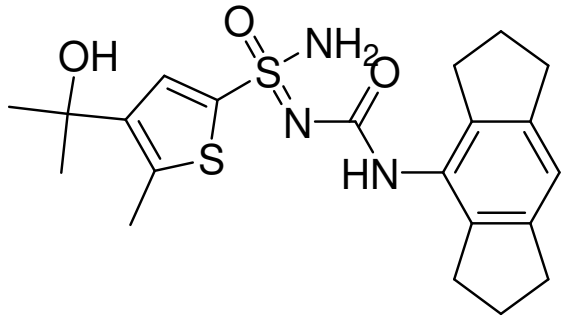
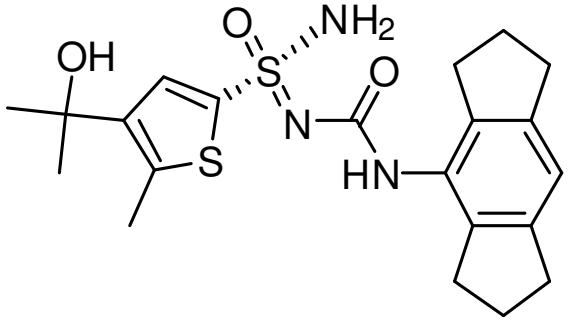
172a	
172b	
173	
173a	
173b	

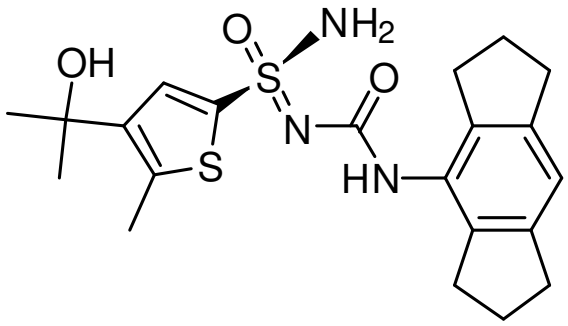
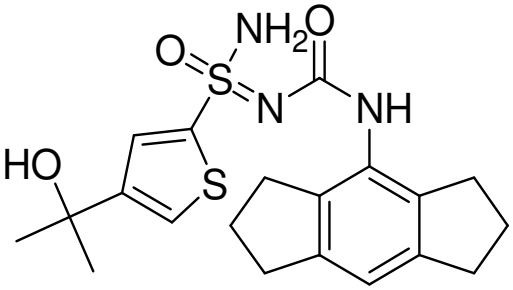
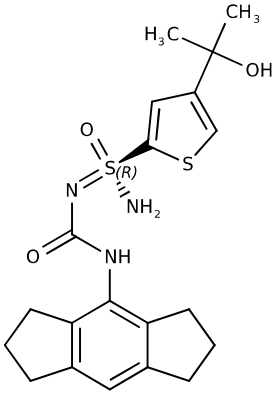
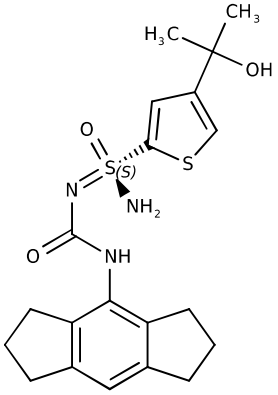
174	
175	
176	
176a	

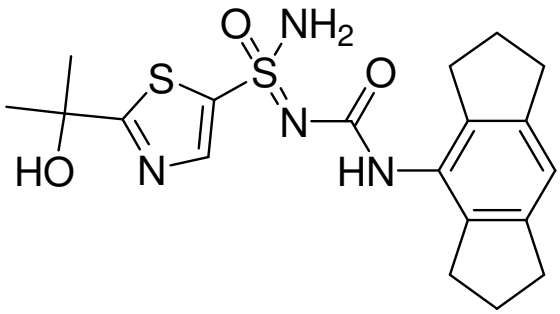
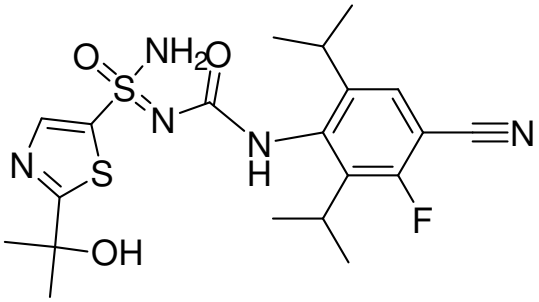
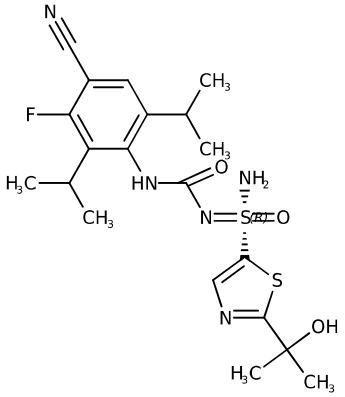
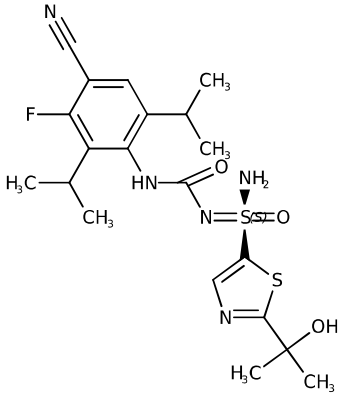
176b	
177	
177a	
177b	

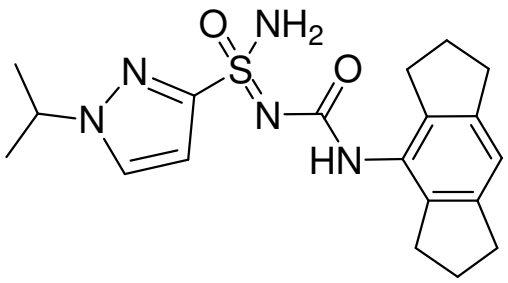
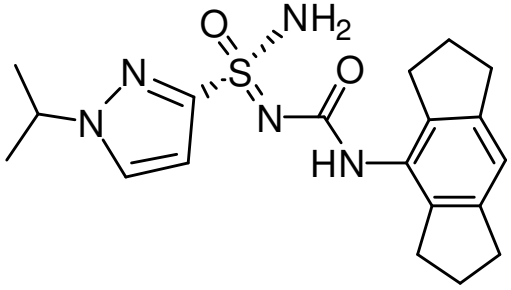
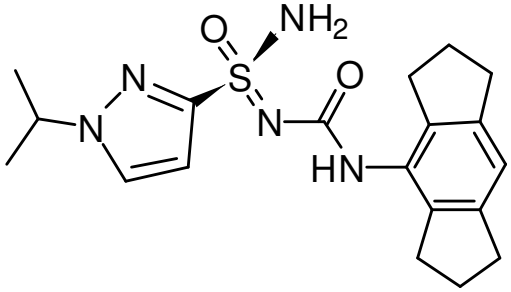
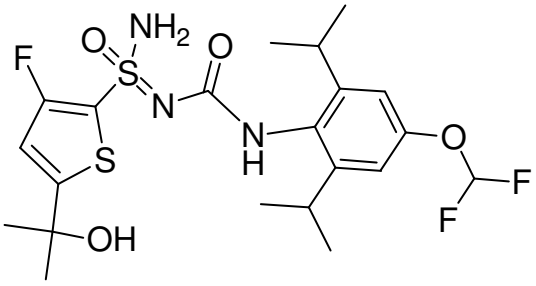
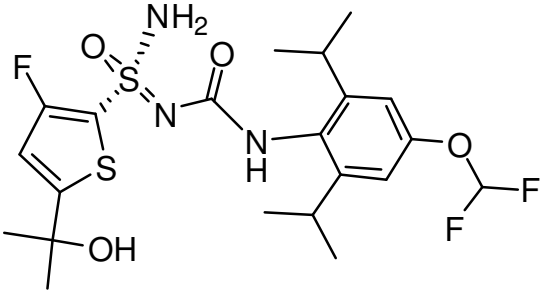
178	
178a	
178b	
179	

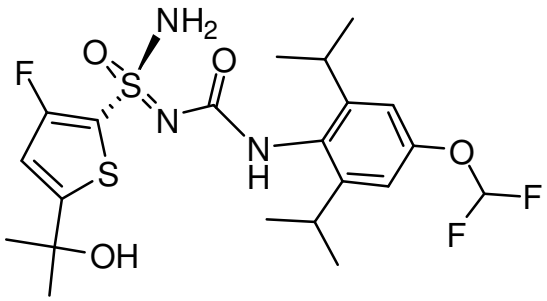
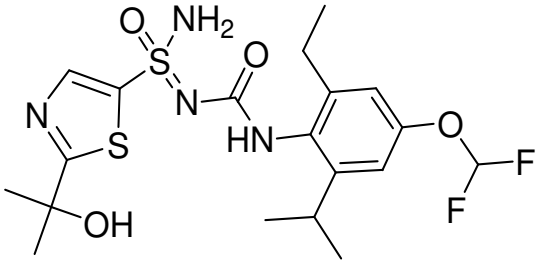
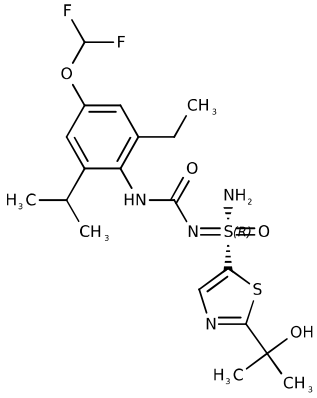
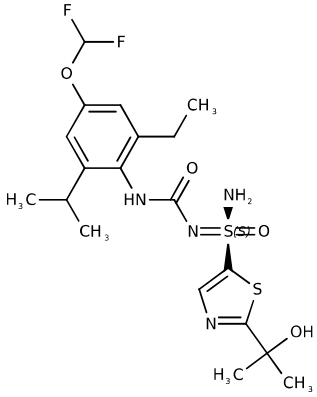
179a	
179b	
180	
180a	
180b	

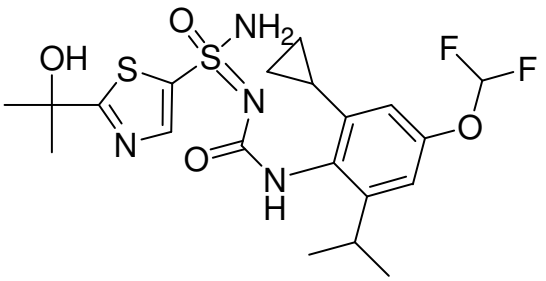
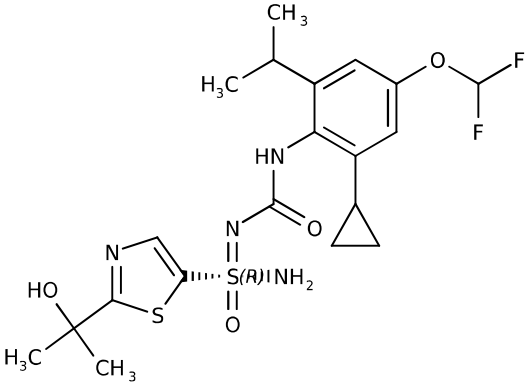
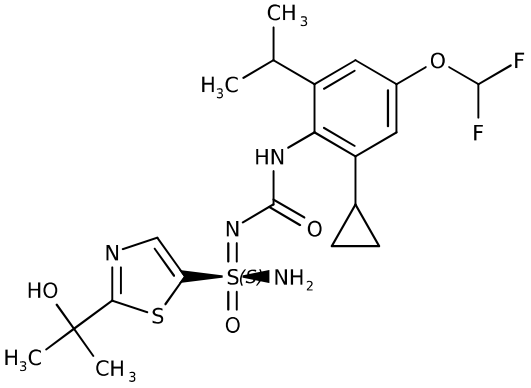
181	
181a	
181b	
182	
182a	

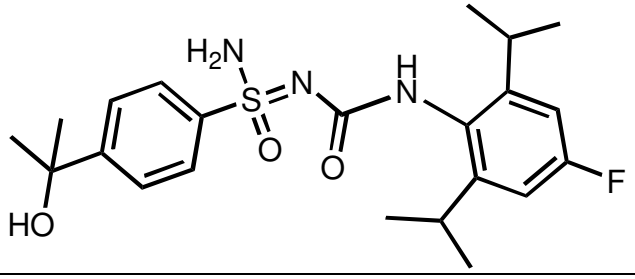
182b	
183	
183a	
183b	

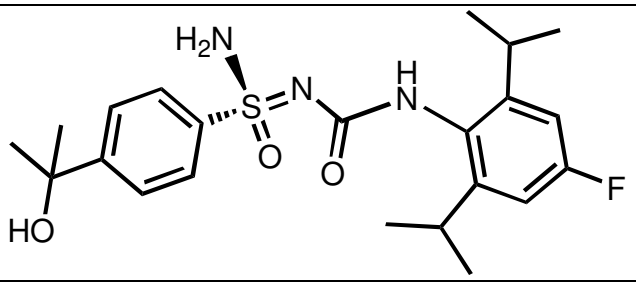
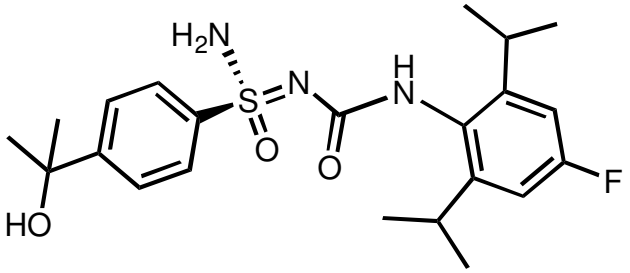
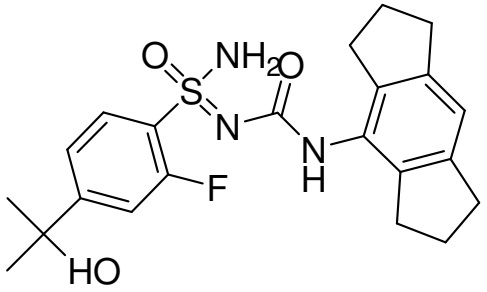
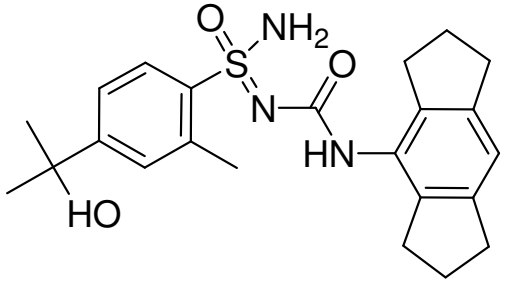
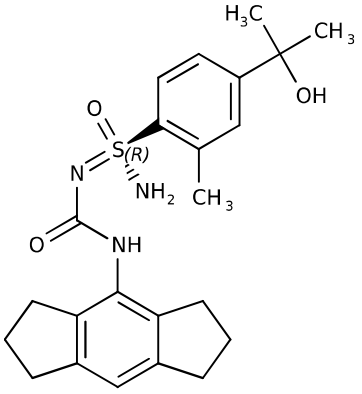
184	
185	
185a	
185b	

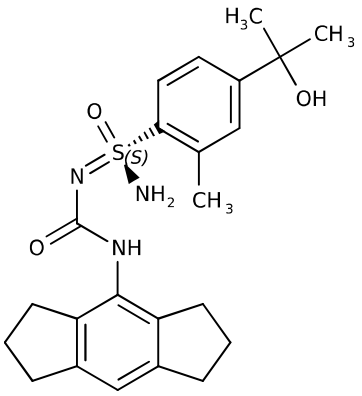
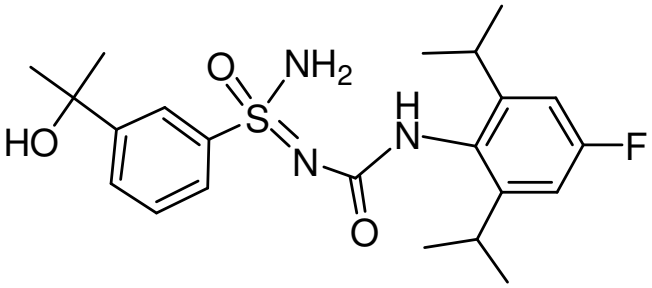
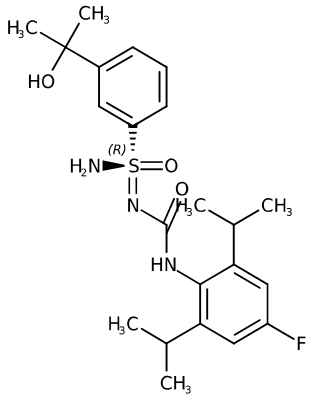
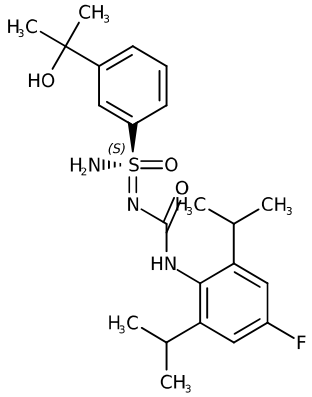
186	
186a	
186b	
187	
187a	

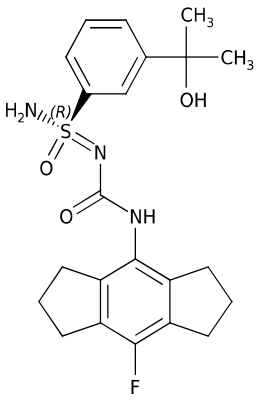
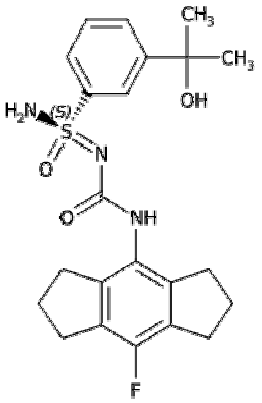
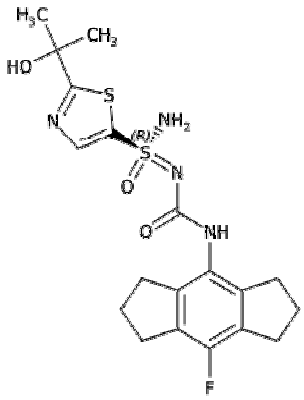
187b	
188	
188a	
188b	

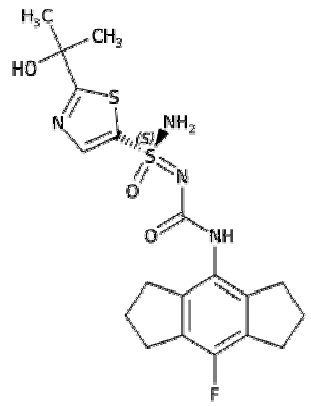
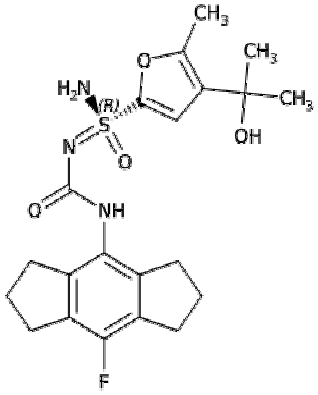
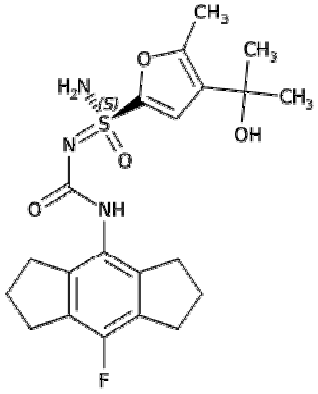
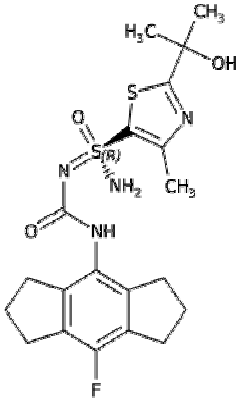
189	
189a	
189b	

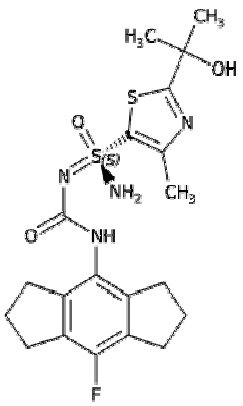
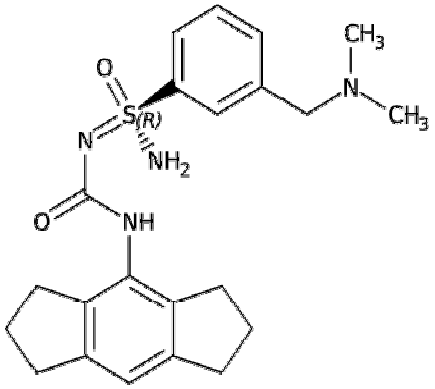
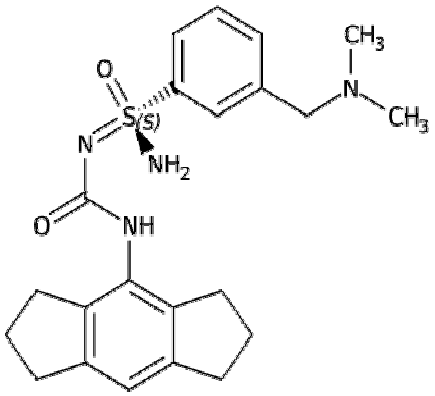
190	

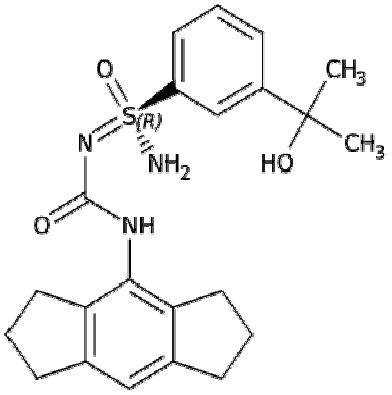
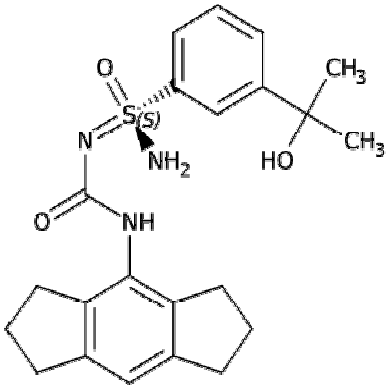
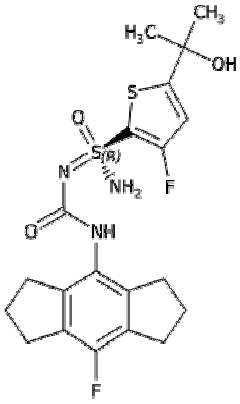
190a	
190b	
191	
192	
192a	

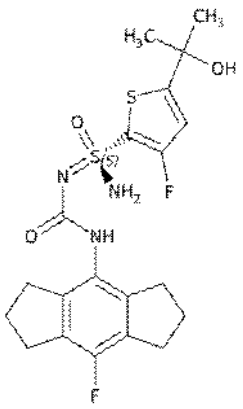
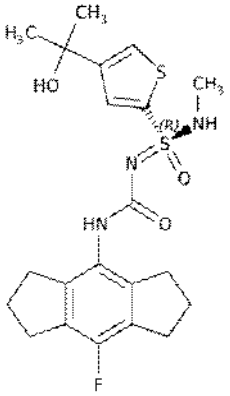
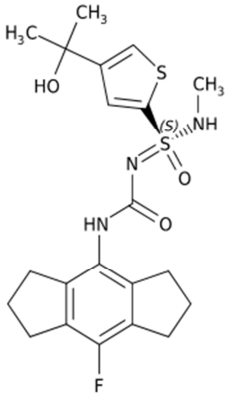
192b	
193	
193a	
193b	

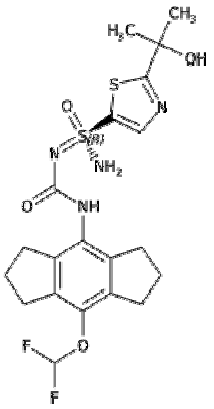
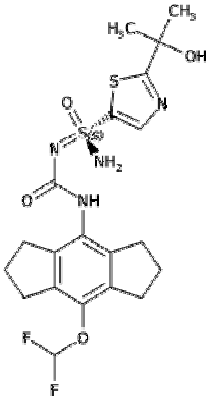
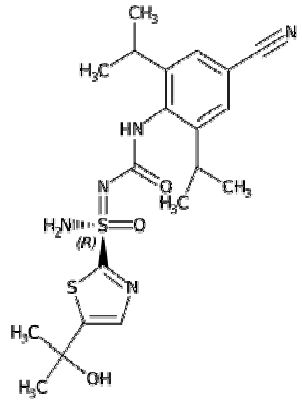
Compound	Structure
105a	
105b	
106a	

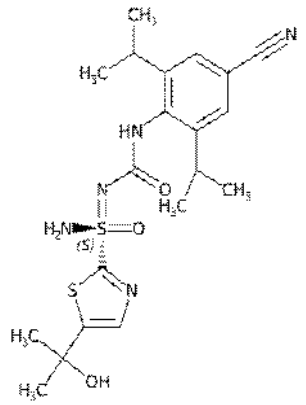
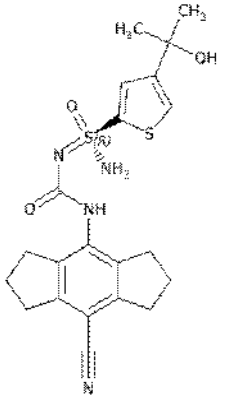
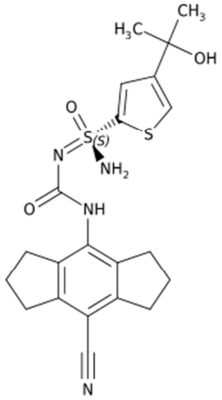
106b	
107a	
107b	
108a	

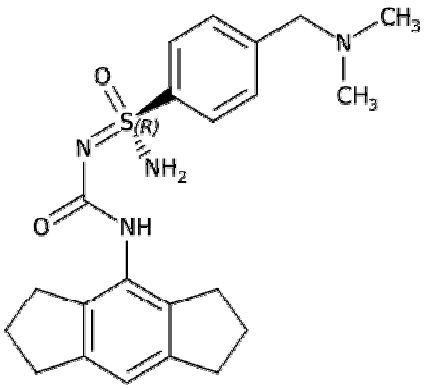
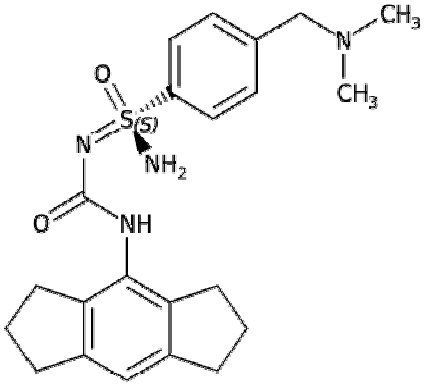
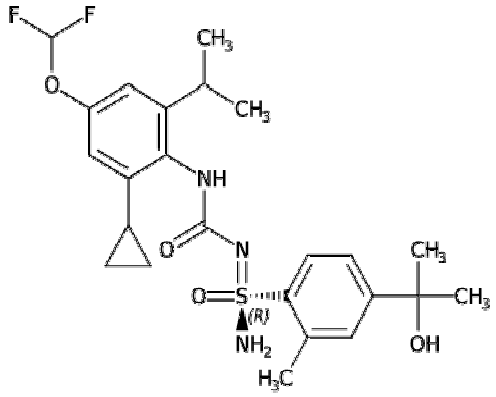
108b	
109a	
109b	

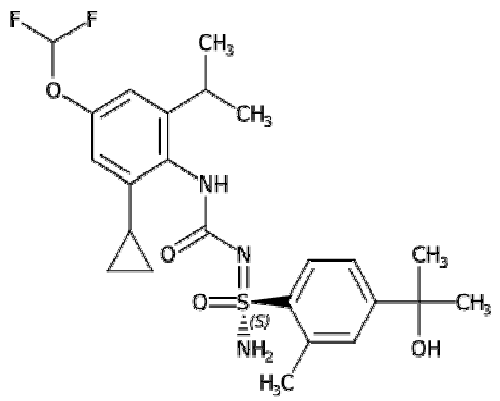
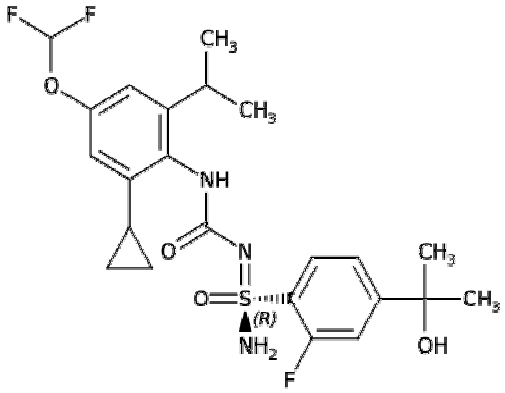
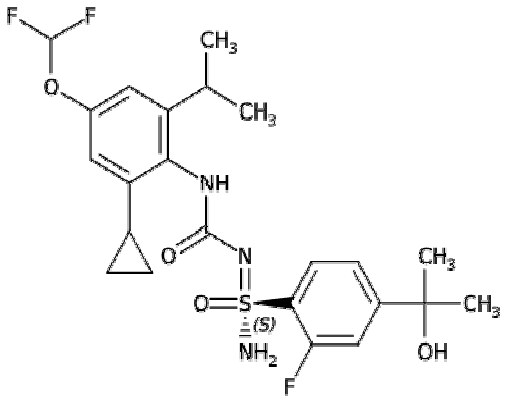
110a	
110b	
112a	

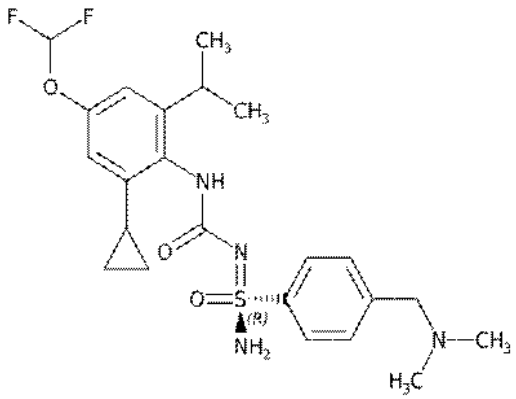
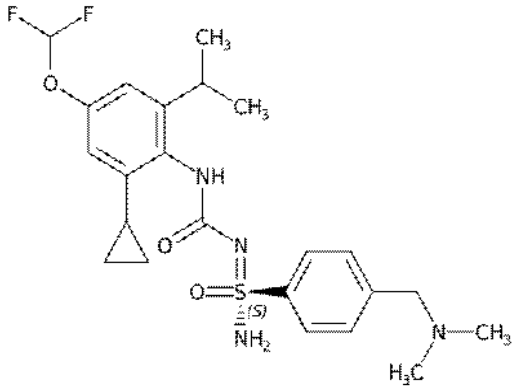
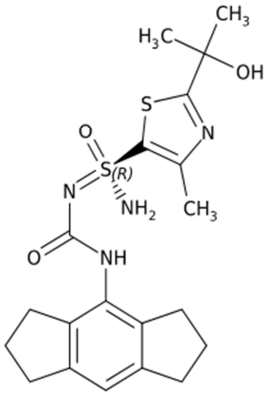
112b	
116a	
116b	

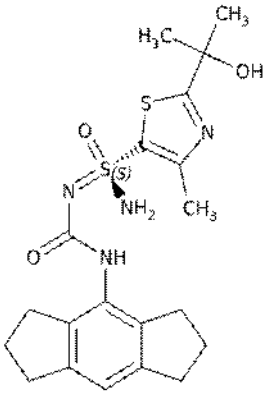
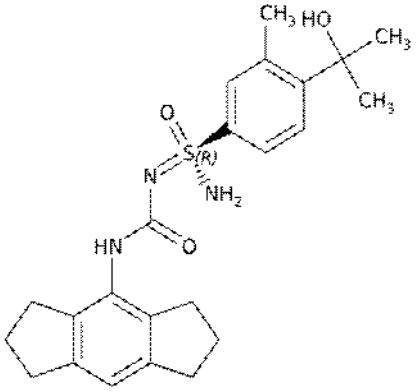
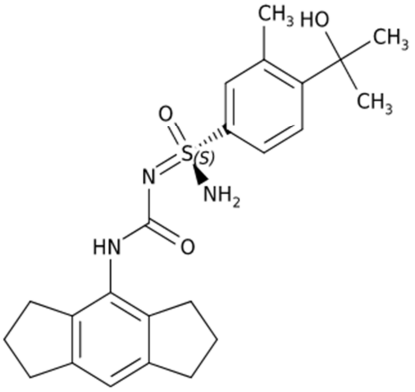
120a	
120b	
121a	

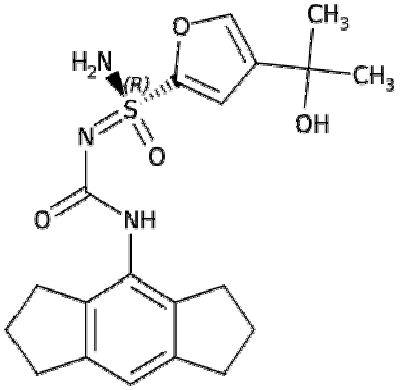
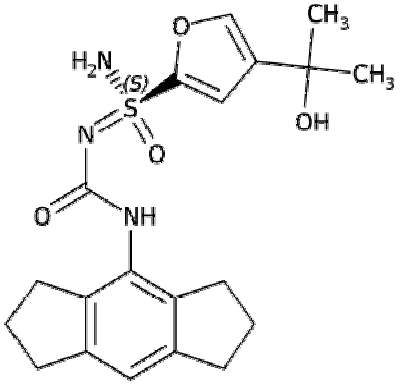
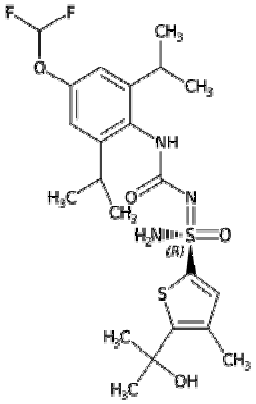
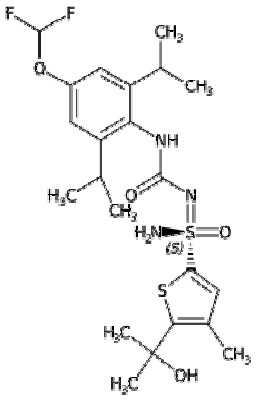
121b	
122a	
122b	

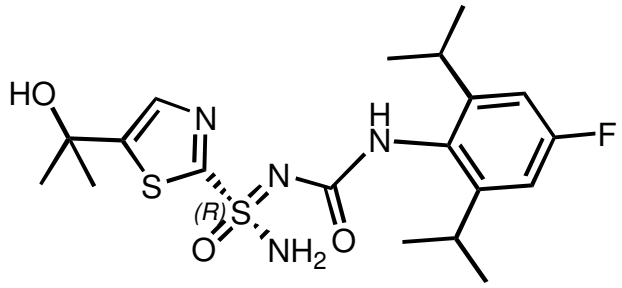
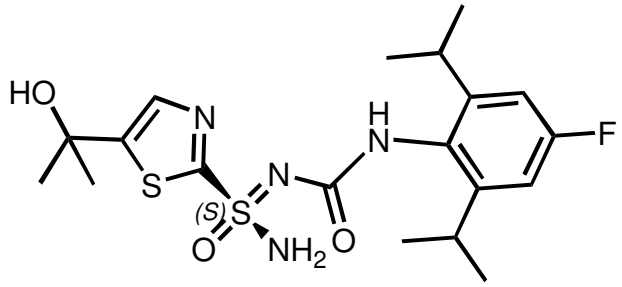
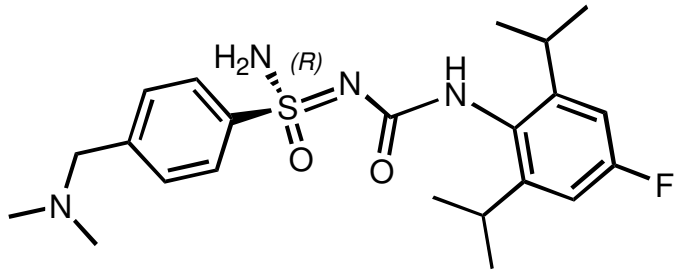
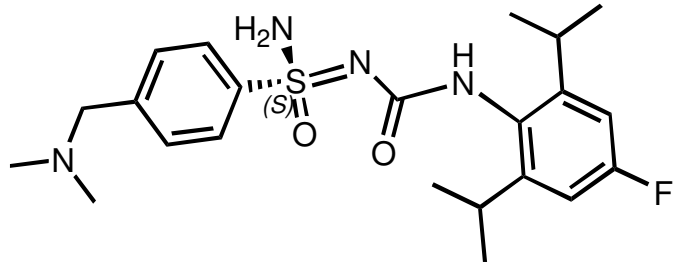
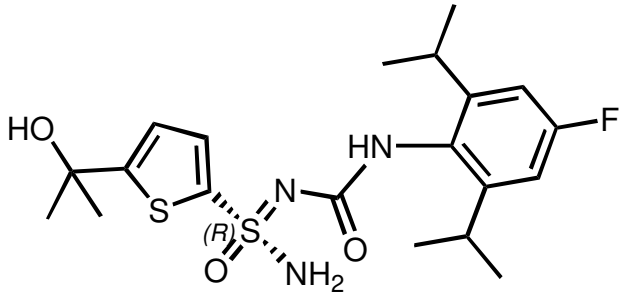
125a	
125b	
129a	

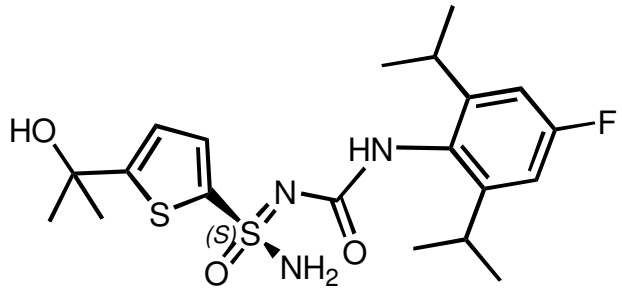
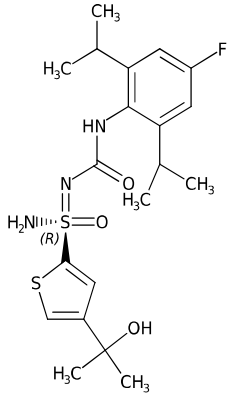
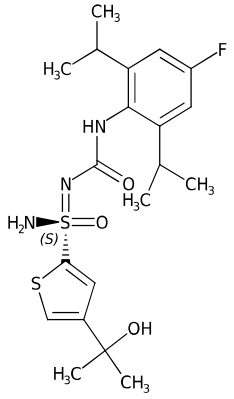
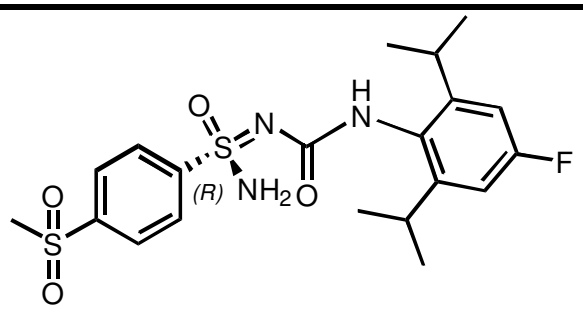
129b	
130a	
130b	

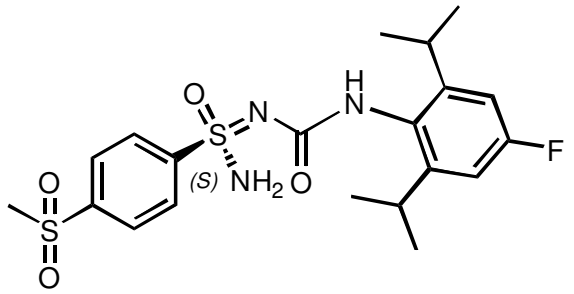
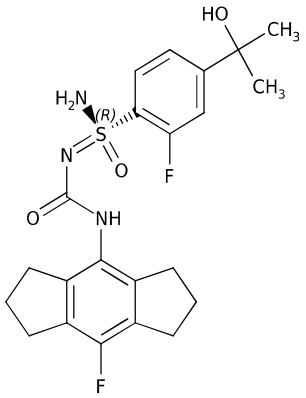
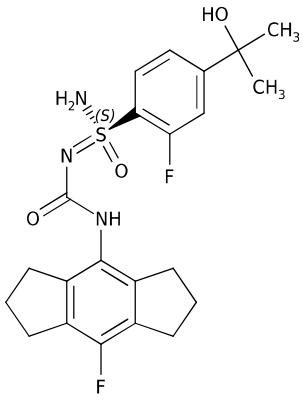
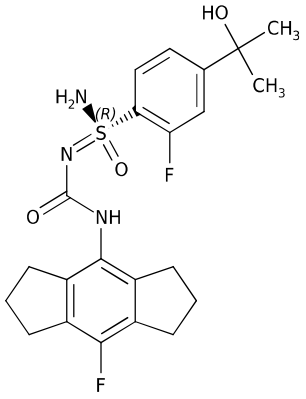
131a		
131b		
134a		

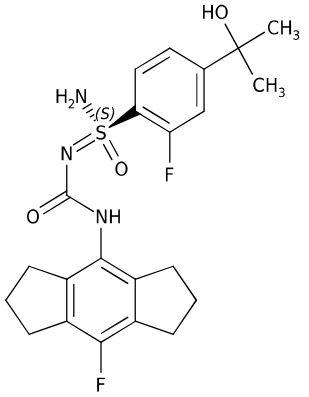
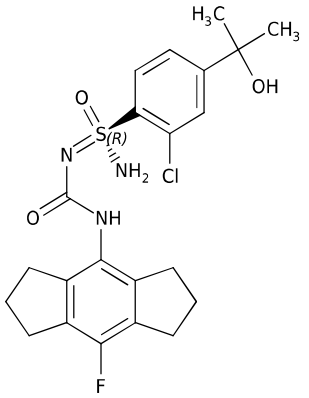
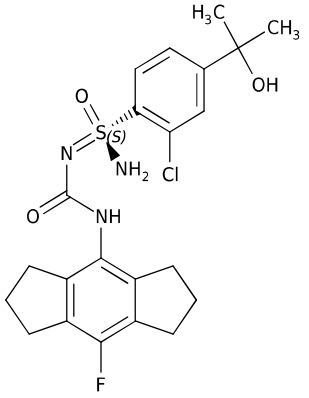
134b	
135a	
135b	

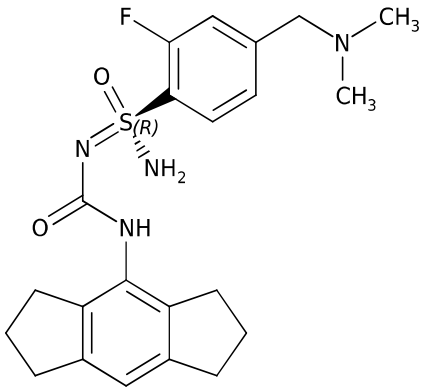
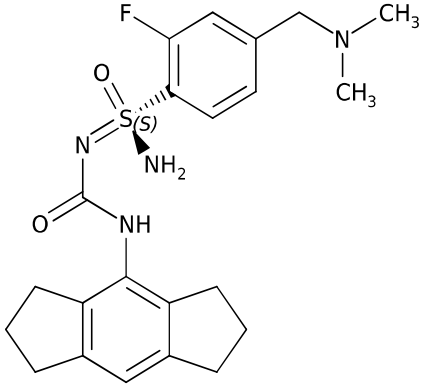
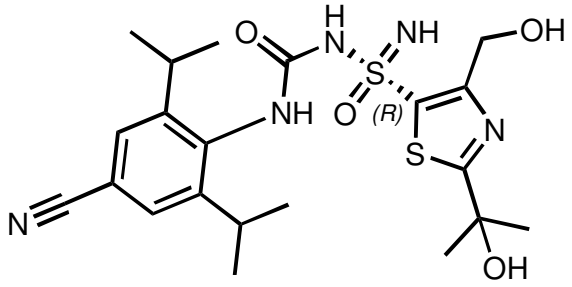
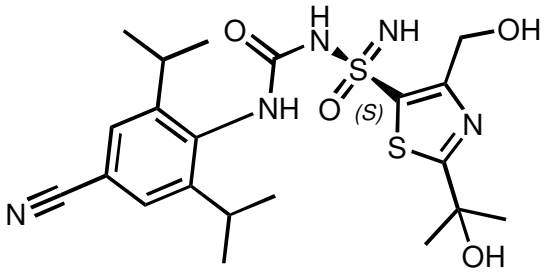
136a	
136b	
143a	
143b	

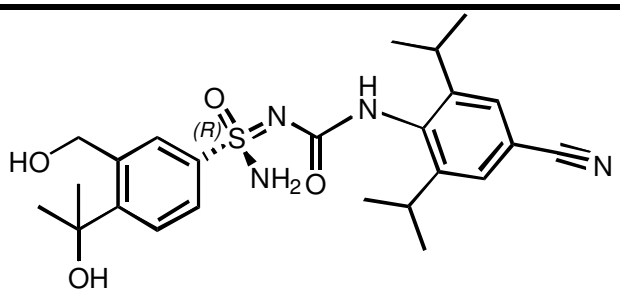
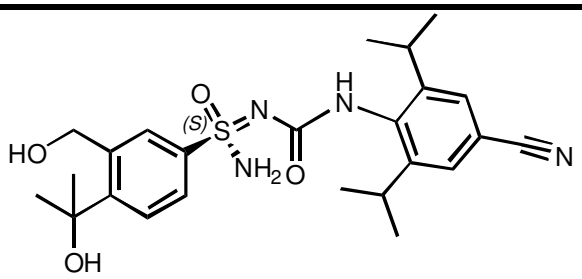
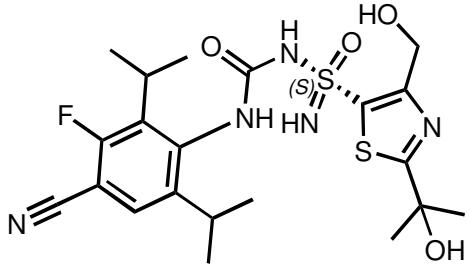
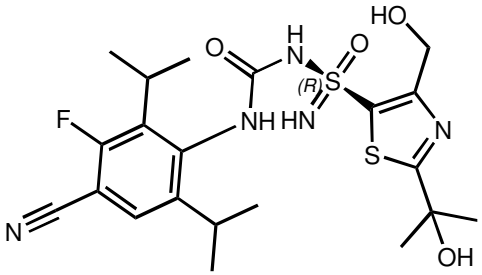
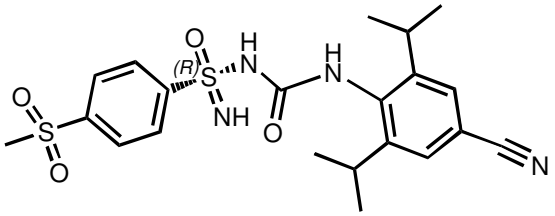
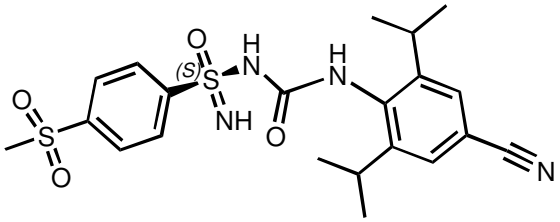
144a	
144b	
145a	
145b	
148a	

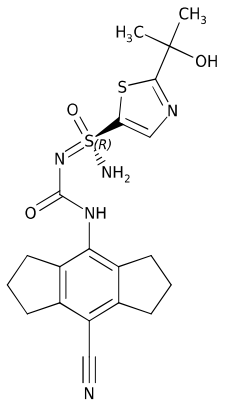
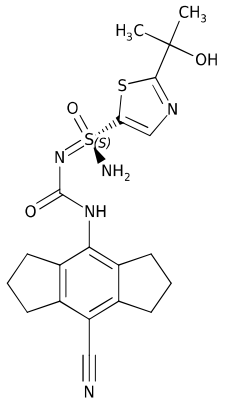
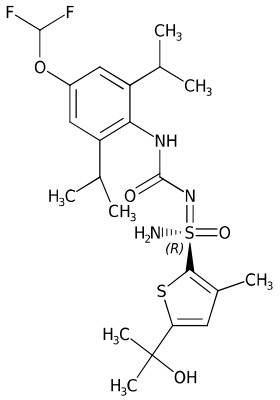
148b	
149a	
149b	
151a’	

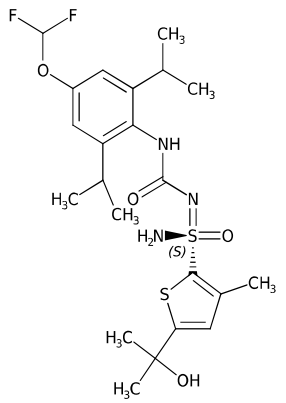
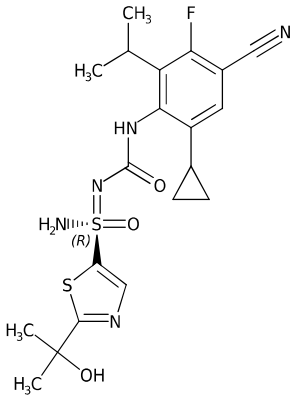
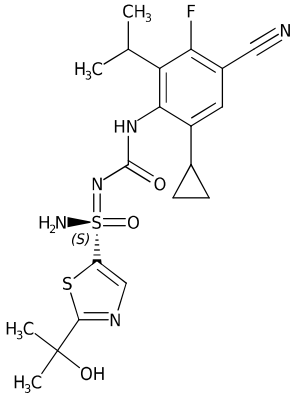
151b’	
151a	
151b	
152a	

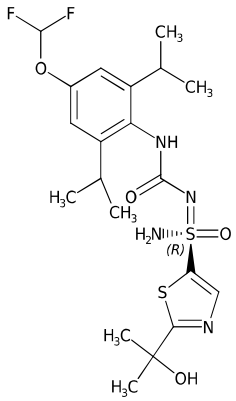
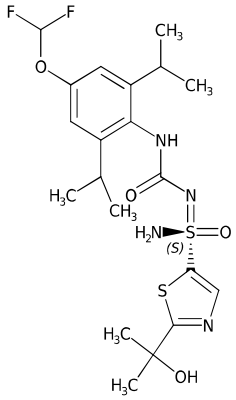
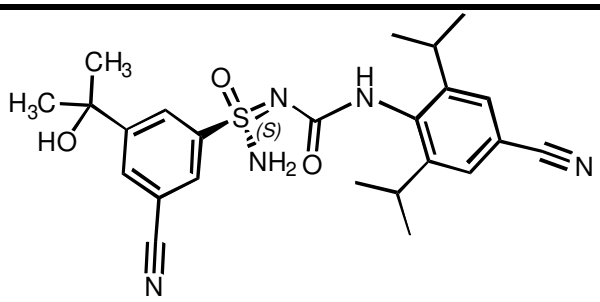
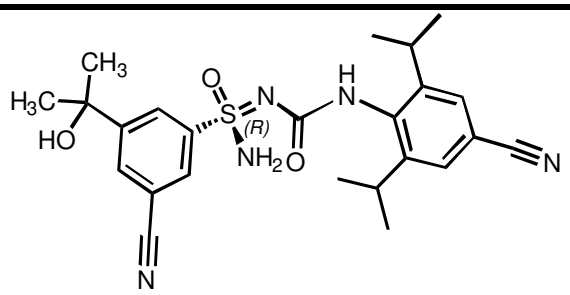
152b	
153a	
153b	

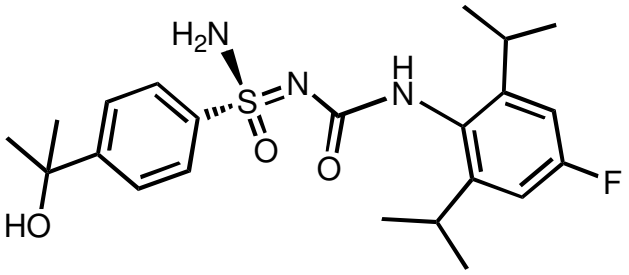
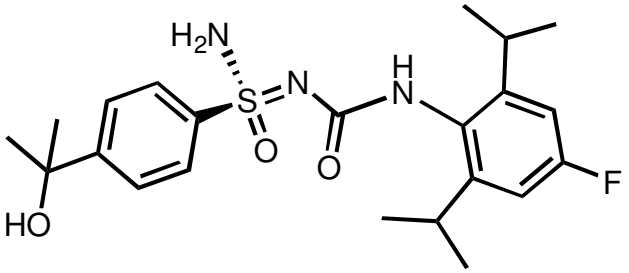
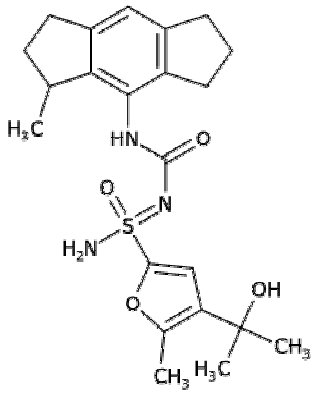
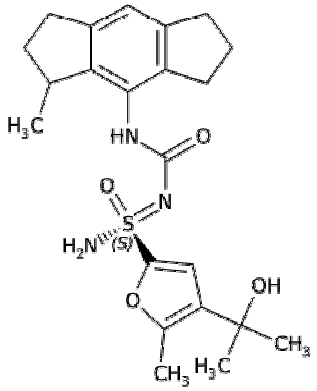
154a	
154b	
157a	
157b	

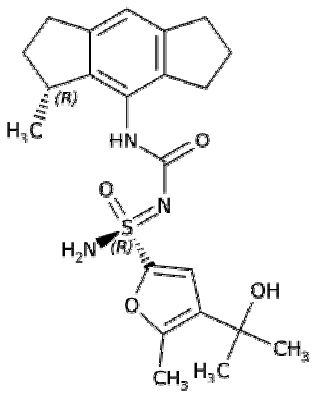
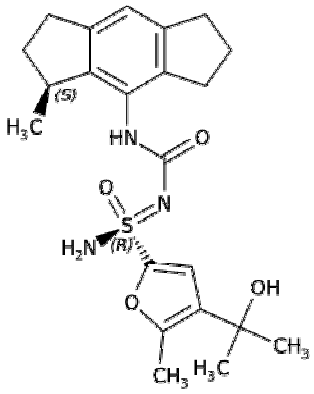
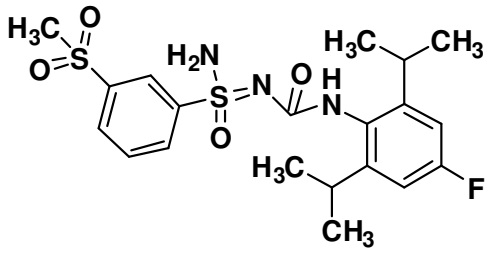
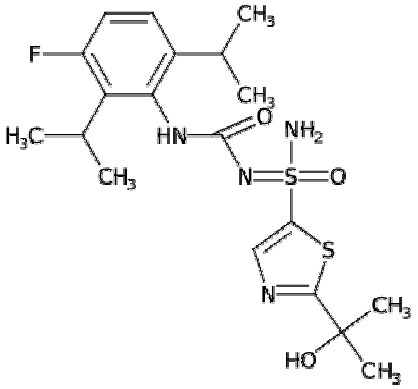
158a	
158b	
161a	
161b	
165a	
165b	

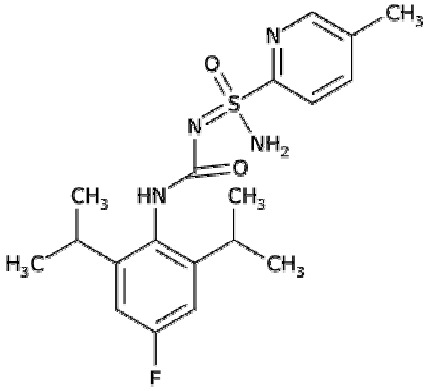
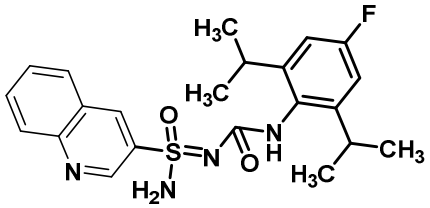
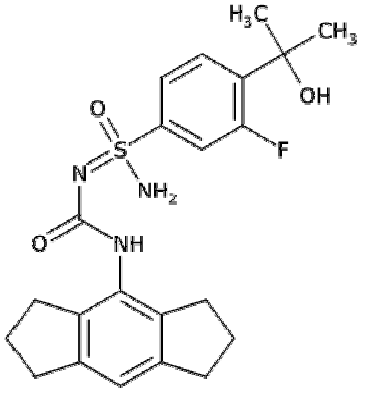
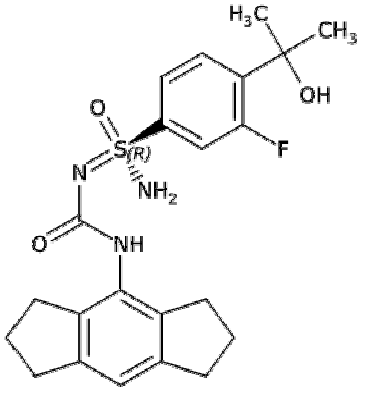
167a	
167b	
168a	

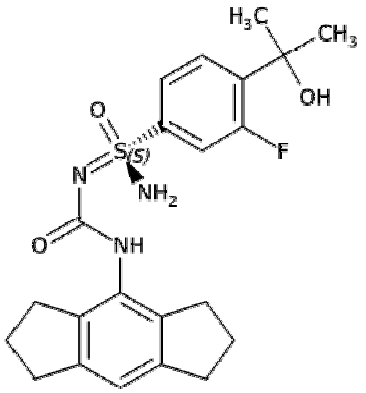
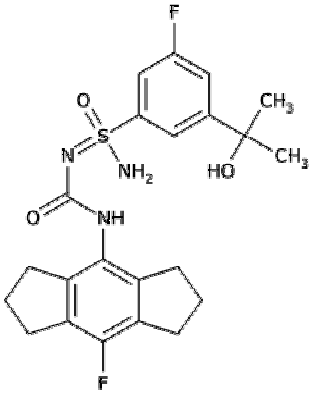
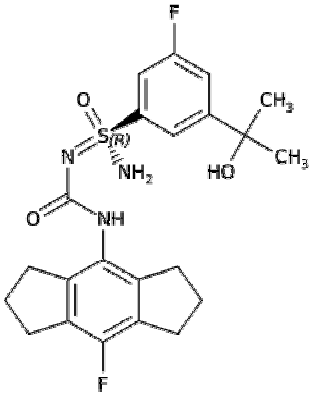
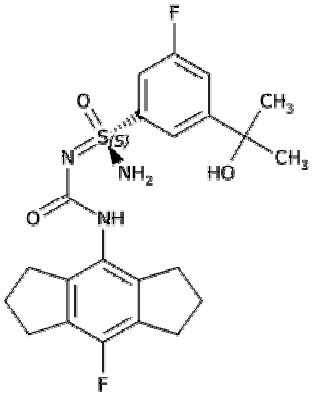
168b	
170a	
170b	

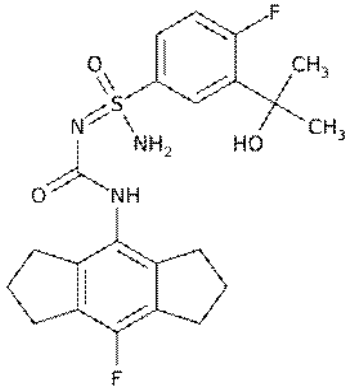
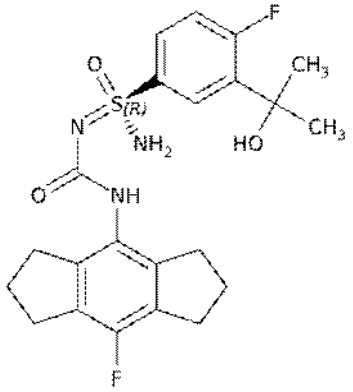
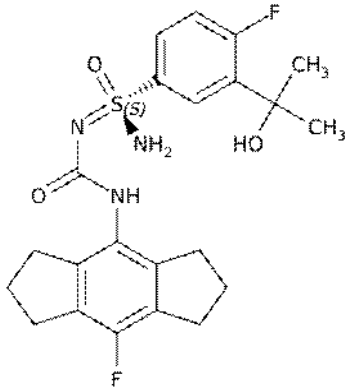
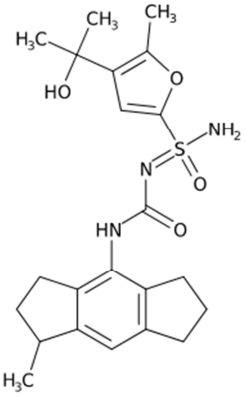
171a	
171b	
174a	
174b	

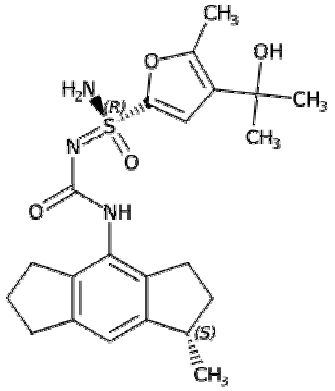
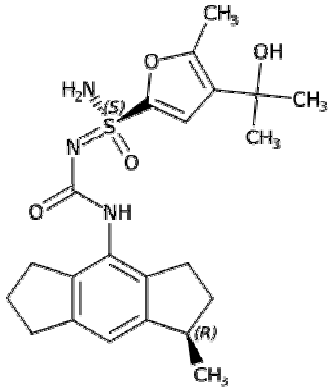
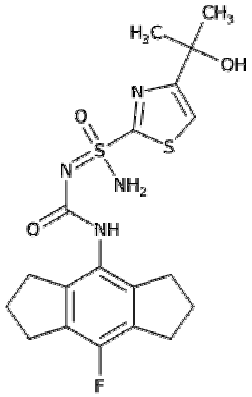
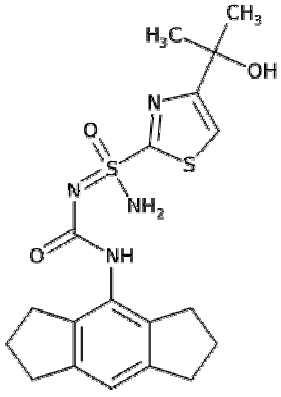
191a	
191b	
195	
195a	

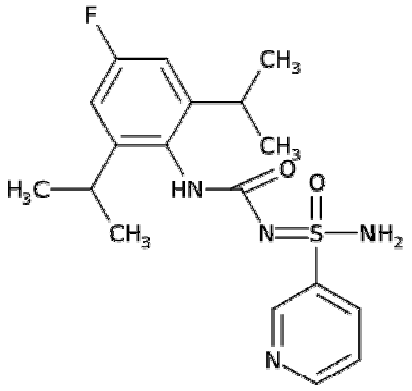
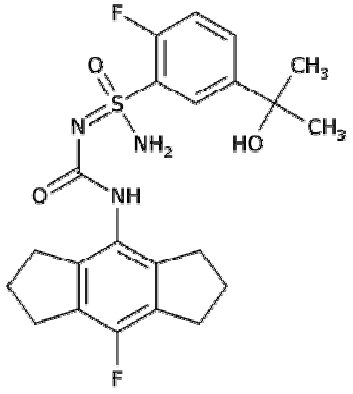
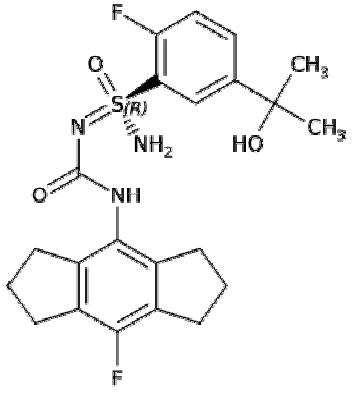
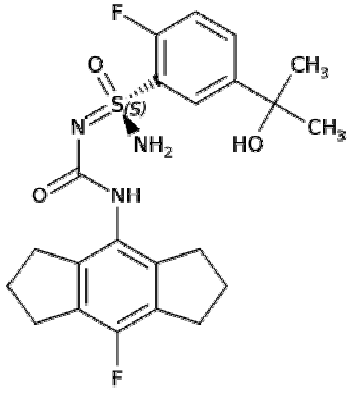
195ba	
195bb	
196	
197	

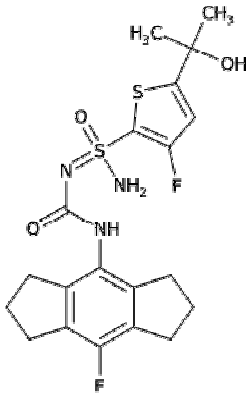
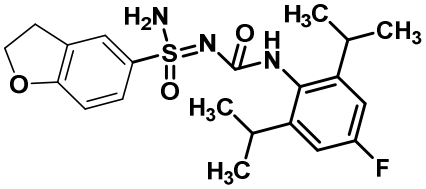
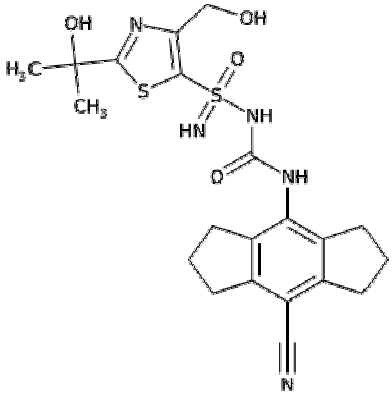
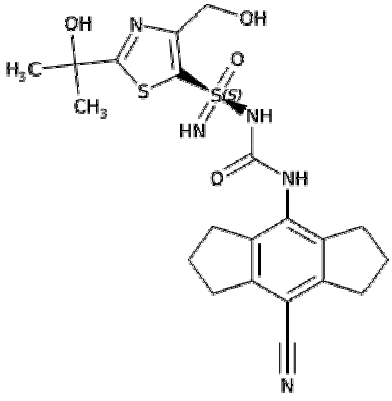
198	
200	
202	
202a	

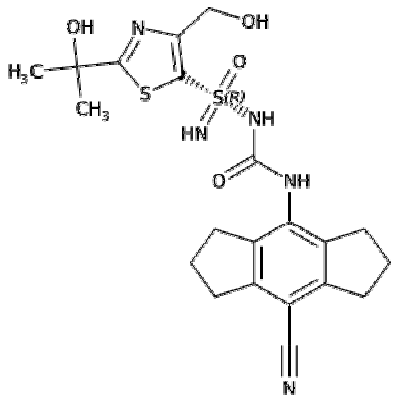
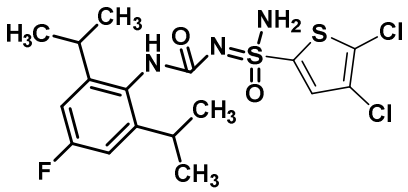
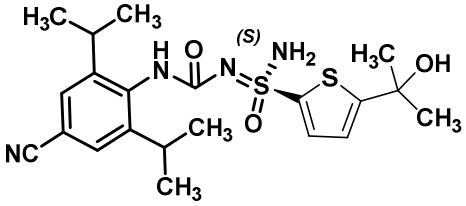
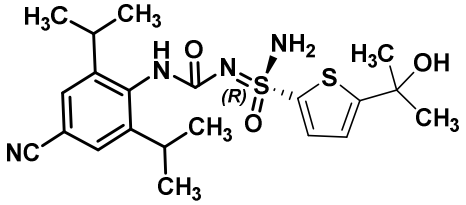
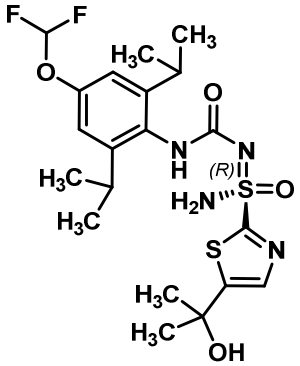
202b	
205	
205a	
205b	

206		
206a		
206b		
207		

207a	
207b	
208	
209	

211	
212	
212a	
212b	

213	
216	
220	
220a	

220b	
221	
223a	
223b	
225a	
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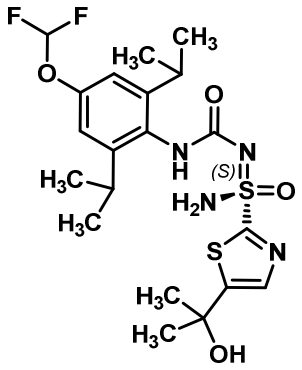
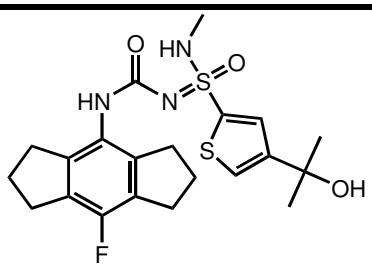
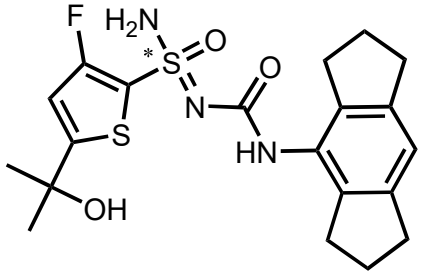
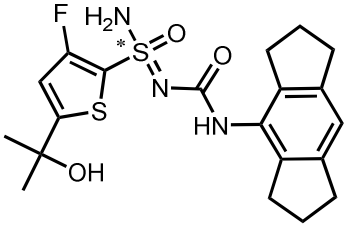
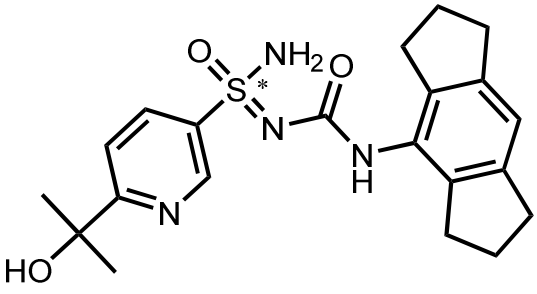
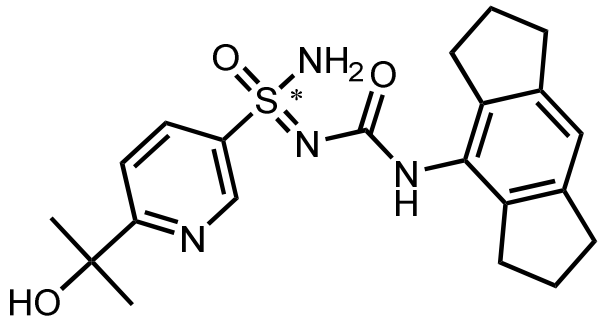
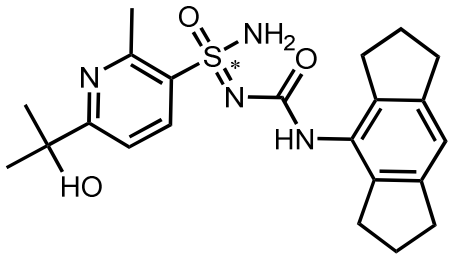
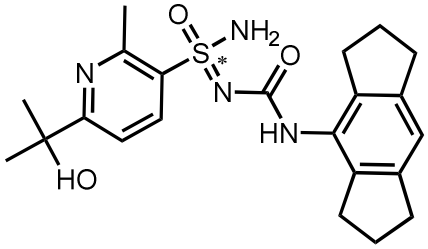
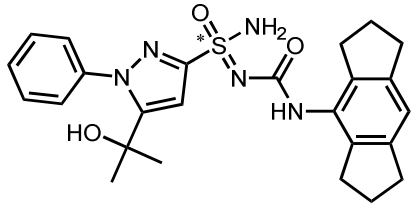
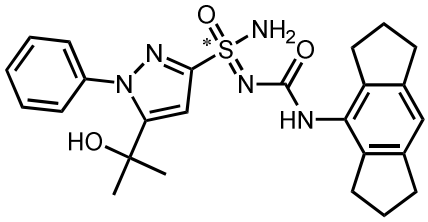
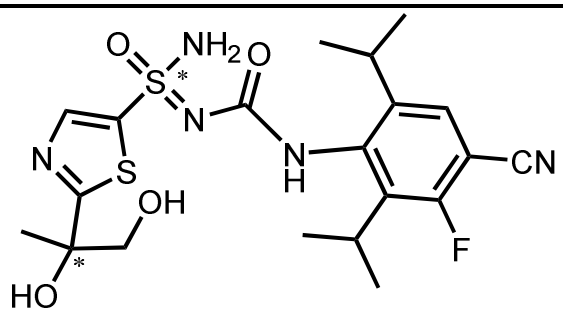
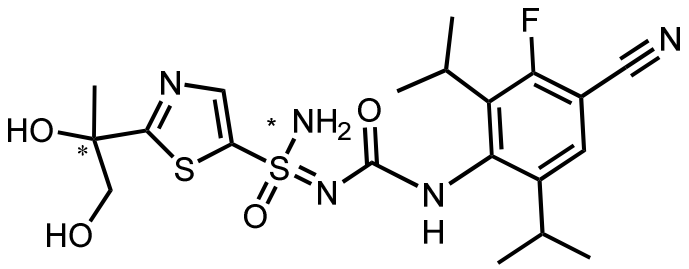
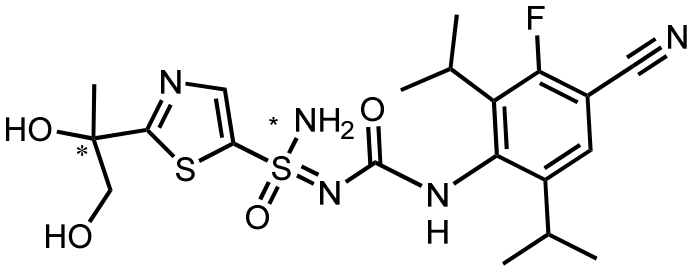
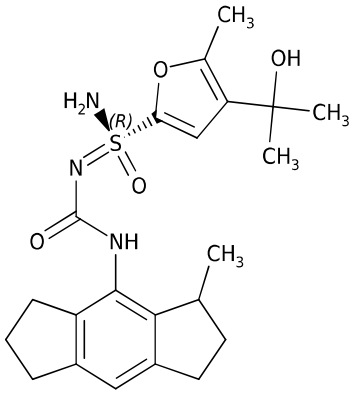
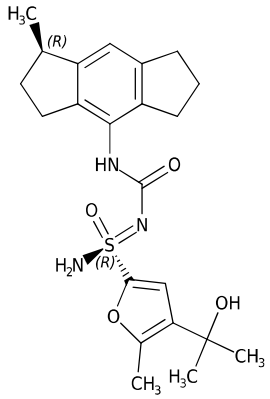
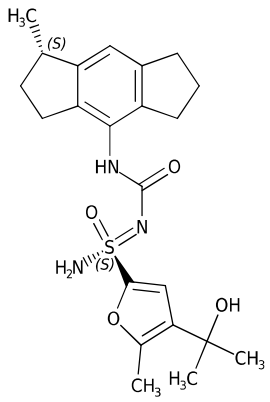
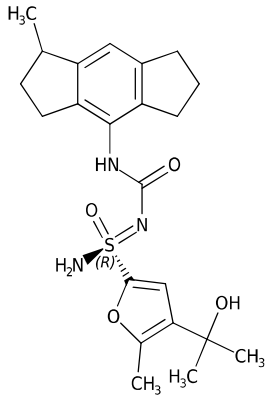
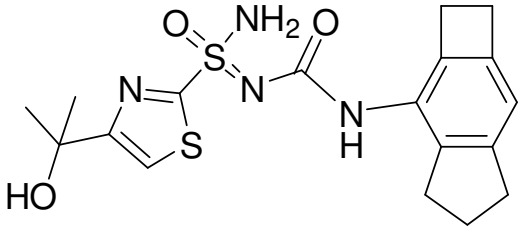
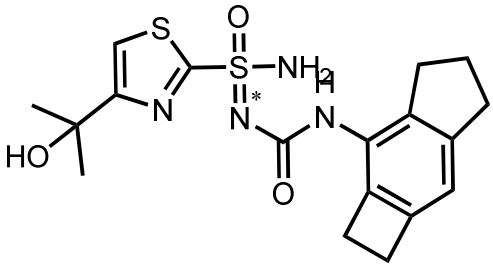
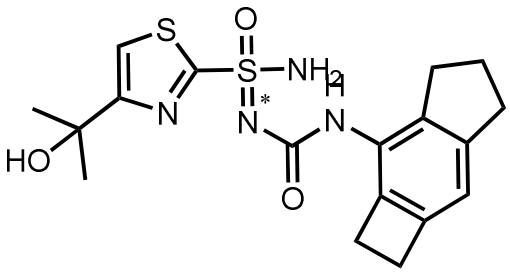
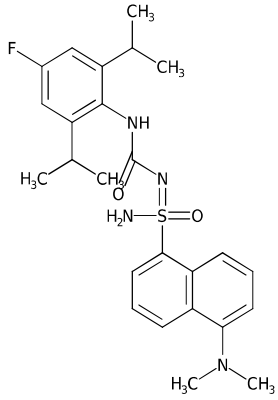
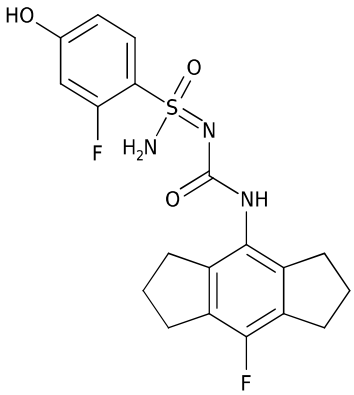
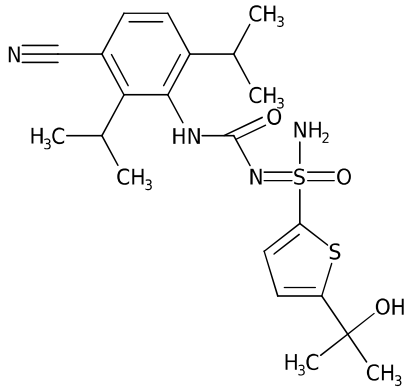
	
270	

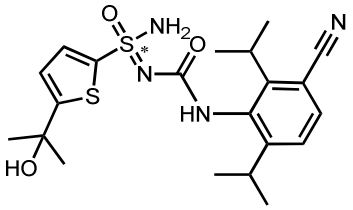
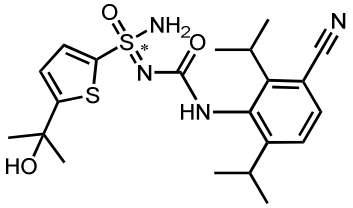
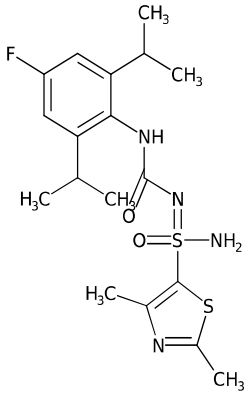
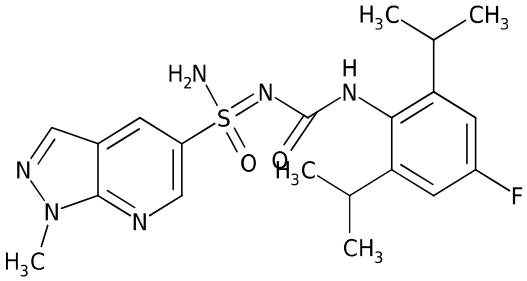
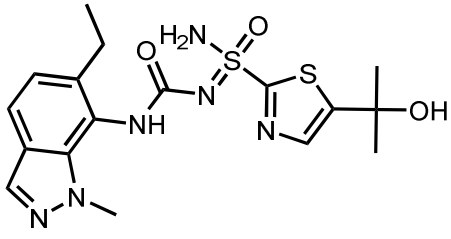
113a	
113b	
137a	

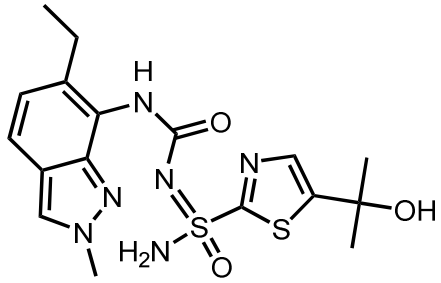
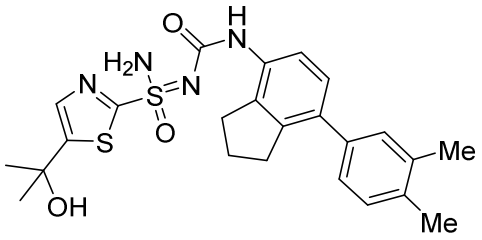
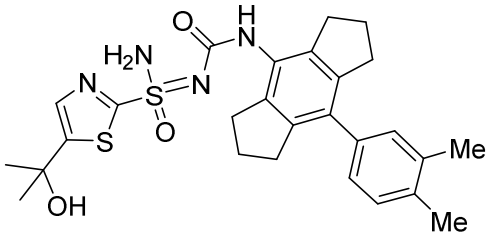
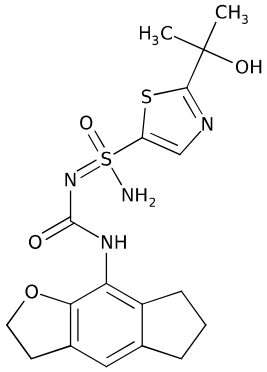
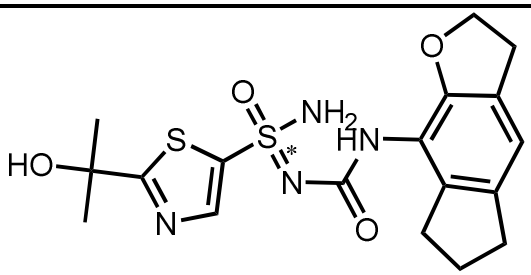
137b	
138a	
138b	
139a	
139b	
159a	

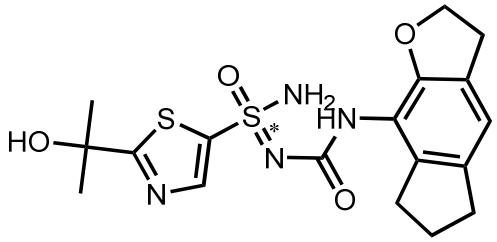
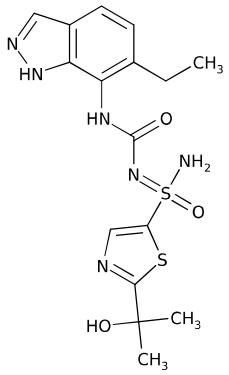
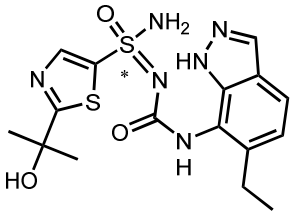
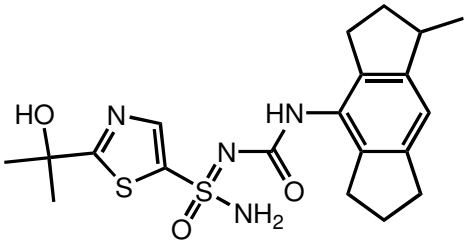
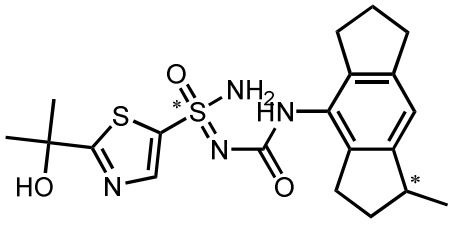
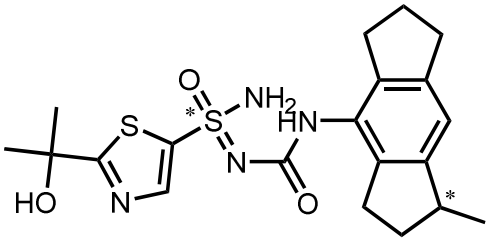
159ba	
159ab	
195e	
207bb	

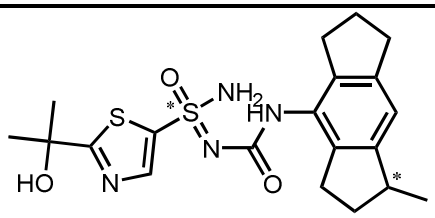
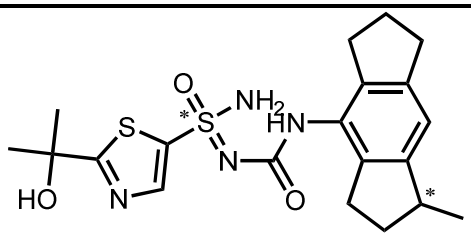
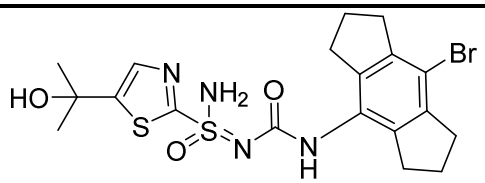
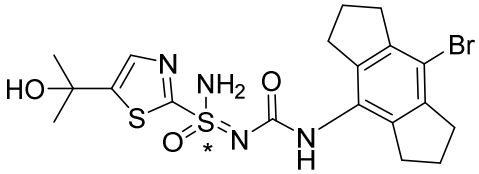
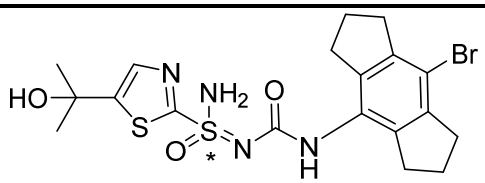
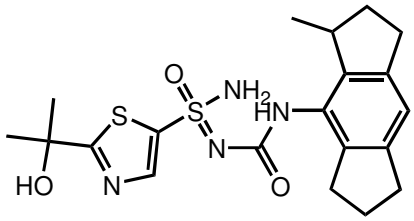
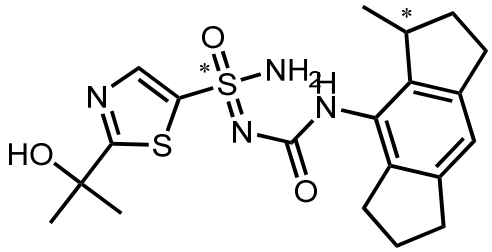
207aa	
207c	
303	
303a	

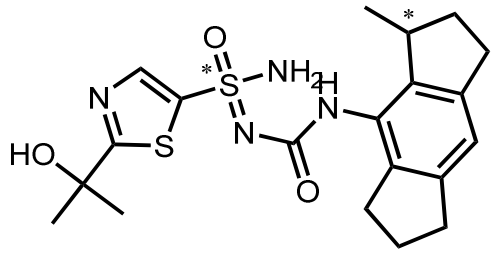
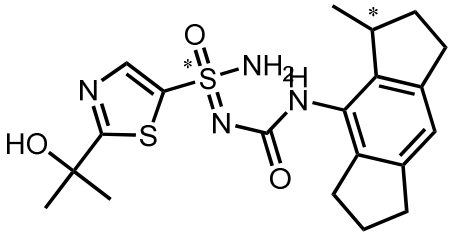
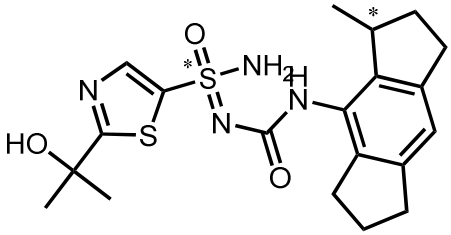
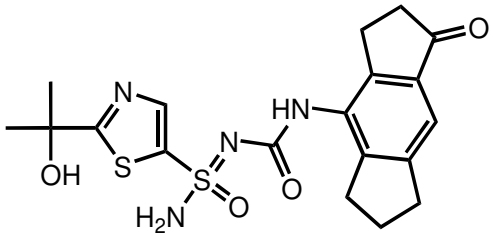
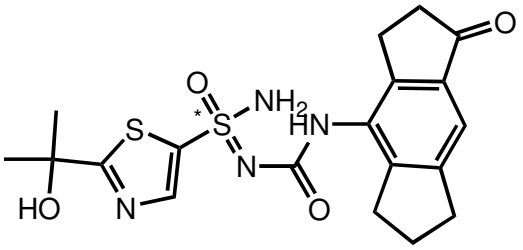
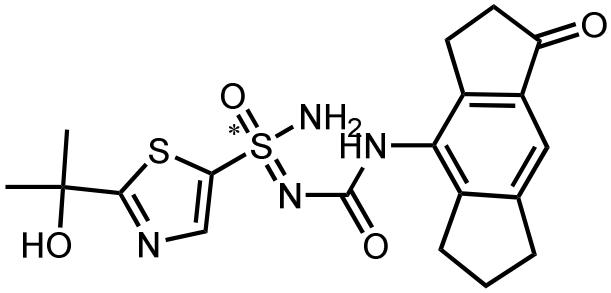
303b	
306	
307	
308	

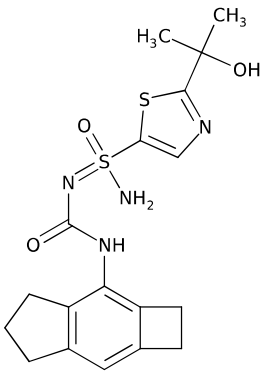
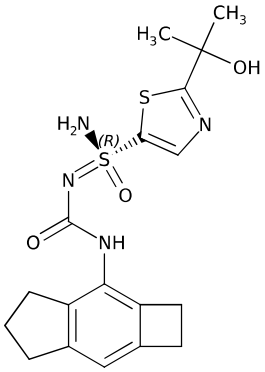
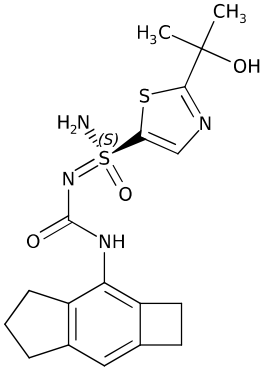
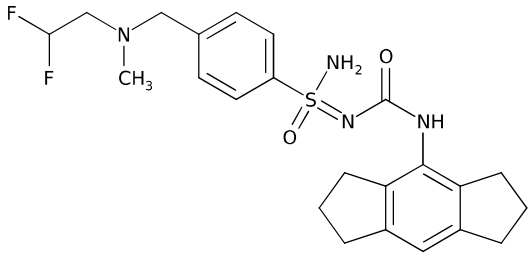
308a	
308b	
309	
310	
311	

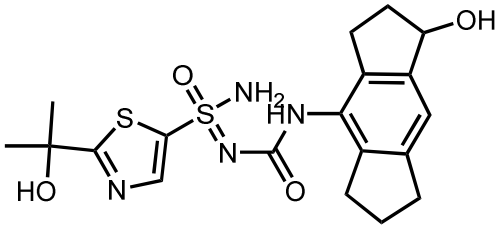
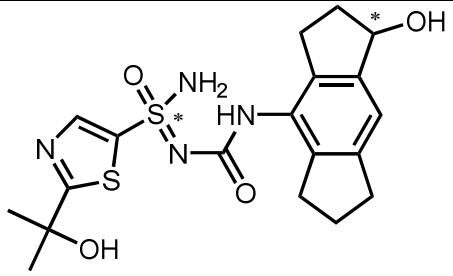
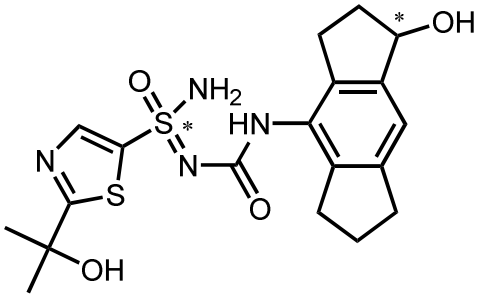
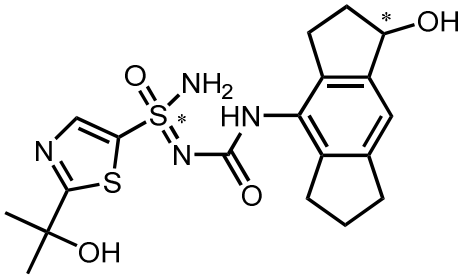
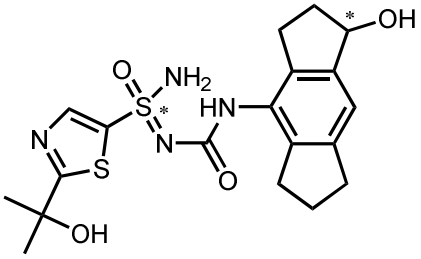
312	
313	
314	
315	
315b	

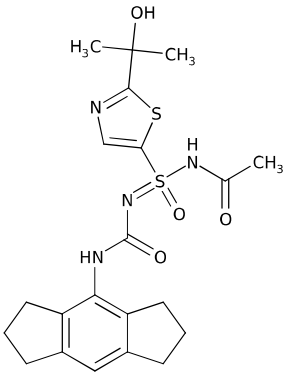
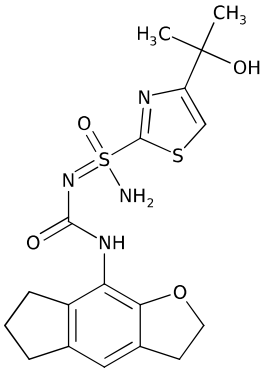
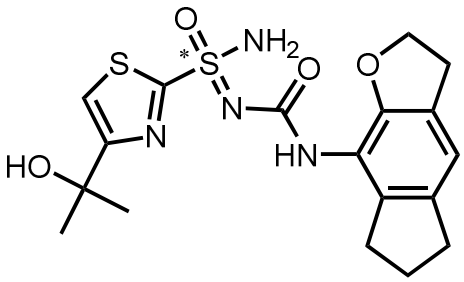
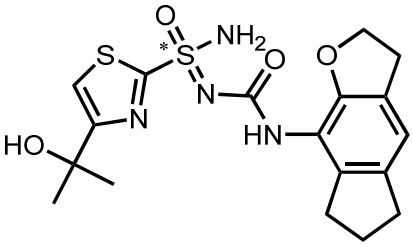
315a	
316	
316b	
317	
317ab	
317aa	

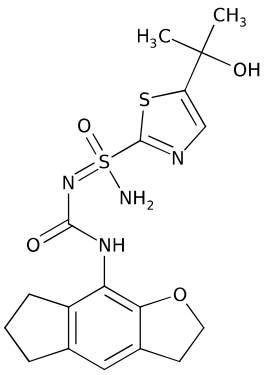
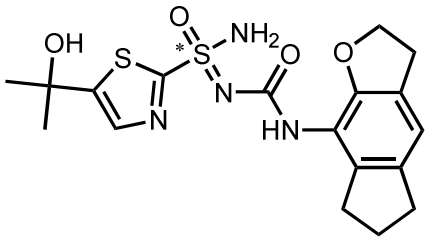
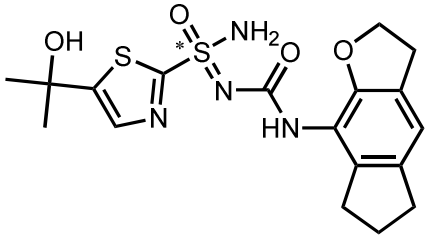
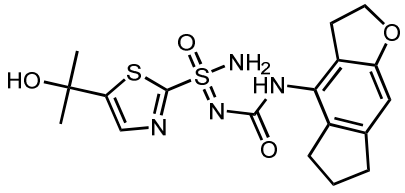
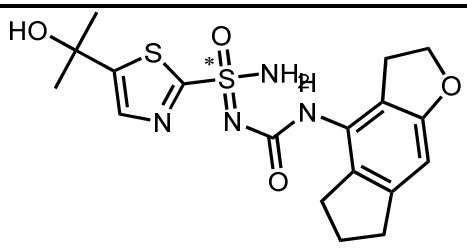
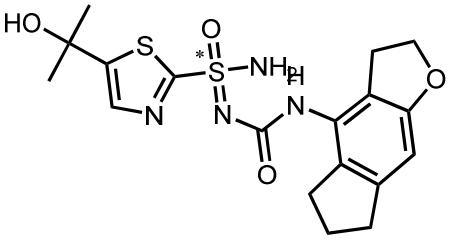
317bb	
317ba	
318	
318a	
318b	
319	
319ab	

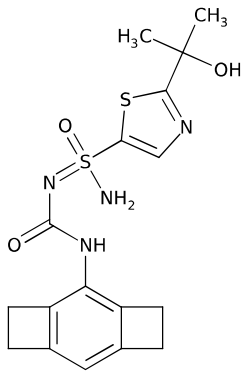
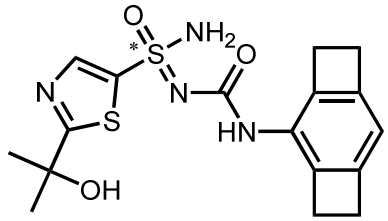
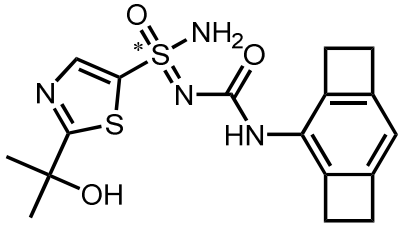
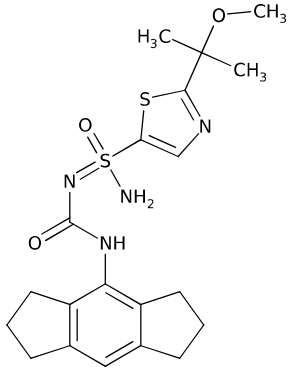
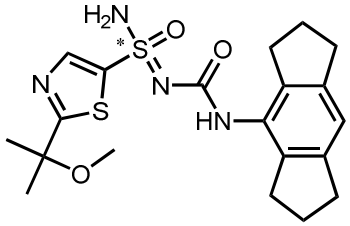
319ba	
319aa	
319bb	
320	
320a	
320b	

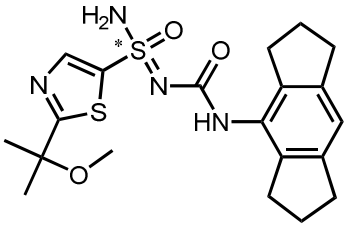
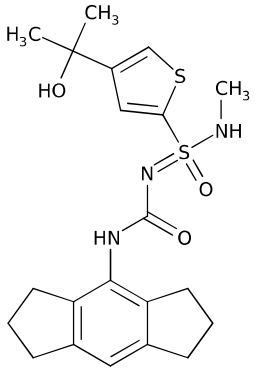
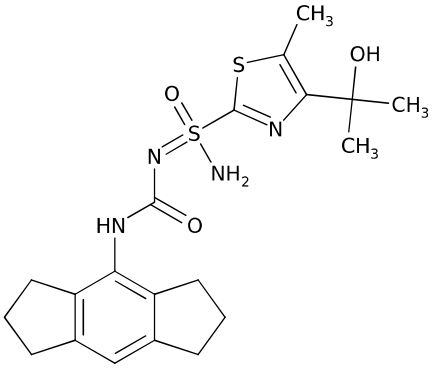
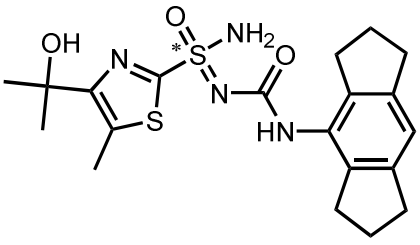
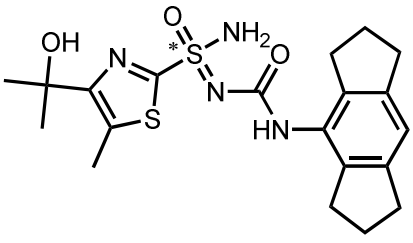
321	
321b	
321a	
322	

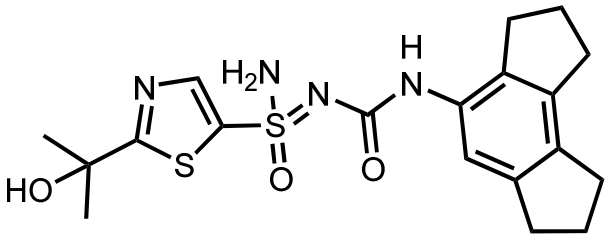
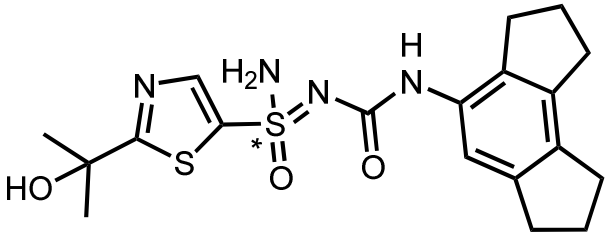
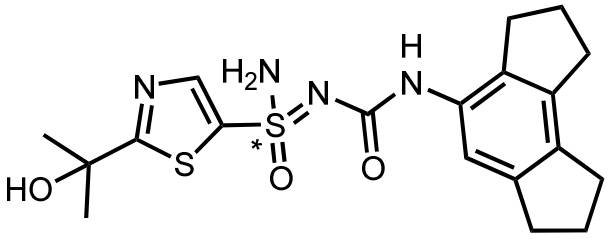
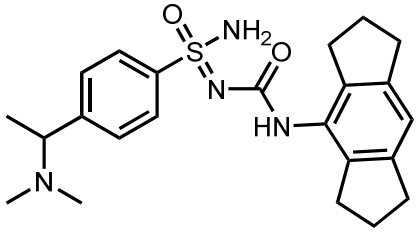
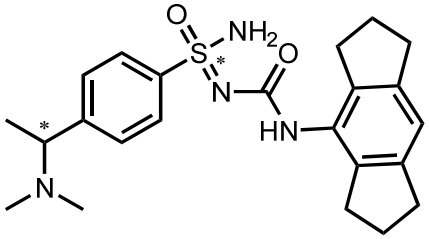
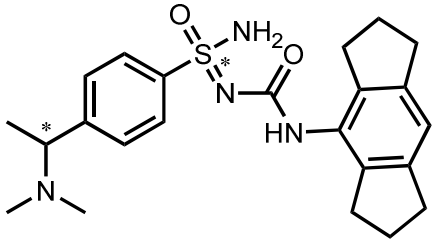
323	
323ab	
323aa	
323bb	
323ba	

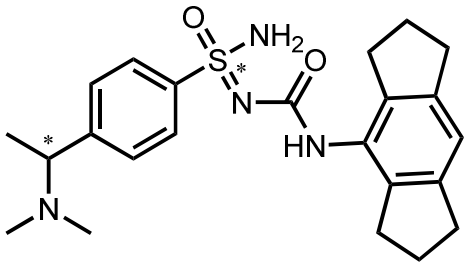
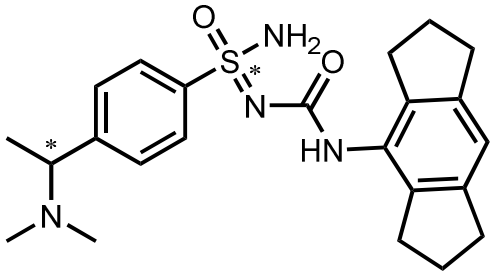
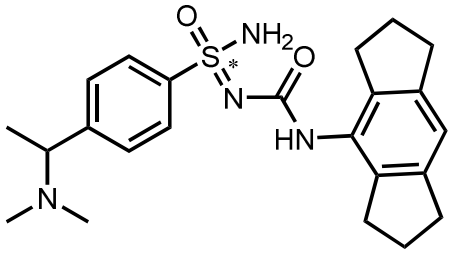
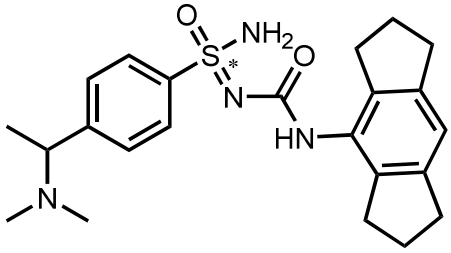
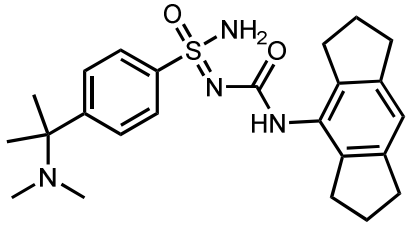
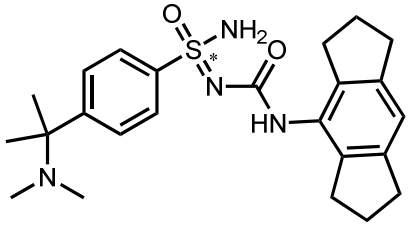
324	
325	
325a	
325b	

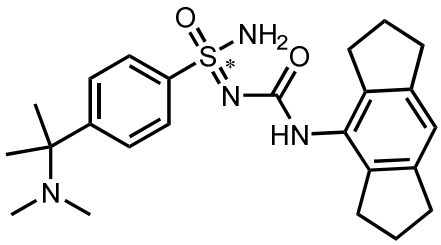
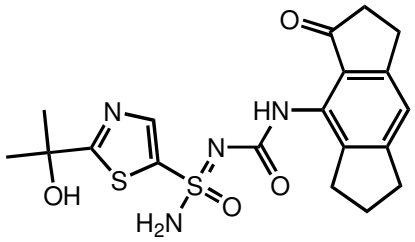
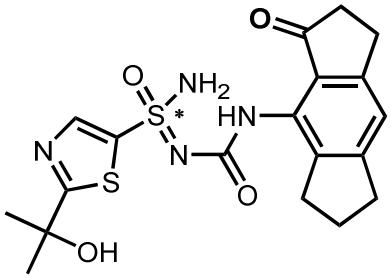
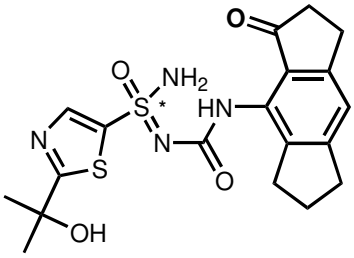
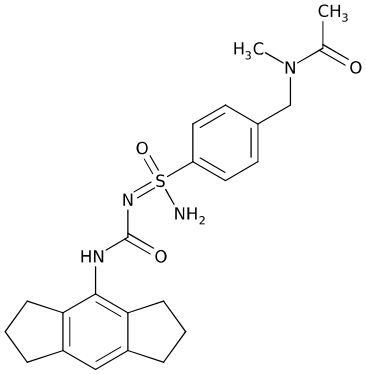
326	
326b	
326a	
327	
328b	
328a	

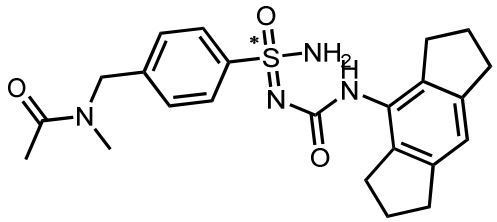
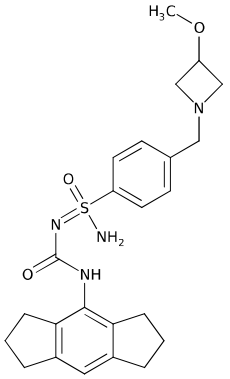
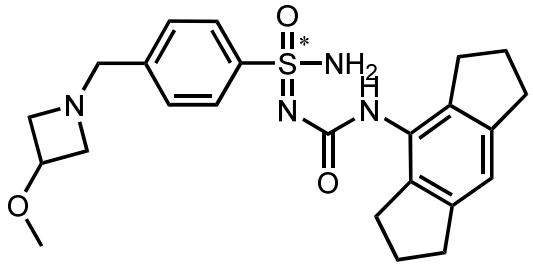
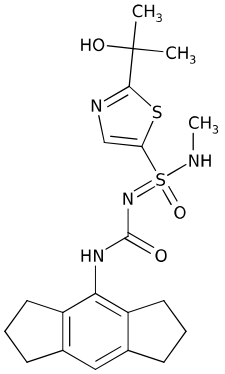
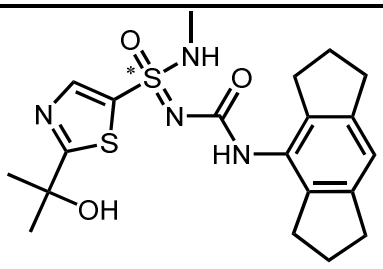
329	
329a	
329b	
330	
330a	

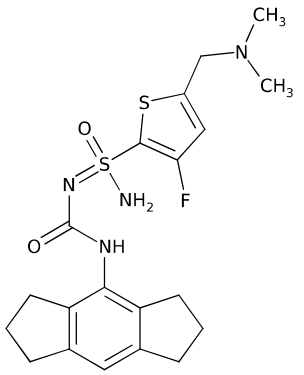
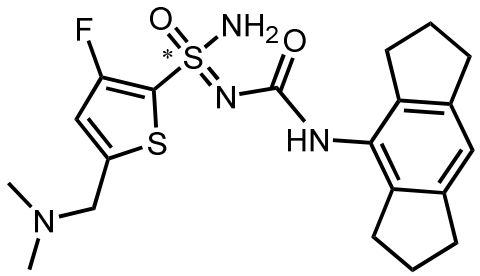
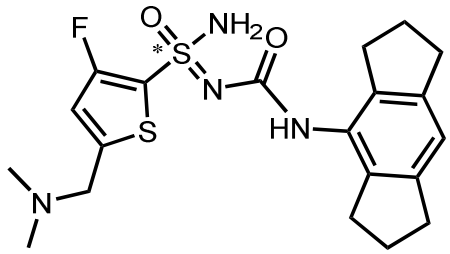
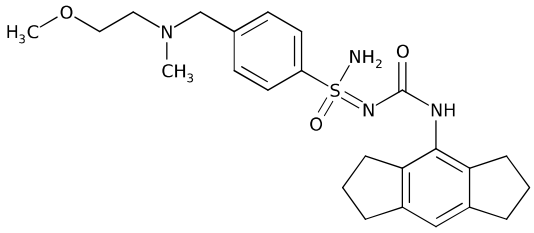
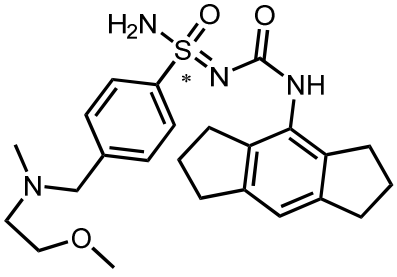
330b	
331	
332	
332a	
332b	

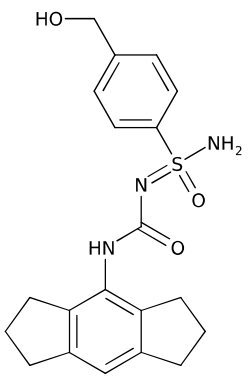
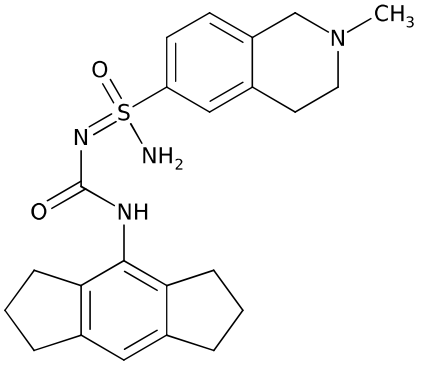
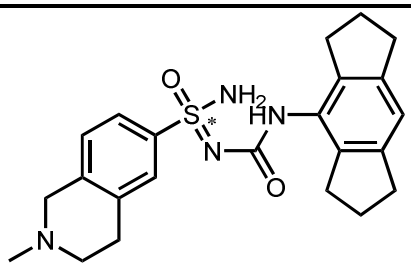
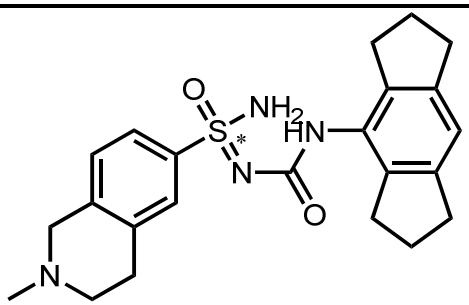
333	
333a	
333b	
334	
334ba	
334bb	

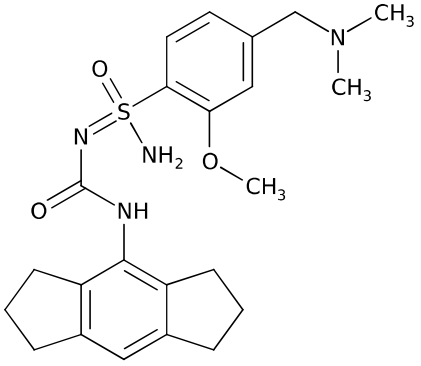
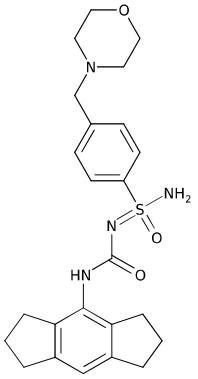
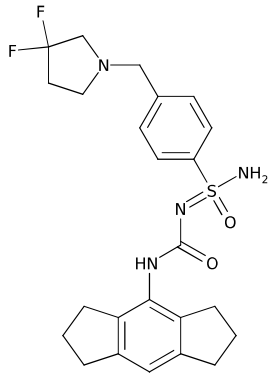
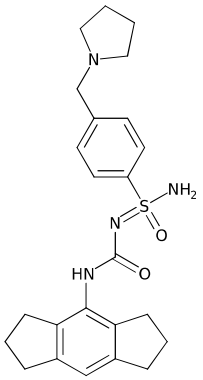
334aa	
334ab	
334b	
334a	
335	
335b	

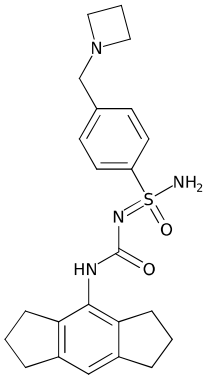
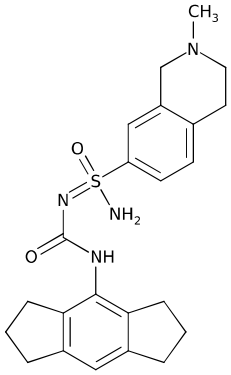
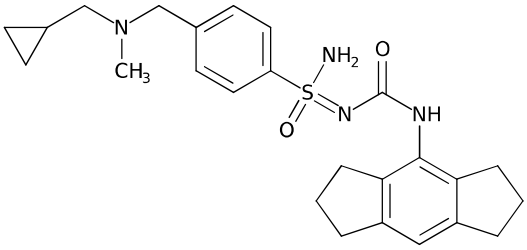
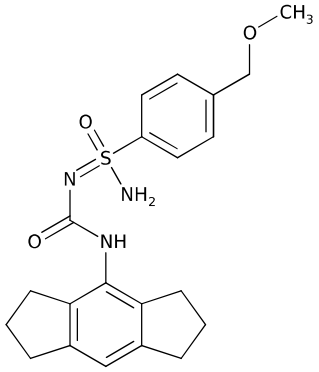
335a	
336	
336a	
336b	
337	

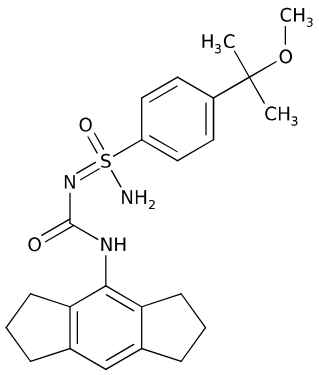
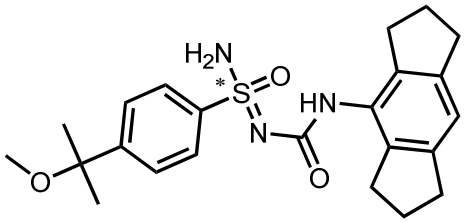
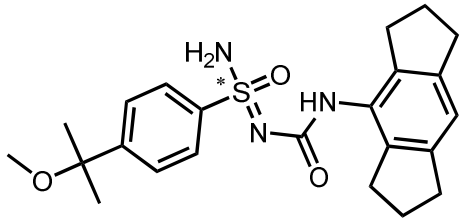
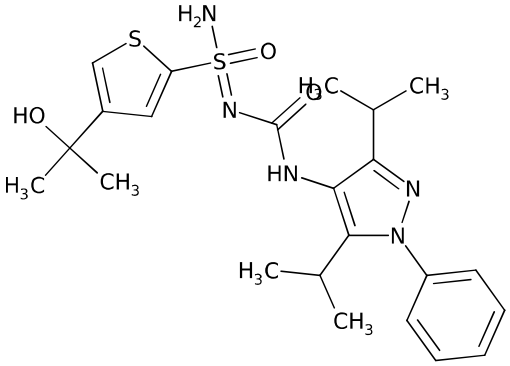
337b	
338	
338a	
339	
339a	

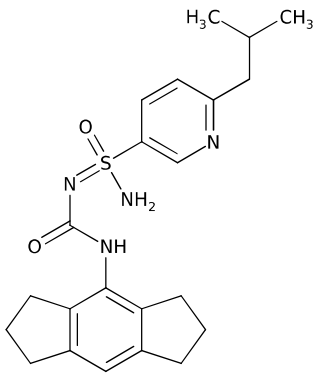
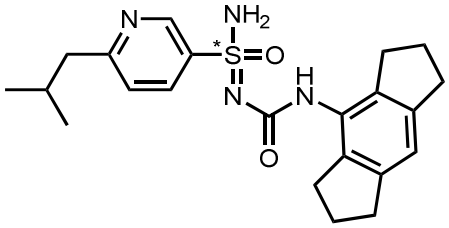
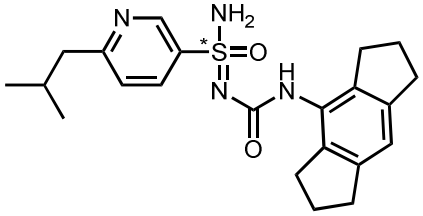
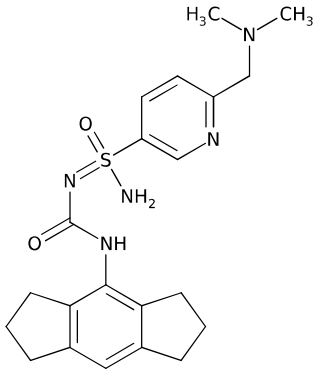
340	
340a	
340b	
341	
341b	

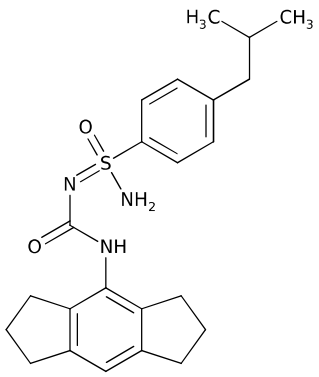
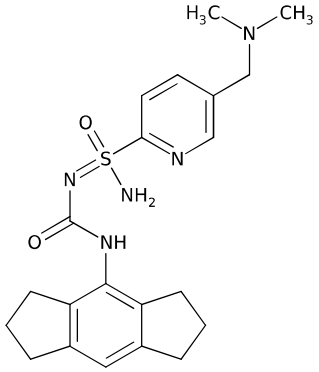
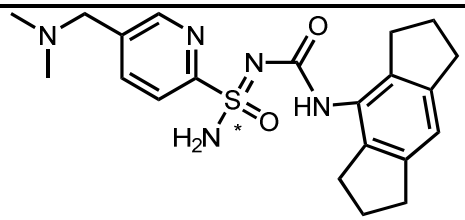
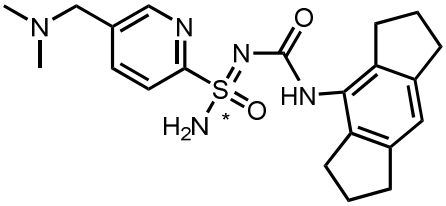
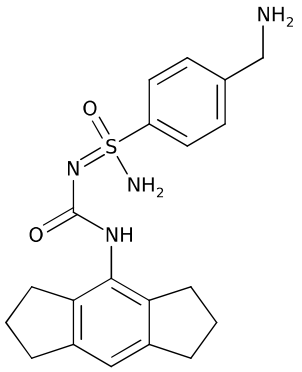
342	
343	
343a	
343b	

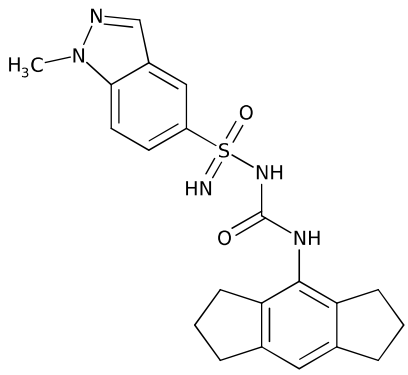
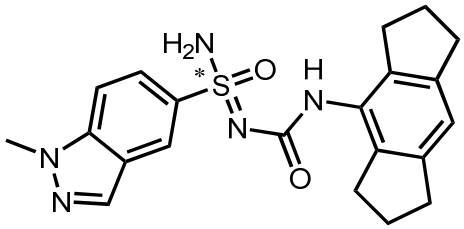
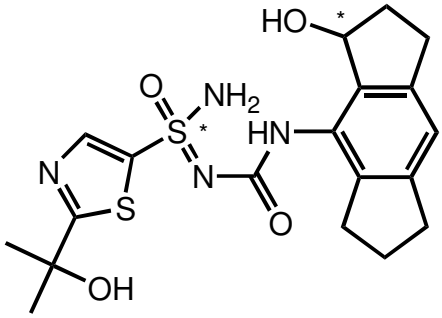
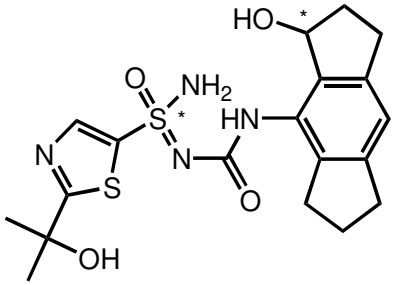
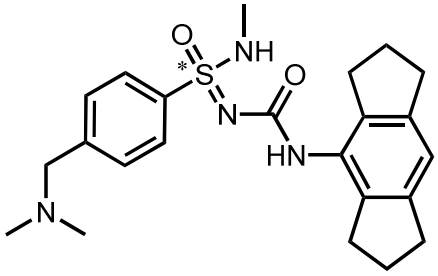
344	
345	
346	
347	

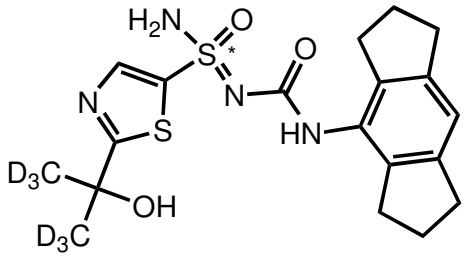
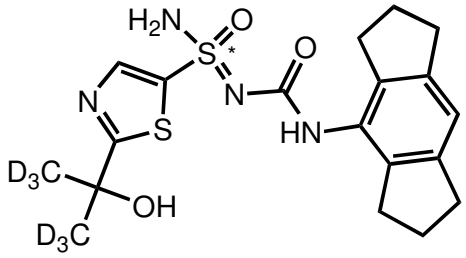
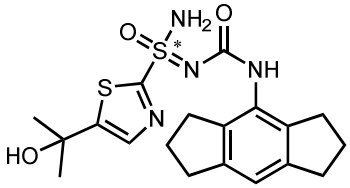
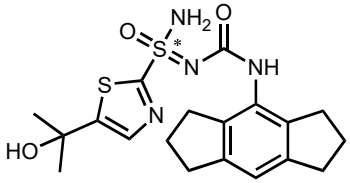
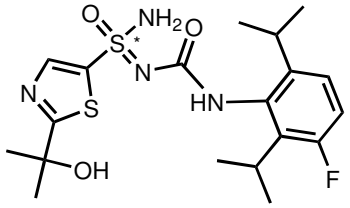
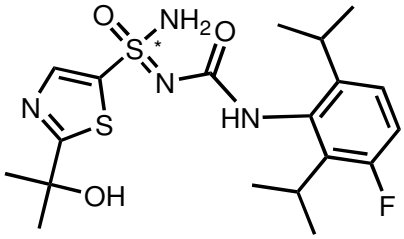
348	
349	
350	
351	

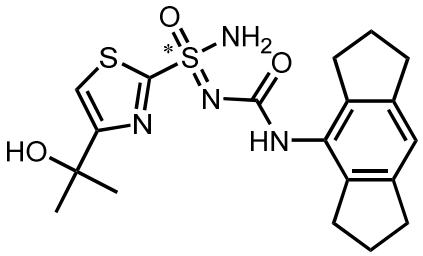
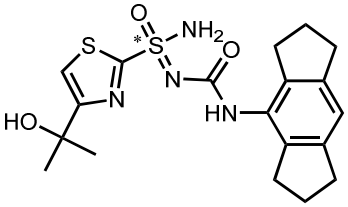
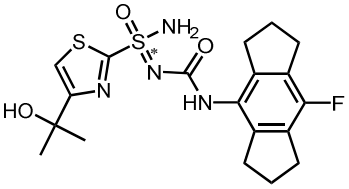
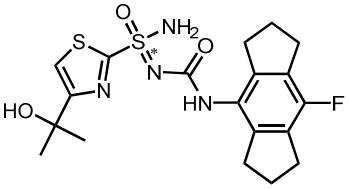
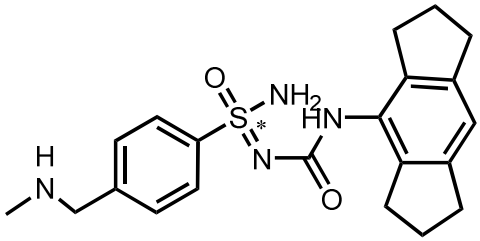
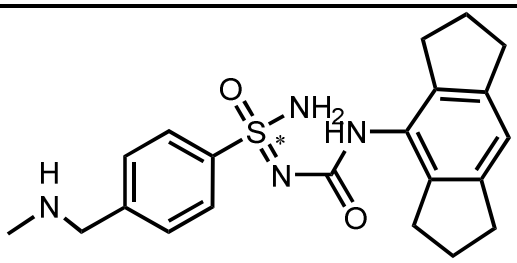
352	
352b	
352a	
353	

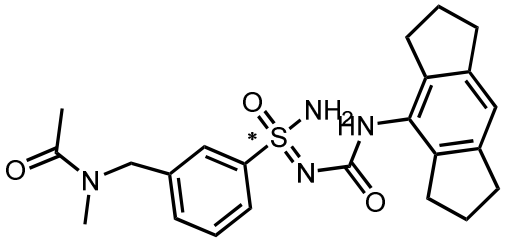
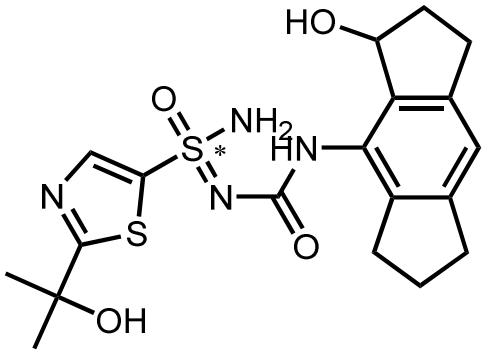
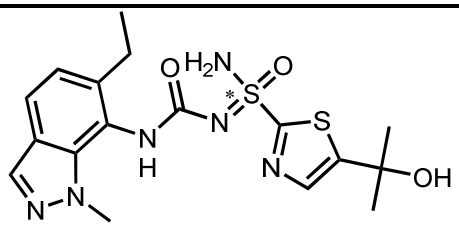
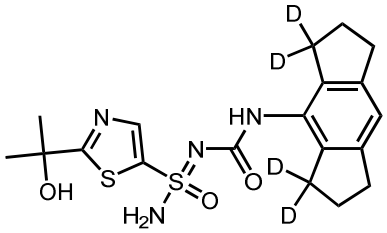
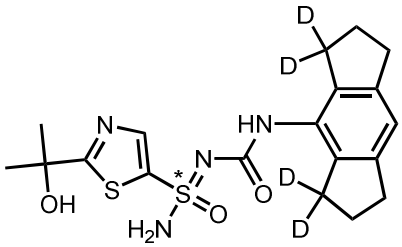
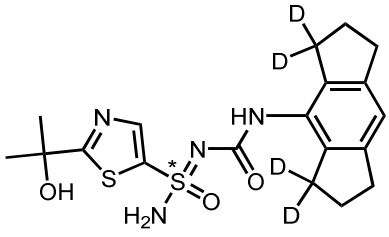
354	
354a	
354b	
355	

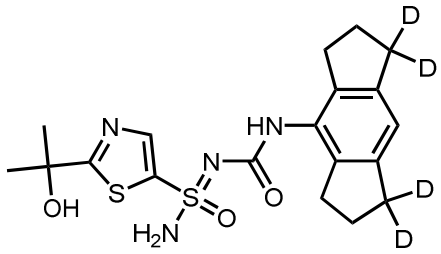
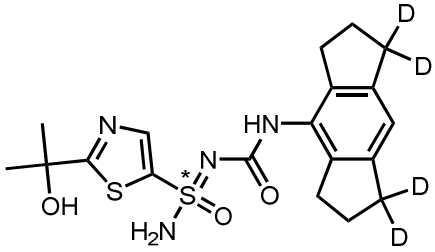
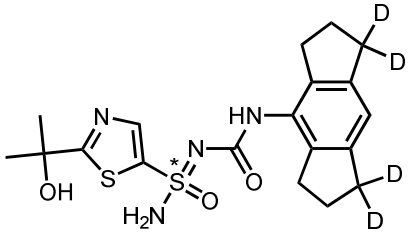
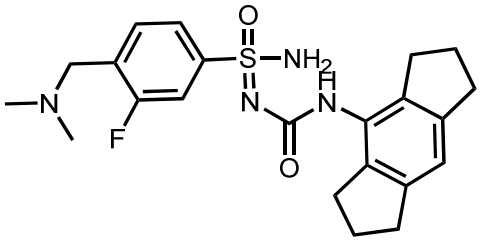
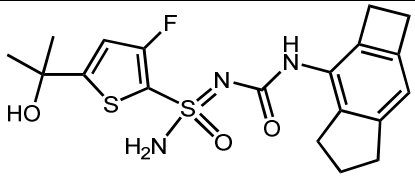
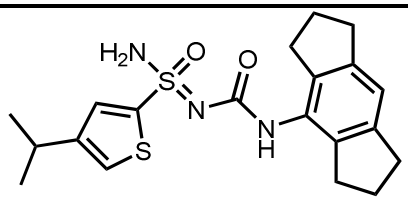
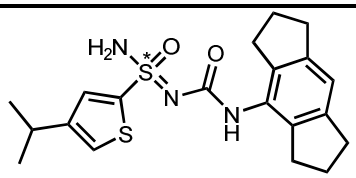
356	
357	
357a	
357b	
358	

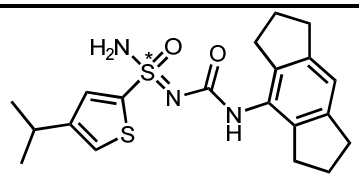
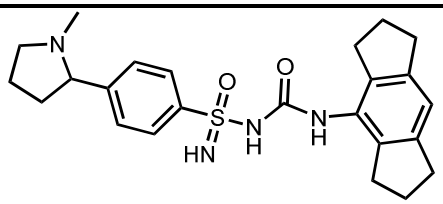
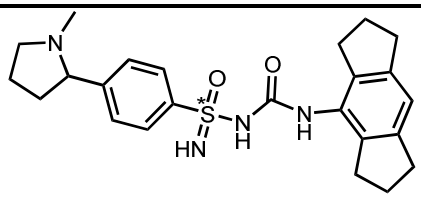
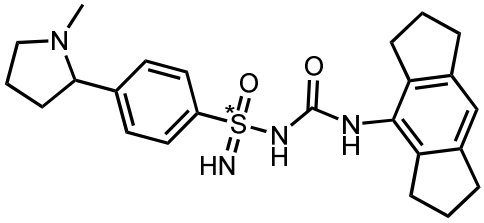
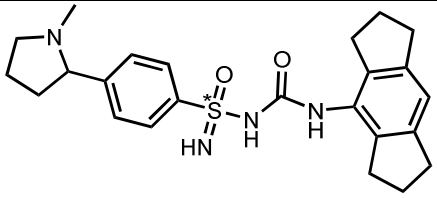
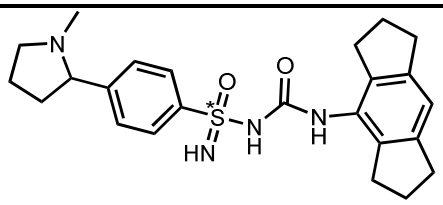
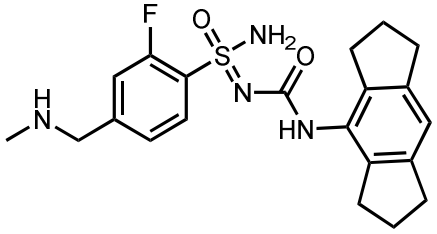
359	
359a	
360ba	
360bb	
361b	

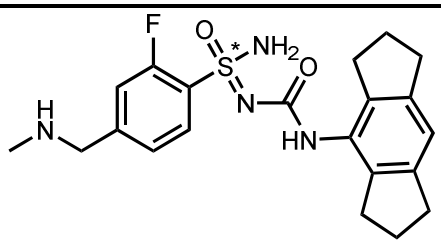
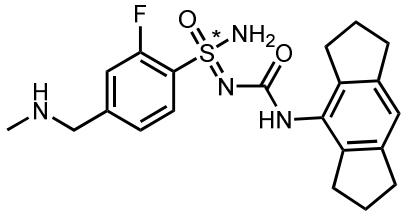
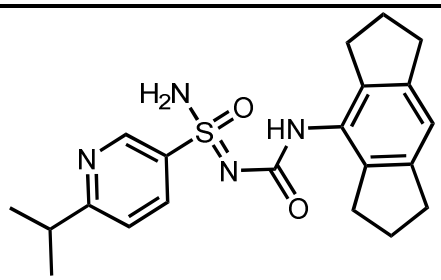
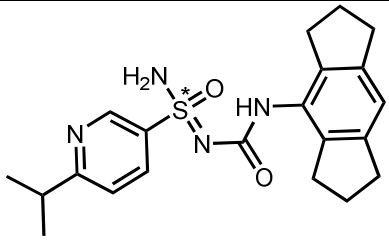
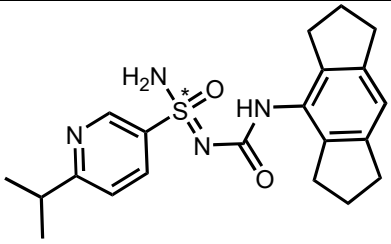
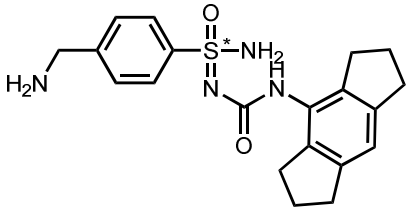
363b	
363a	
364a	
364b	
365a	
365b	

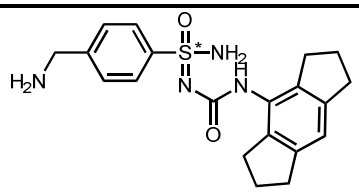
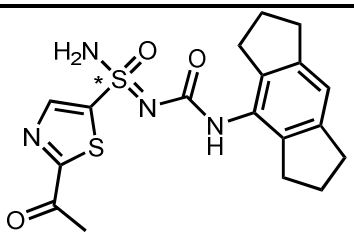
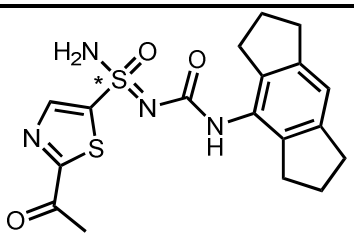
366a	
366b	
367a	
367b	
369a	
369b	

371b	
372b	
373b	
375	
375a	
375b	

376	
376a	
376b	
377	
378	
379	
379a	

379b	
380	
380a	
380b	
380c	
380d	
382	

382a	
382b	
383	
383a	
383b	
384a	

384b	
387a	
387b	

and pharmaceutically acceptable salts thereof.

13. The compound of any one of the preceding claims, wherein the sulfur in the moiety $S(=O)(NHR^3)=N-$ has (S) stereochemistry.

14. The compound of any one of claims 1 to 12, wherein the sulfur in the moiety $S(=O)(NHR^3)=N-$ has (R) stereochemistry.

15. A pharmaceutical composition comprising a compound or salt as claimed in any one of claims 1 to 14 and one or more pharmaceutically acceptable excipients.

16. The compound of any preceding claim 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.

17. The compound for use according to claim 16 wherein said use is for the treatment of a 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.

18. The compound for use according to claim 16 or 17, further comprising administering a therapeutically effective amount of an anti-TNFα agent to the subject; optionally wherein:

the NLRP3 antagonist is administered to the subject prior to administration of the anti-TNFα agent to the subject; or

wherein the anti-TNFα agent is administered to the subject prior to the administration of the NLRP3 antagonist to the subject; or

wherein the NLRP3 antagonist and the anti-TNFα agent are administered to the subject at substantially the same time.