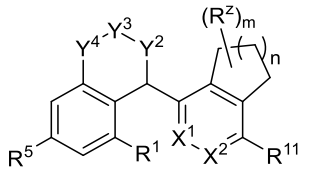
CLAIMS:

1. A compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof having a structure of Formula (IV-b):



(IV-b)

wherein

the subscript m is 1, 2, 3, 4, 5, 6, 7, or 8;

the subscript n is 1 or 2;

R^z represents one or more of R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, and R^{19};

Y^2, Y^3, and Y^4 are each CR^2R^3;

R^1 is selected from the group consisting of halogen, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $-S(O)_2R^a$, and $-C(O)NR^aR^b$;

each R^2 and R^3 are each independently selected from the group consisting of H, halogen, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-4} alkoxyC_{1-4}alkyl, C_{3-8} cycloalkyl, $-S(O)_2R^a$, and $-C(O)NR^aR^b$;

R^5 is selected from the group consisting of H, halogen, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl, $-S(O)_2R^a$, $-C(O)NR^aR^b$, and $-S(O)_2NR^aR^b$;

X^1 is N or CR^{8a};

X^2 is N or CR^{8b};

R^{8a} and R^{8b} are independently selected from the group consisting of H, halogen, CN, NH_2, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-4} alkoxyC_{1-4}alkyl, C_{3-6} cycloalkyl, $-C(O)NR^aR^b$, $-S(O)_2NR^aR^b$, and $-S(O)_2R^a$;

R^{11} is selected from the group consisting of halogen, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} hydroxyhaloalkyl, C_{1-4} alkoxyC_{1-4}alkyl, C_{3-8} cycloalkyl, $-NR^cR^b$, $-C(O)NR^cR^b$, $-C(O)OH$, $-S(O)_2NR^cR^b$, $-S(O)(=NH)R^c$, $-S(O)_2R^c$, phenyl, 5- to 6-membered heterocyclic or 5- to 10-membered heteroaryl ring, wherein the heterocyclic and heteroaryl rings have from 1-3 heteroatoms as ring vertices selected from N, O, and S; wherein the phenyl is optionally fused to a 5- or 6-membered heterocycle having from 1-2 heteroatoms as ring vertices selected from N, O, and S; and

wherein the phenyl, heterocyclic or heteroaryl rings are optionally substituted with from one to three members independently selected from halogen, CN, NO_2, NH_2, $C(O)NH_2$, $S(O)_2CH_3$, $-CH_2NH_2$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} hydroxyhaloalkyl, and C_{1-4} alkoxyC_{1-4}alkyl; optionally wherein two members attached to the same carbon of the heterocyclic ring taken together form $=CH_2$ or oxo (=O);

each of R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, and R^{19} is independently selected from the group consisting of H, halogen, CN, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyC_{1-4}alkyl, and $-NR^aR^b$; or two R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, and R^{19} moieties on the same carbon atom combine to form oxo;

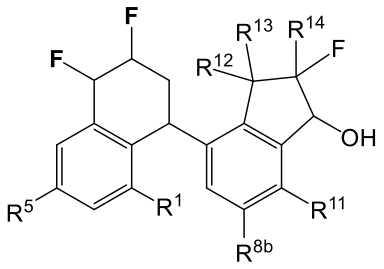
each R^a and R^b is independently selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, and C_{1-8} hydroxyalkyl; and

R^c, when present, is selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{1-8} hydroxyalkyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocycloalkyl, and 5- or 6- membered heteroaryl, wherein the heterocycloalkyl or heteroaryl ring each have from 1-4 heteroatoms as ring vertices selected from N, O, and S.

2. The compound of claim **1**, wherein R^{11} is a phenyl, 5- or 6-membered heterocyclic ring, or 5- to 10-membered heteroaryl ring, wherein the heterocyclic or heteroaryl ring has from 1-3 heteroatoms as ring vertices selected from N, O, and S; wherein the phenyl is optionally fused to a 5- or 6-membered heterocycle having from 1-2 heteroatoms as ring vertices selected from N, O, and S; and wherein the phenyl, heterocyclic, or heteroaryl ring is optionally substituted with from one to three members independently selected from halogen, CN, NO_2, NH_2, $C(O)NH_2$, $S(O)_2CH_3$, $-CH_2NH_2$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} hydroxyhaloalkyl, and C_{1-4} alkoxyC_{1-4}alkyl; optionally wherein two members attached to the same carbon of the heterocyclic ring taken together form $=CH_2$ or oxo (=O).

3. The compound of claim **1** or claim **2**, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein Y^2 is CR^2R^3, wherein each R^2 and R^3 is H; and Y^3 and Y^4 are each CR^2R^3, wherein each R^2 and R^3 are independently selected from H and F.

4. The compound of any one of claims **1**-**3**, or a pharmaceutically acceptable salt, hydrate or solvate thereof having a structure of Formula (IV-f):



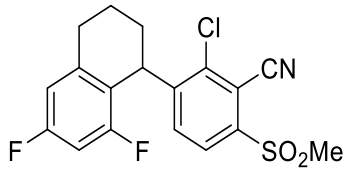
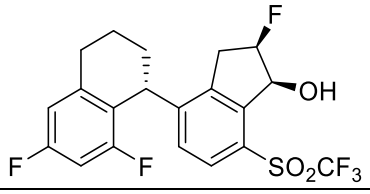
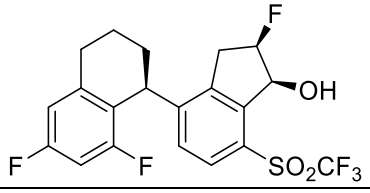
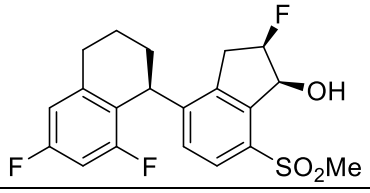
(IV-f).

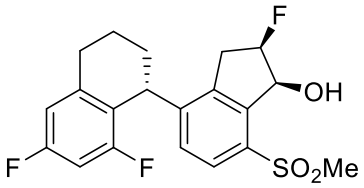
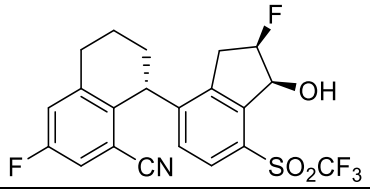
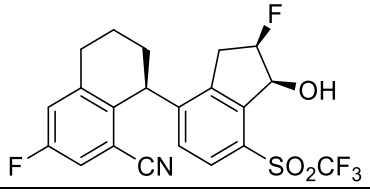
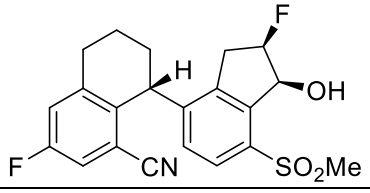
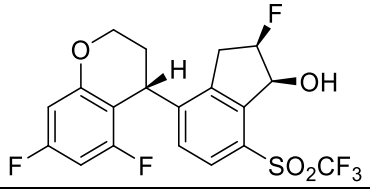
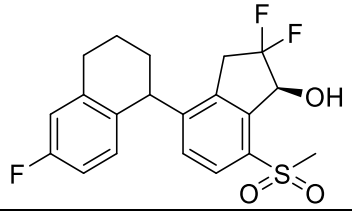
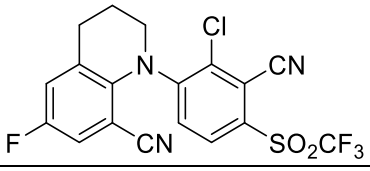
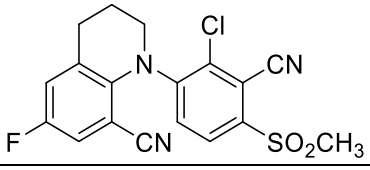
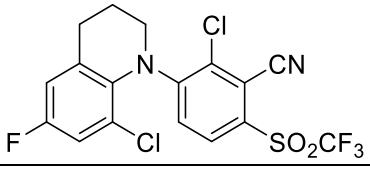
5. The compound of claim **4**, wherein R^{8b} is H.

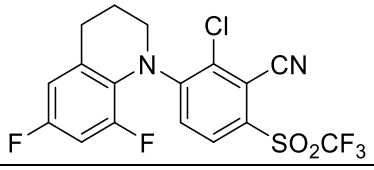
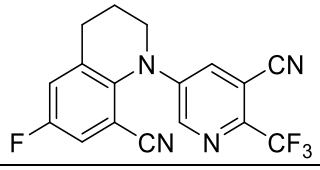
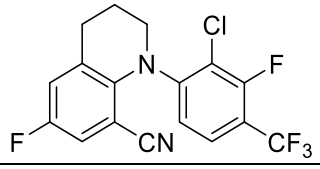
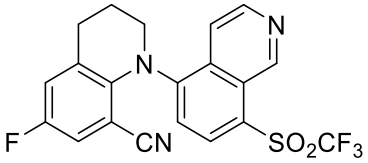
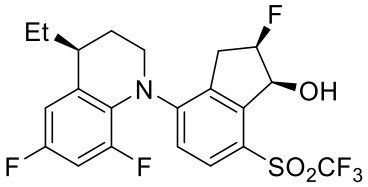
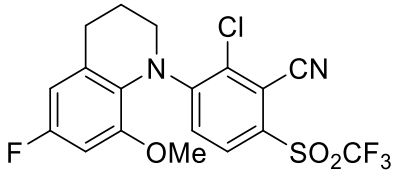
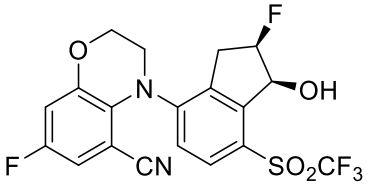
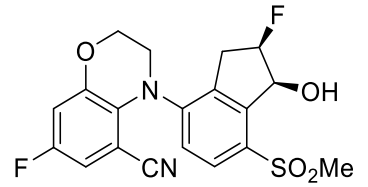
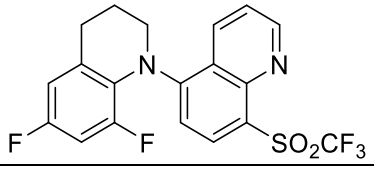
6. The compound of any one of claims **1**-**5**, wherein R^{11} is $-S(O)_2R^c$ and R^c is C_{1-8} alkyl or C_{1-8} haloalkyl.

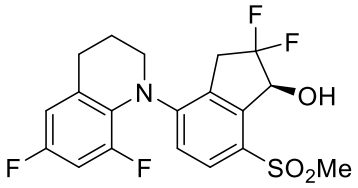
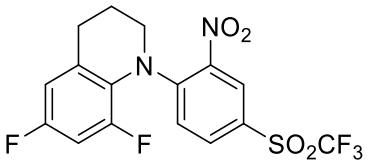
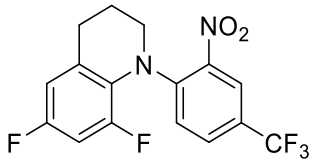
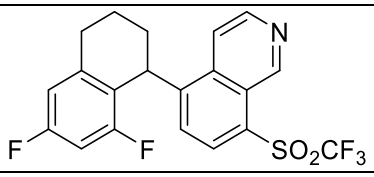
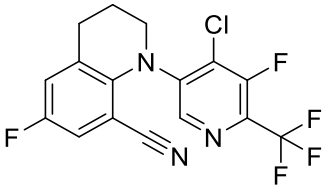
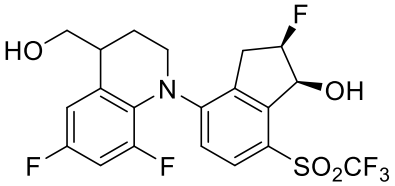
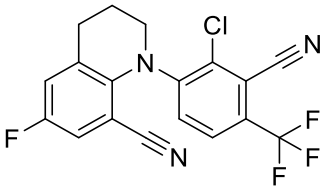
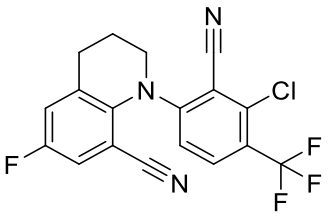
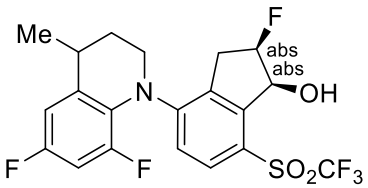
7. The compound of any one of claims **1**-**6**, wherein R^1 is selected from the group consisting of halogen and CN.

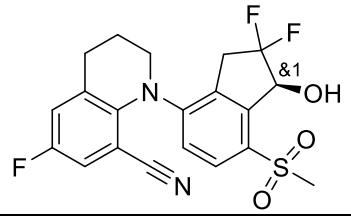
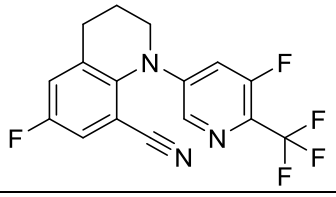
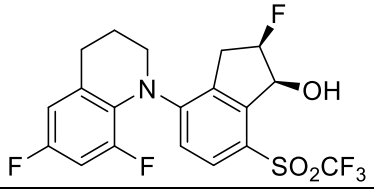
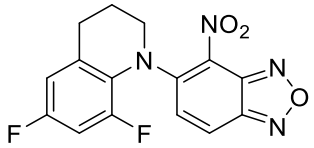
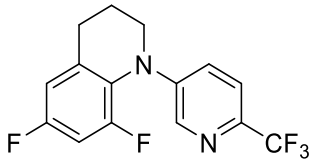
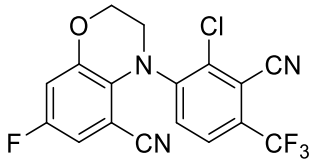
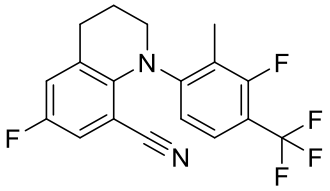
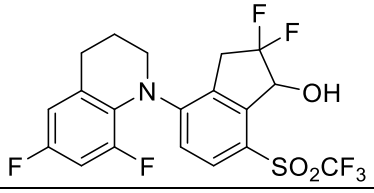
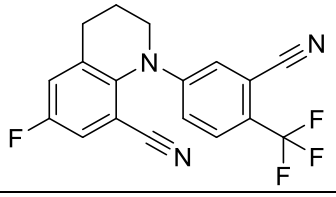
8. A compound selected from the group consisting of:

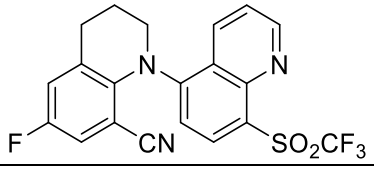
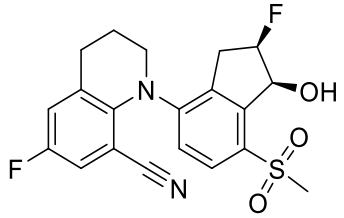
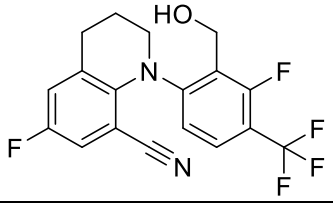
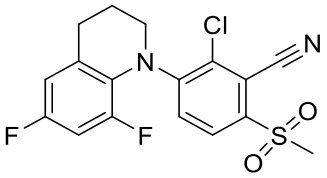
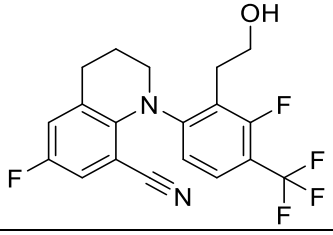
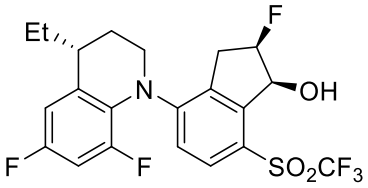
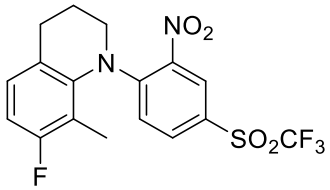
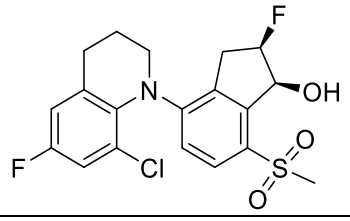
1	
2a	
2b	
3	

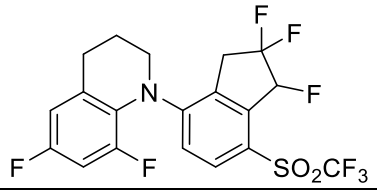
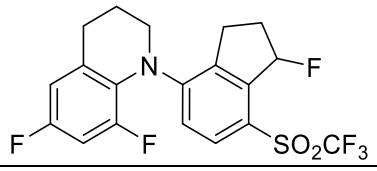
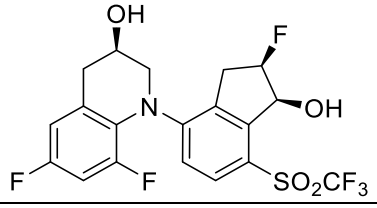
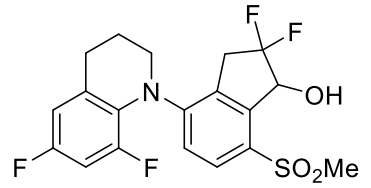
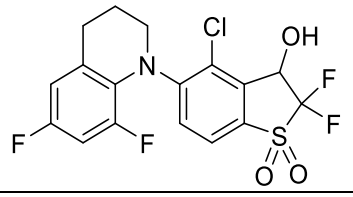
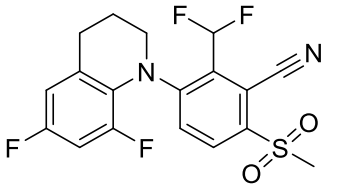
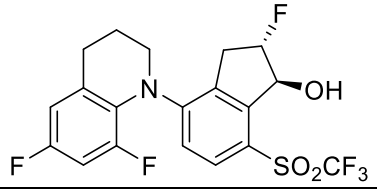
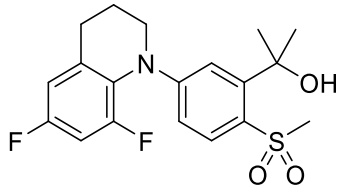
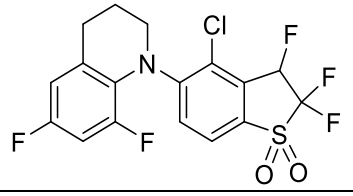
4	
5	
6	
7	
8	
9	
10	
11	
12	

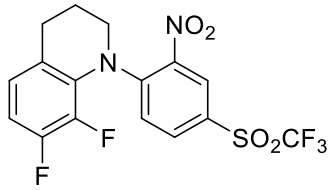
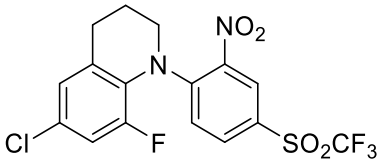
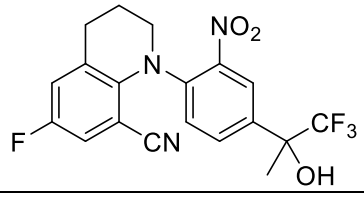
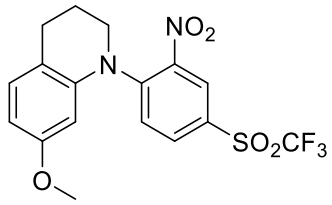
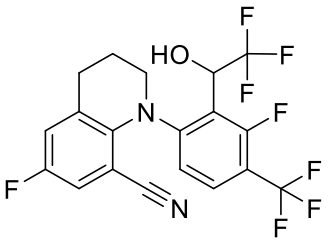
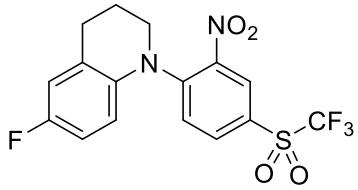
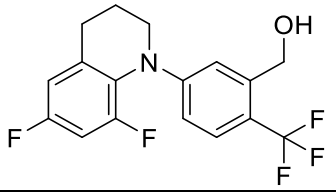
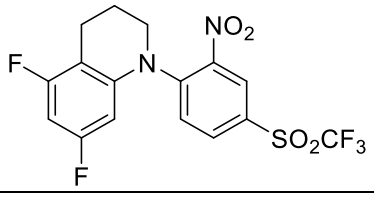
13	
14	
15	
16	
17	
18	
19	
20	
21	

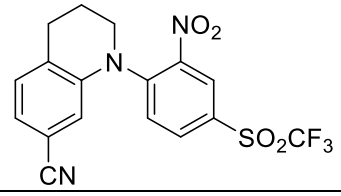
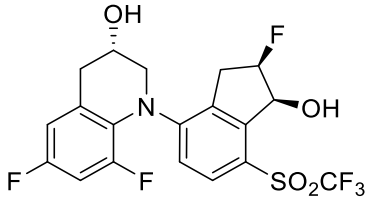
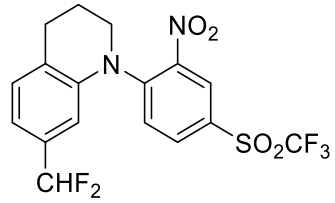
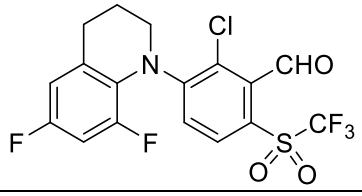
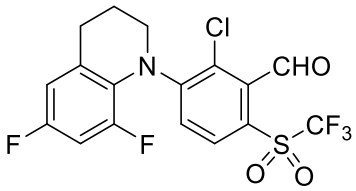
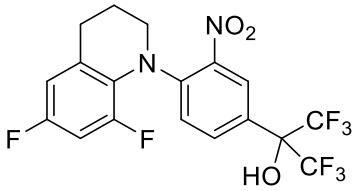
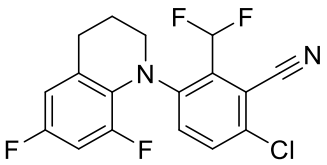
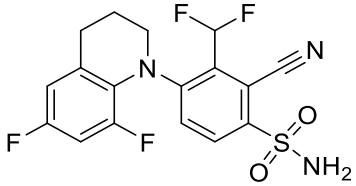
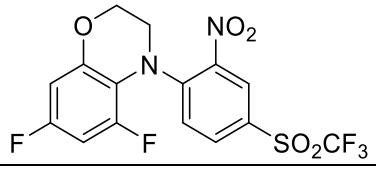
22	
23	
24	
25	
26	
27	
28	
29	
30	

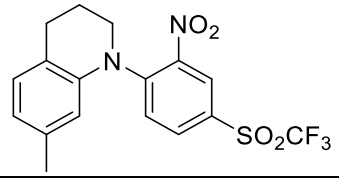
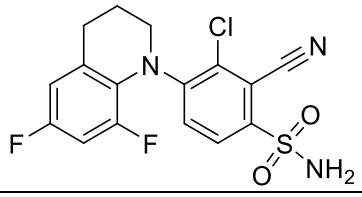
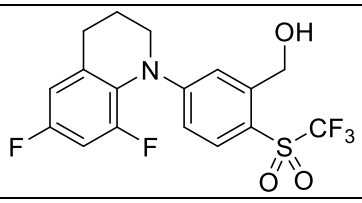
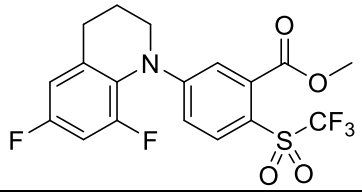
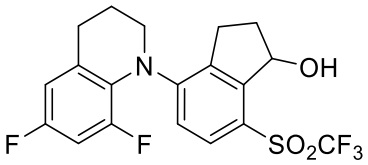
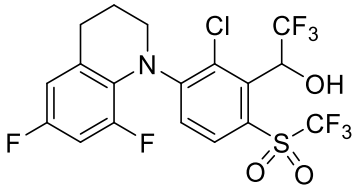
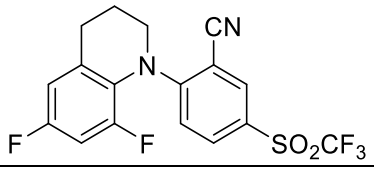
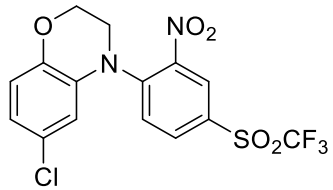
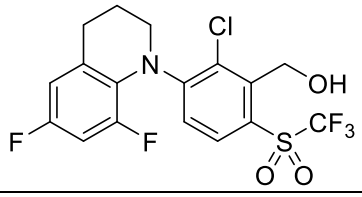
31	
32	
33	
34	
35	
36	
37	
38	
39	

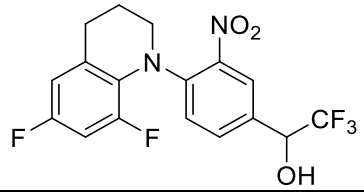
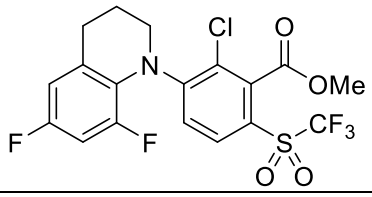
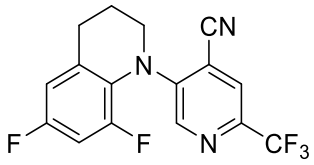
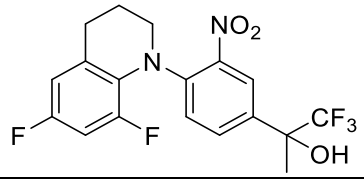
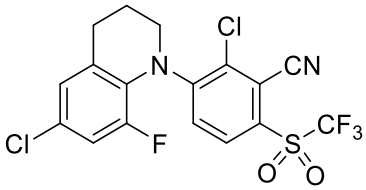
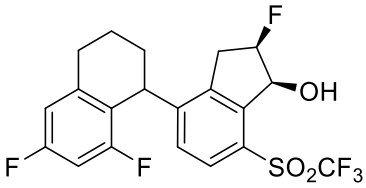
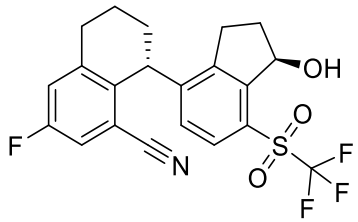
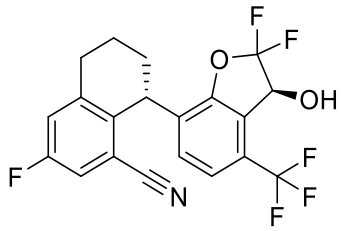
40	
41	
42	
43	
44	
45	
46	
47	

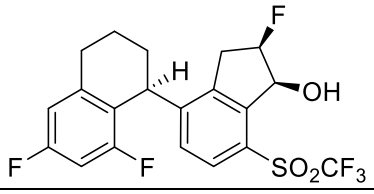
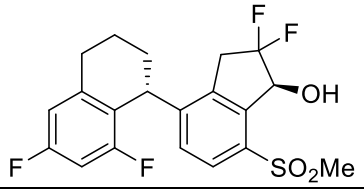
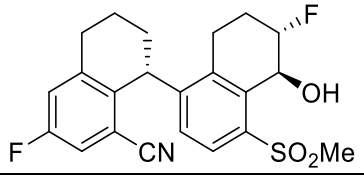
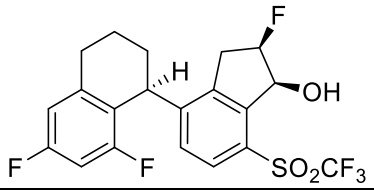
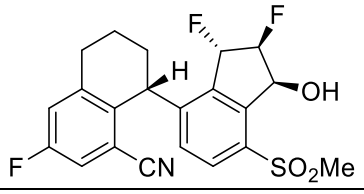
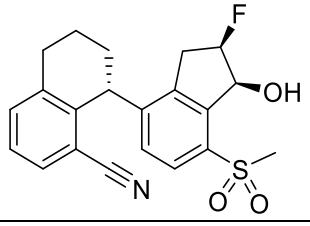
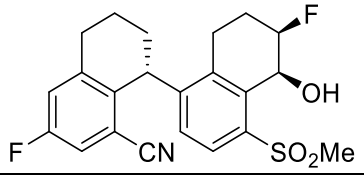
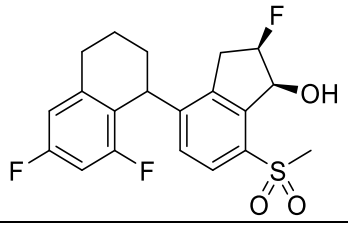
48	
49	
50	
51	
52	
53	
54	
55	
56	

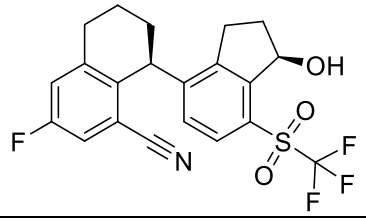
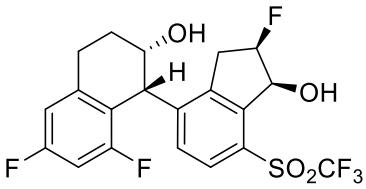
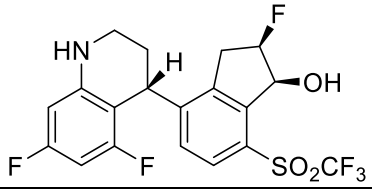
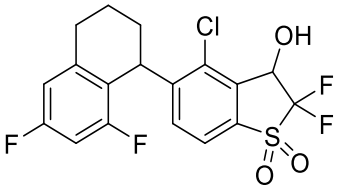
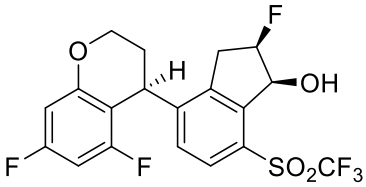
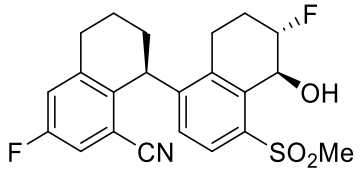
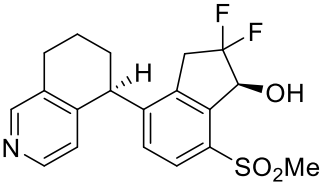
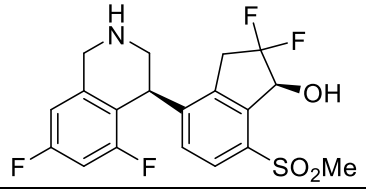
57	
58	
59	
60	
61	
62	
63	
64	

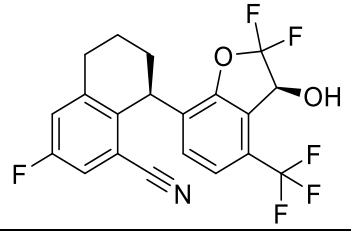
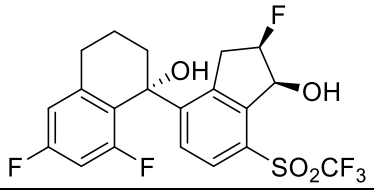
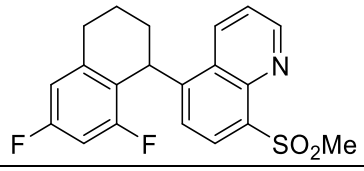
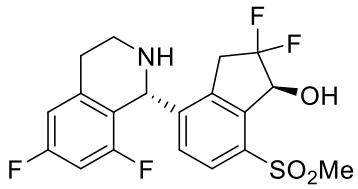
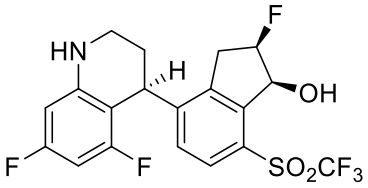
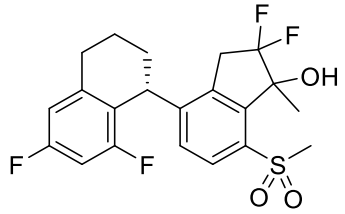
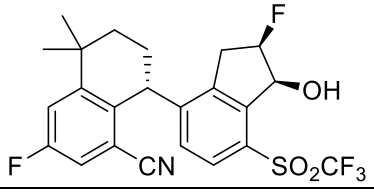
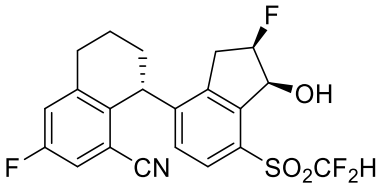
65	
66	
67	
68	
69	
70	
71	
72	
73	

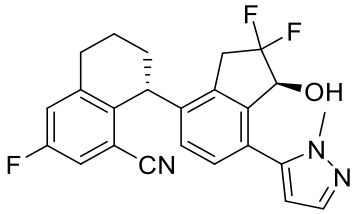
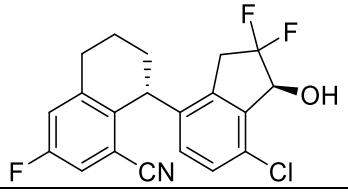
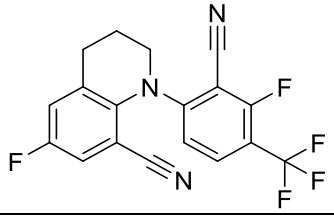
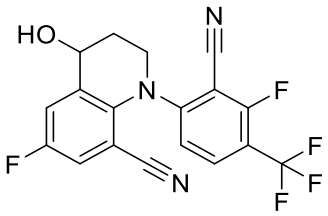
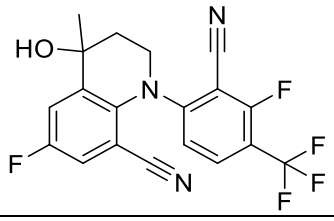
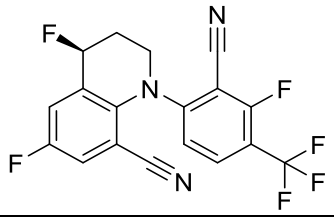
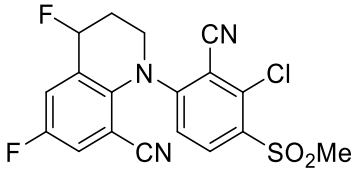
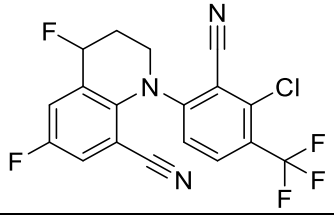
74	
75	
76	
77	
78	
79	
80	
82	
83	

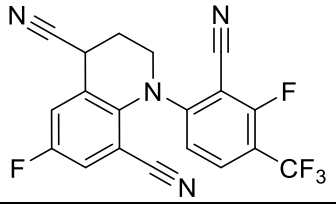
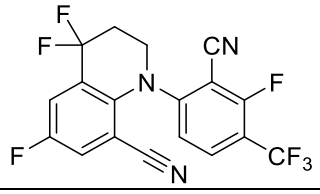
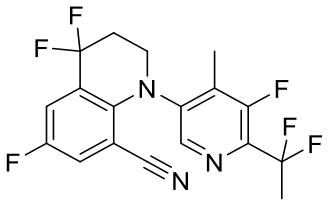
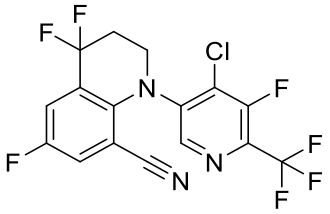
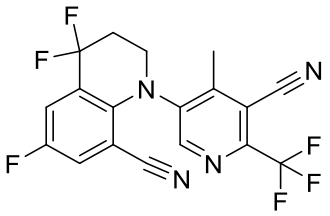
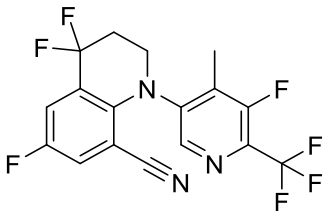
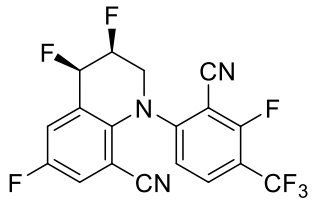
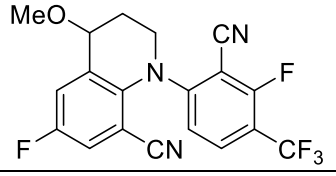
84	
85	
86	
87	
88	
89	
90	
91	

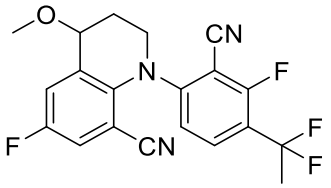
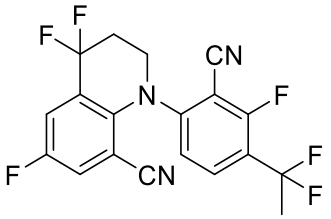
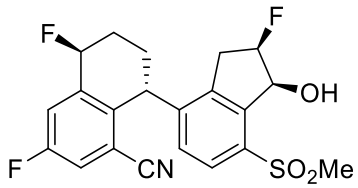
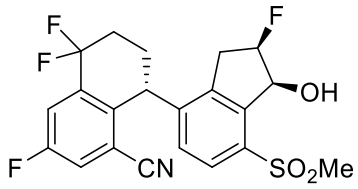
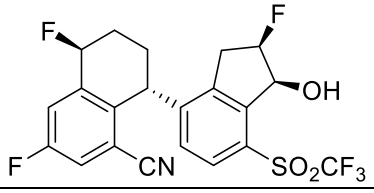
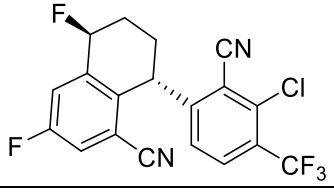
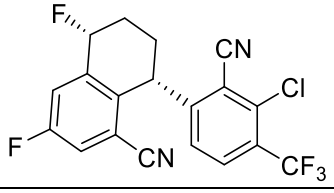
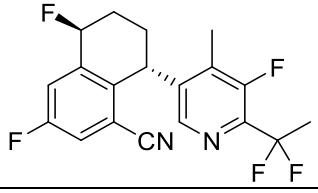
92	
93	
94	
95	
96	
97	
98	
99	

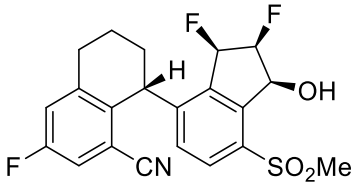
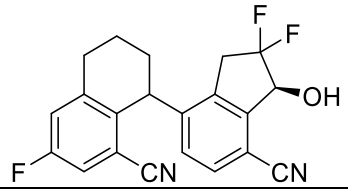
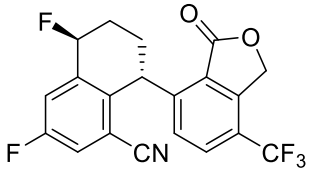
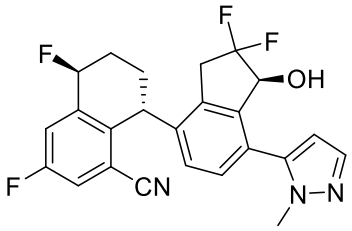
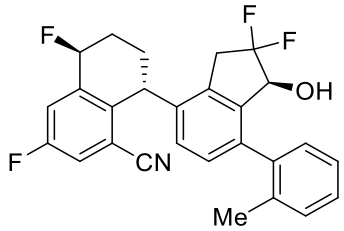
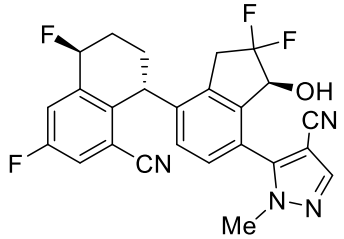
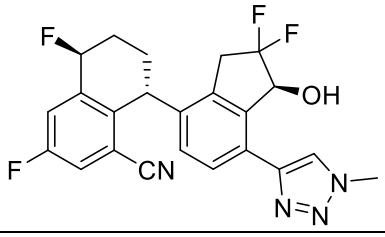
100	
101	
102	
103	
104	
105	
106	
107	

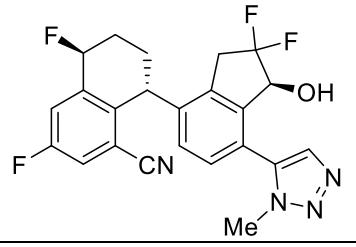
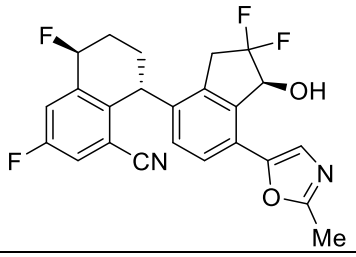
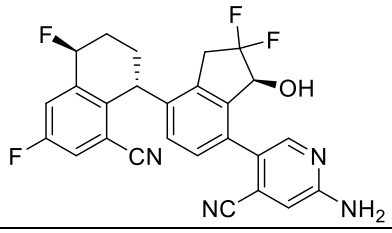
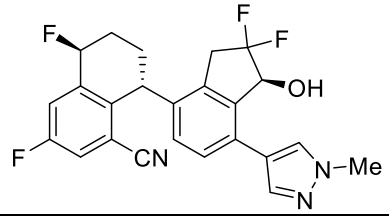
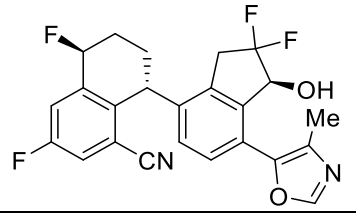
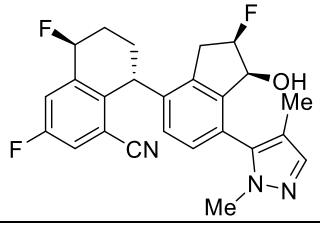
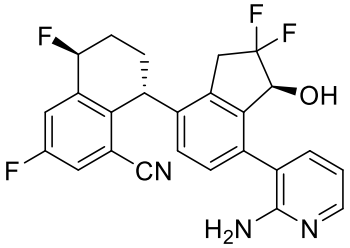
108	
109	
110	
111	
112	
113	
114	
115	

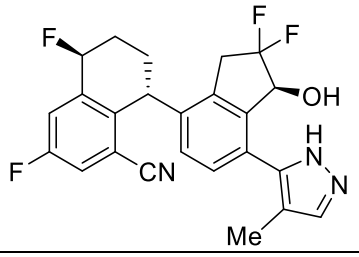
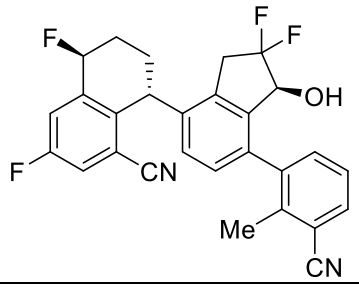
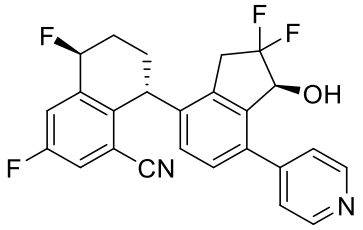
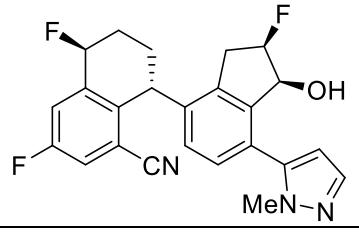
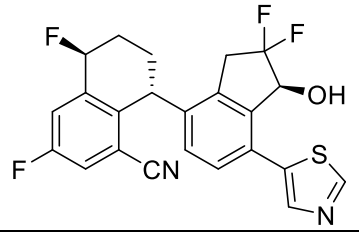
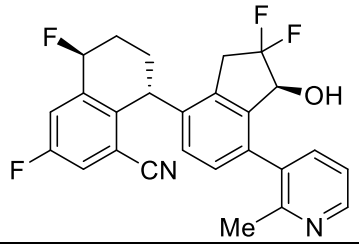
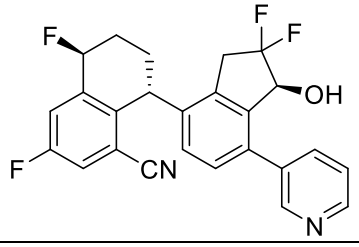
116	
117	
118	
119	
120	
121	
122	
123	

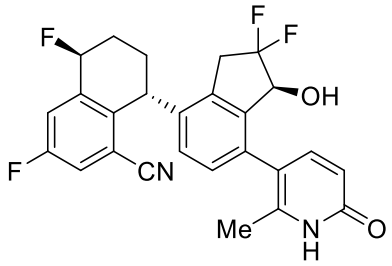
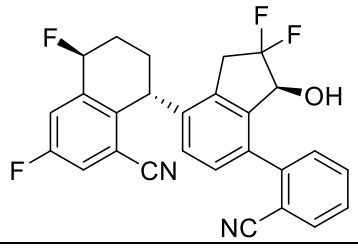
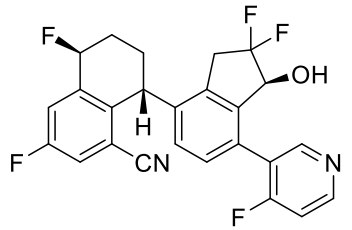
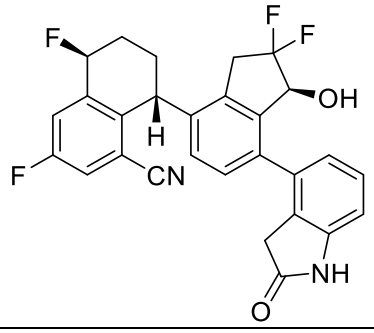
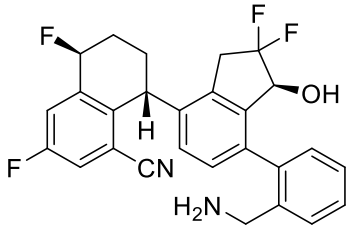
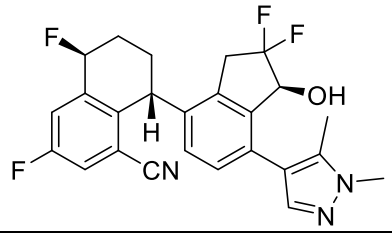
124	
125	
126	
127	
128	
129	
130	
131	

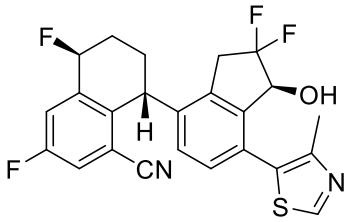
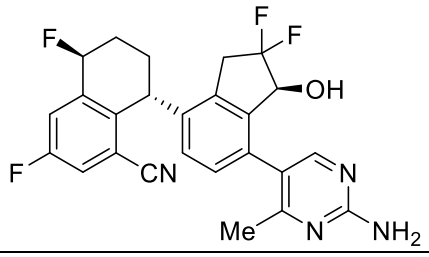
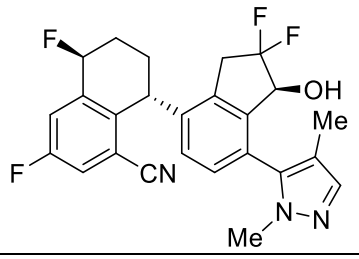
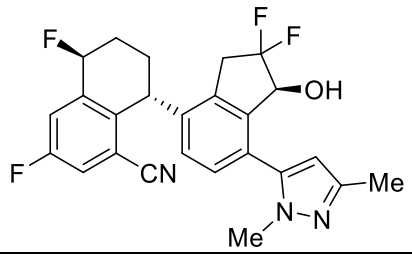
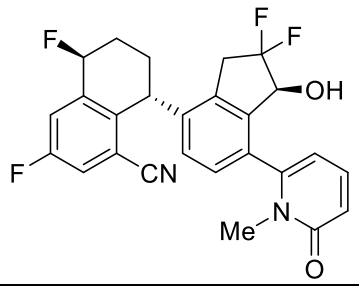
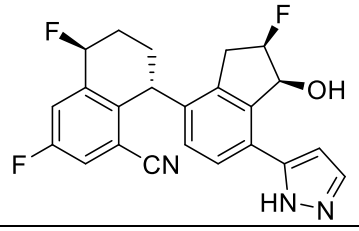
132	
133	
134	
135	
136	
137	
138	
139	

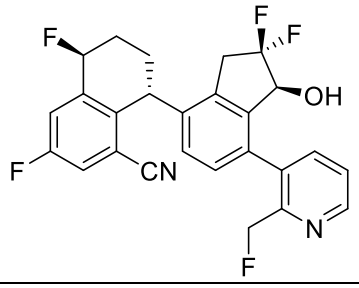
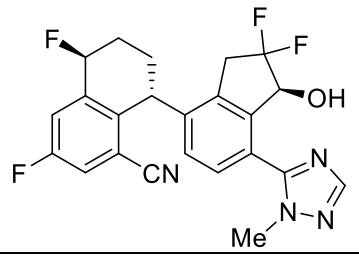
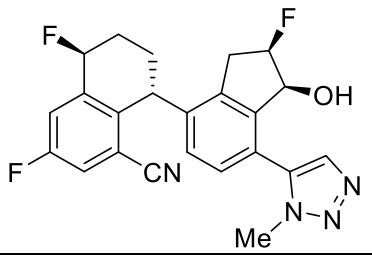
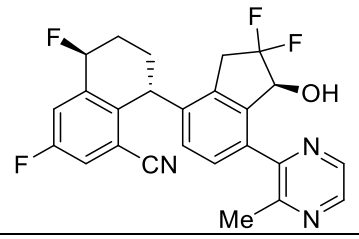
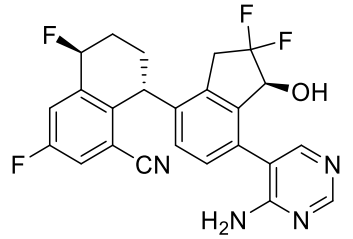
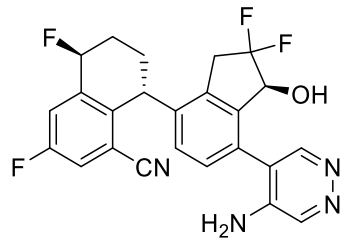
140	
141	
142	
143	
144	
145	
146	

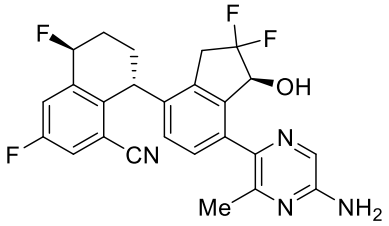
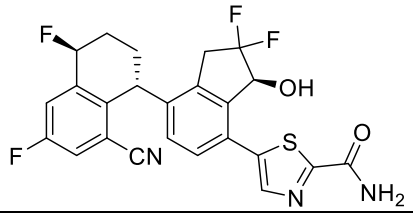
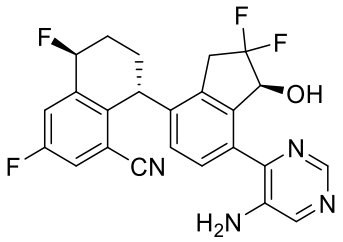
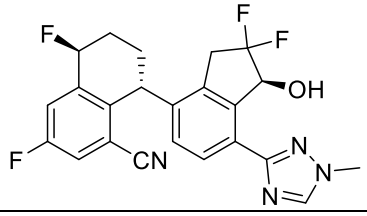
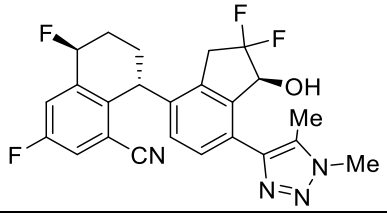
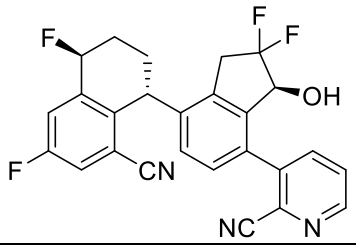
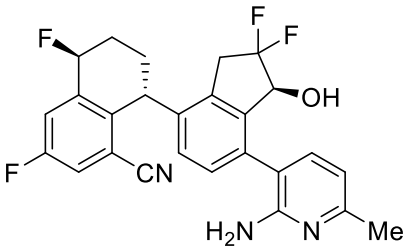
147	
148	
149	
150	
151	
152	
153	

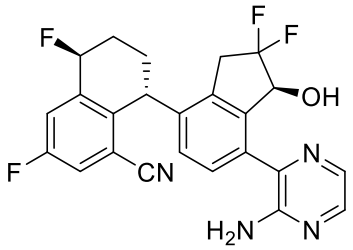
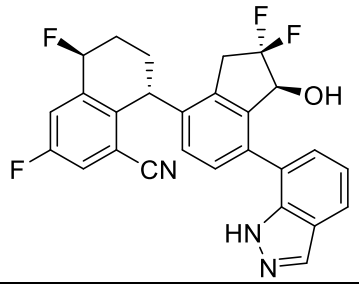
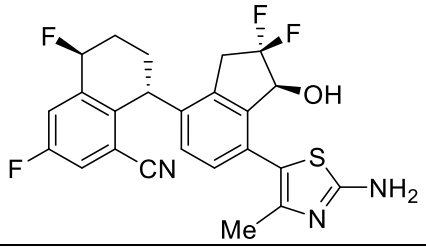
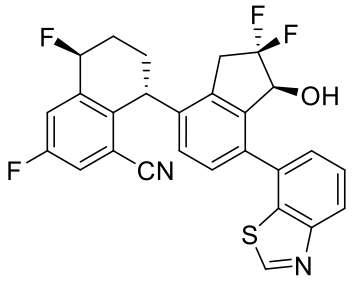
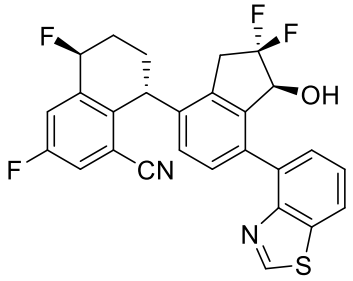
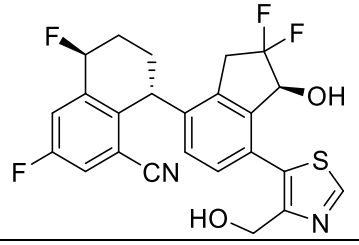
154	
155	
156	
157	
158	
159	
160	

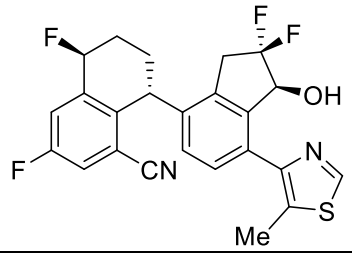
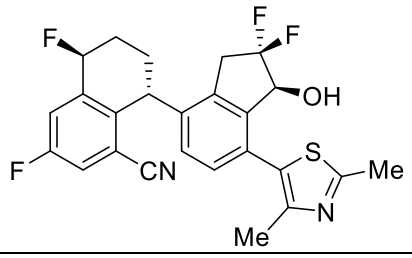
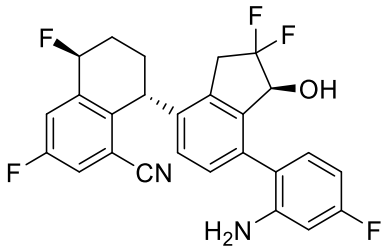
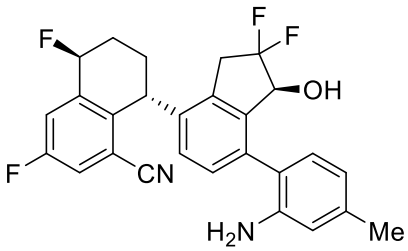
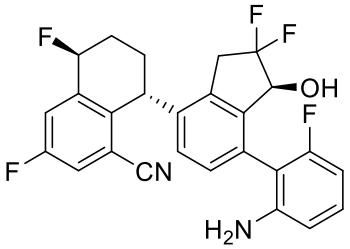
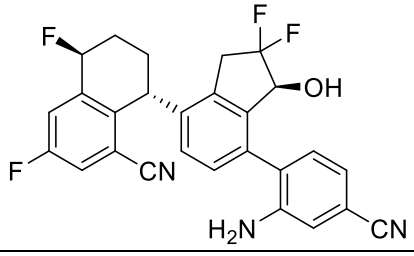
161	
162	
163	
164	
165	
166	

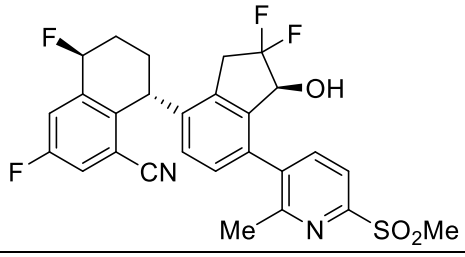
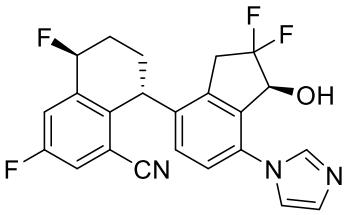
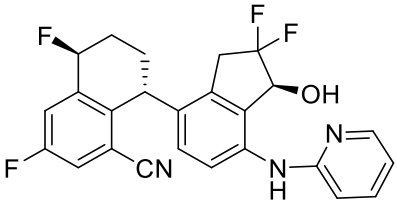
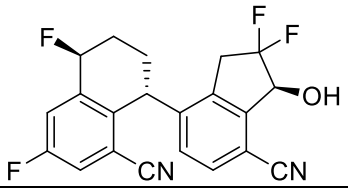
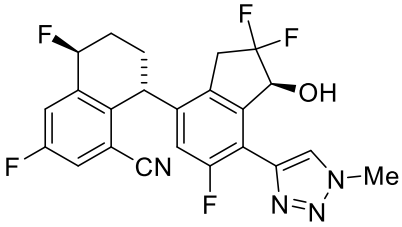
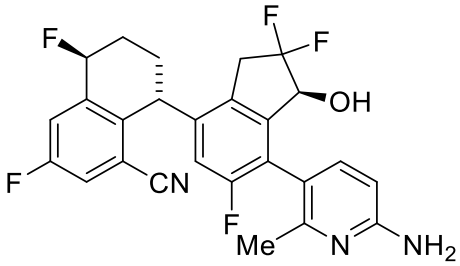
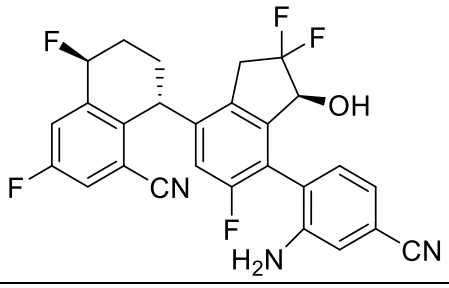
167	
168	
169	
170	
171	
172	

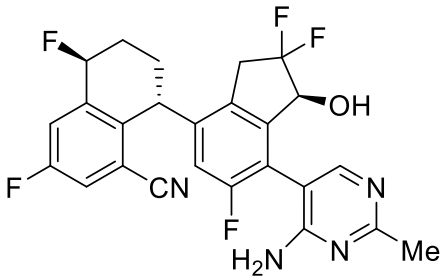
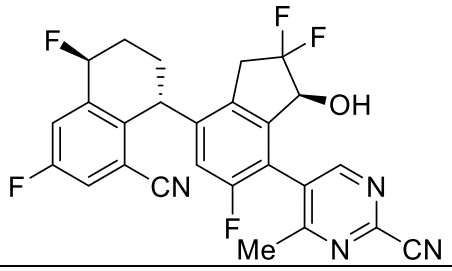
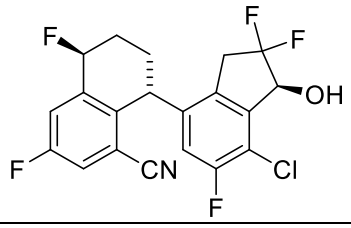
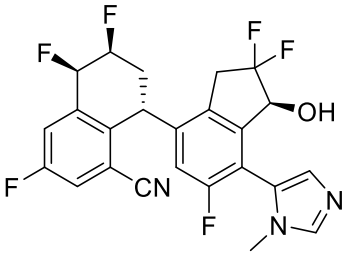
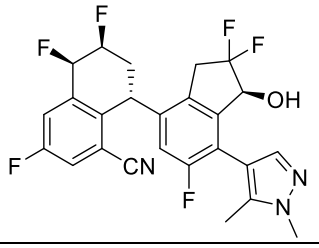
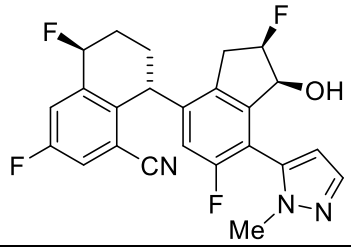
173	
174	
175	
176	
177	
178	

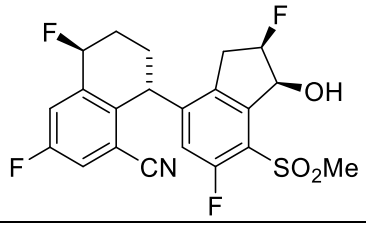
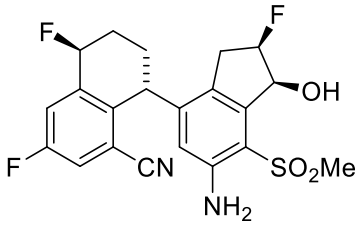
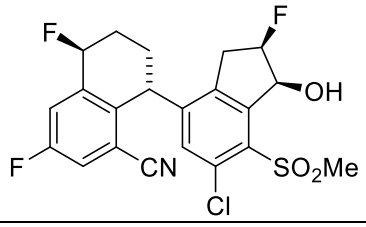
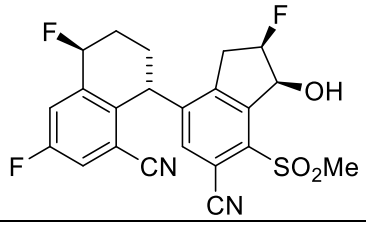
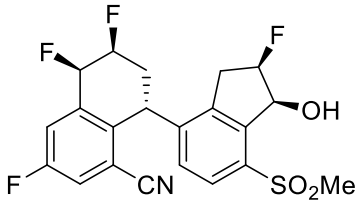
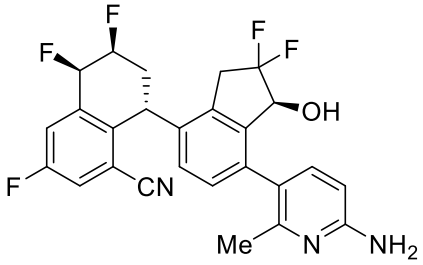
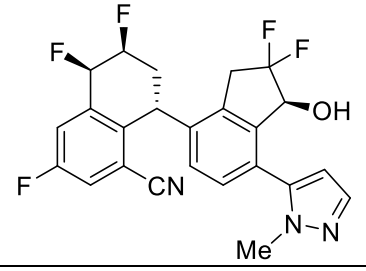
179	
180	
181	
182	
183	
184	
185	

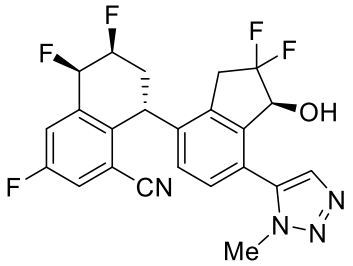
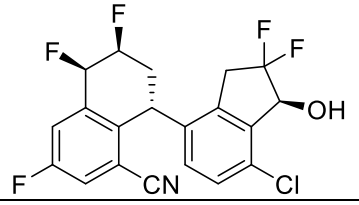
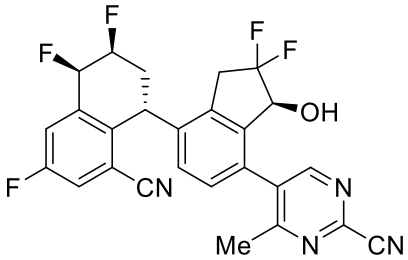
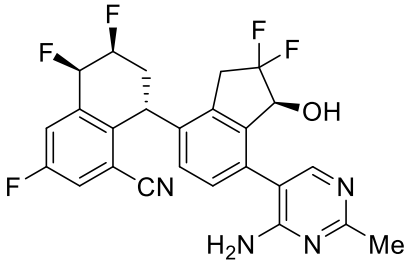
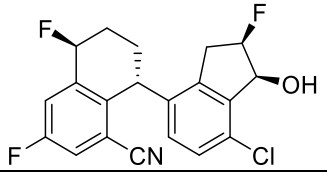
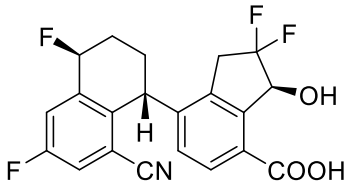
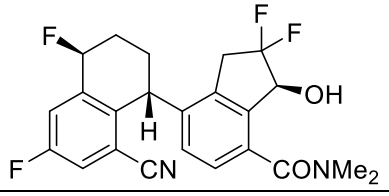
186	
187	
188	
189	
190	
191	

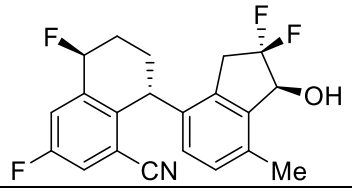
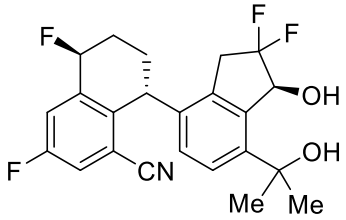
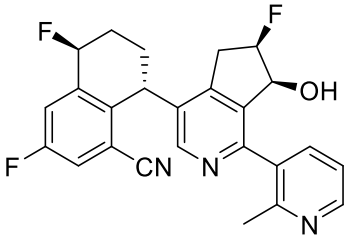
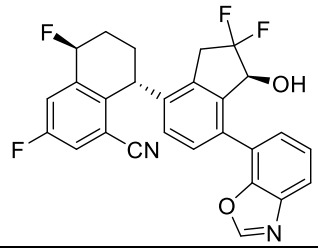
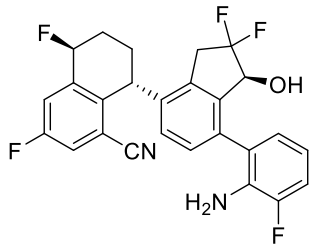
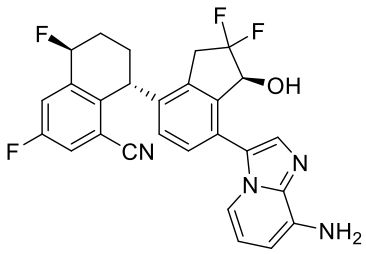
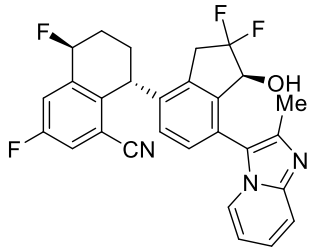
192	
193	
194	
195	
196	
197	

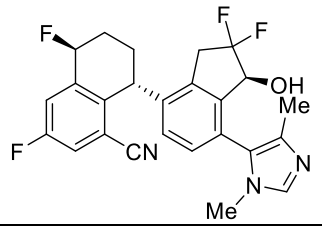
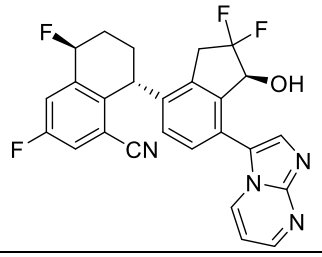
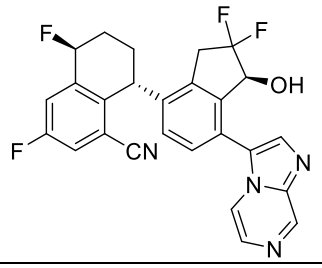
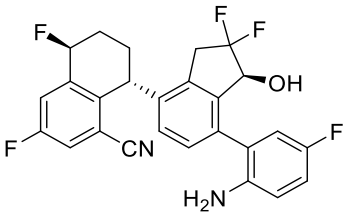
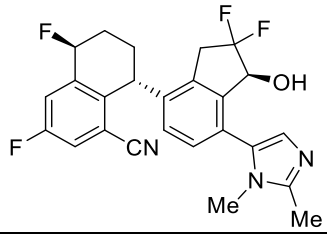
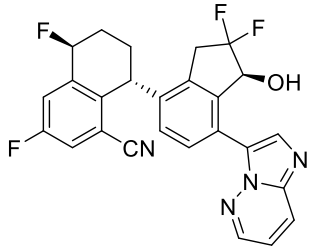
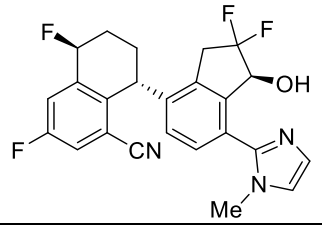
198	
199	
200	
201	
202	
203	
204	

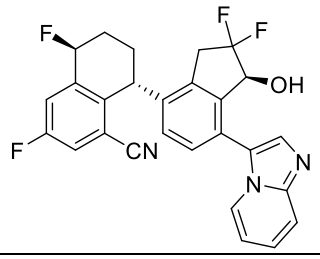
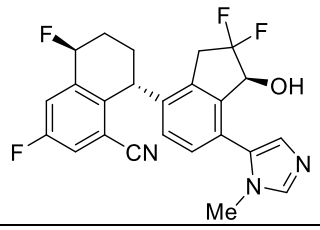
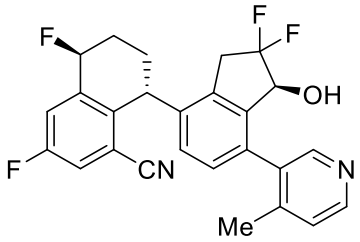
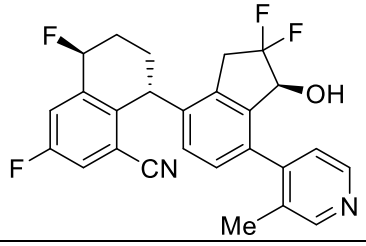
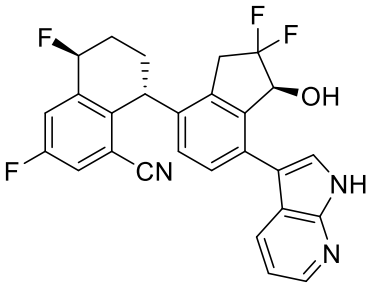
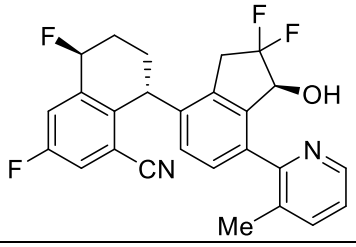
205	
206	
207	
208	
209	
210	

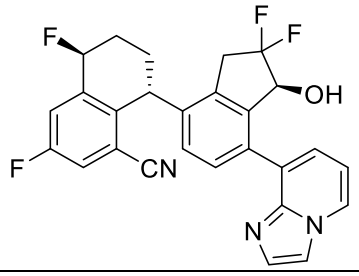
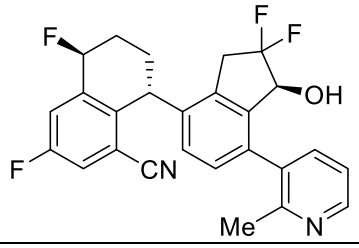
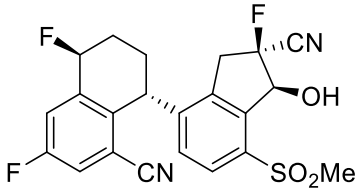
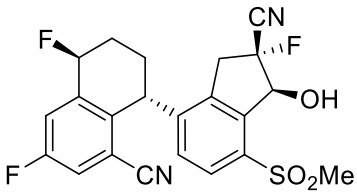
211	
212	
213	
214	
215	
216	
217	

218	
219	
220	
221	
222	
223	
224	

225	
226	
227	
228	
229	
230	
231	

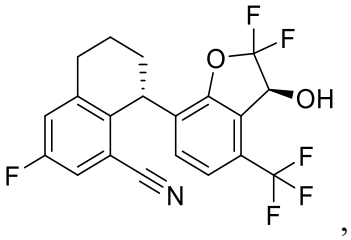
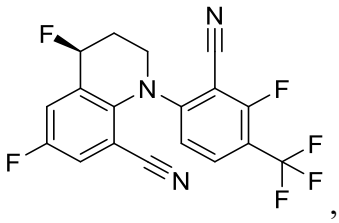
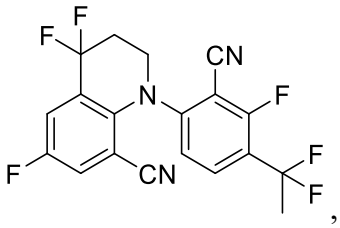
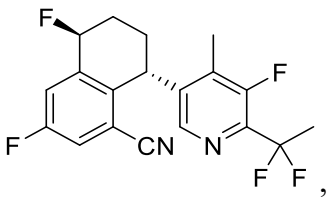
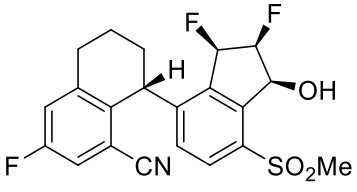
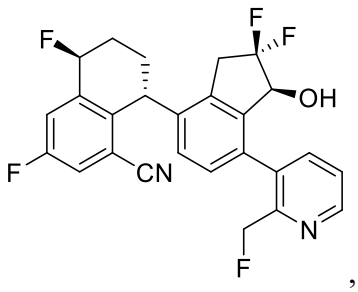
232	
233	
234	
235	
236	
237	
238	

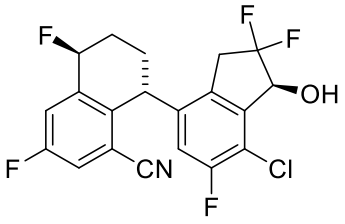
239	
240	
241	
242	
243	
244	

245	
246	
247	 , and
248	 ,

or a pharmaceutically acceptable salt thereof.

9. The compound of claim **8**, selected from the group consisting of

 ,
 ,
 ,
 ,
 ,
 ,



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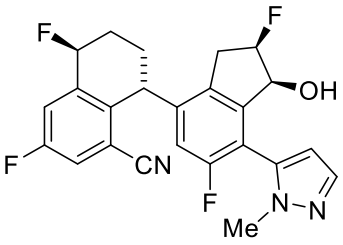

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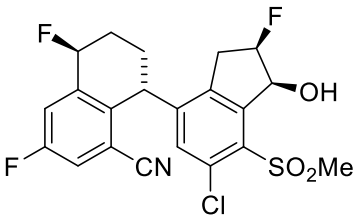

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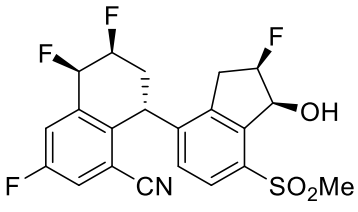

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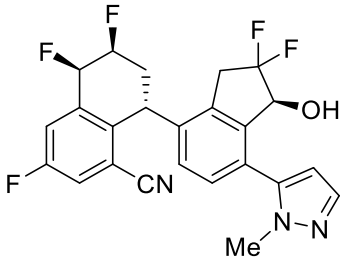
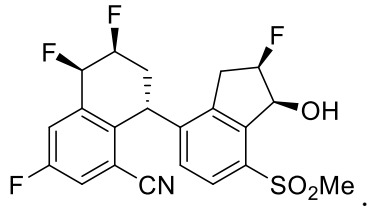


or a pharmaceutically acceptable salt thereof.

10. The compound of claim **8**, having the structure



.

11. A pharmaceutical composition comprising a compound of any one of claims **1**-**10**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

12. Use of a compound of any one of claims **1**-**10**, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim **11**, in the manufacture of a medicament for the treatment of a disease, disorder, or condition, mediated at least in part by HIF-2α.

13. The use of claim **12**, wherein said disease, disorder, or condition is cancer.

14. The use of claim **13**, wherein said cancer is a cancer of the prostate, colon, rectum, pancreas, cervix, stomach, endometrium, uterus, brain, liver, bladder, ovary, testis, head, neck, skin (including melanoma and basal carcinoma), mesothelial lining, white blood cell (including lymphoma and leukemia), esophagus, breast, muscle, connective tissue, intestine, lung (including small-cell lung carcinoma and non-small-cell lung carcinoma), adrenal gland, thyroid,

kidney, or bone; or is glioblastoma, mesothelioma, renal cell carcinoma, gastric carcinoma, sarcoma (including Kaposi's sarcoma), choriocarcinoma, cutaneous basocellular carcinoma, or testicular seminoma.

15. The use of claim **13**, wherein said cancer is selected from the group consisting of melanoma, colorectal cancer, pancreatic cancer, breast cancer, prostate cancer, lung cancer, leukemia, a brain tumor, lymphoma, ovarian cancer, Kaposi's sarcoma, renal cell carcinoma, head and neck cancer, esophageal cancer and urothelieal carcinoma.

16. The use of claim **13**, wherein said cancer is renal cell carcinoma.

17. The use of claim **12**, wherein the medicament is to be administered with at least one additional therapeutic agent.

18. The use of claim **17**, wherein said at least one additional therapeutic agent is an immune checkpoint inhibitor.

19. The use of claim **18**, wherein said immune checkpoint inhibitor blocks the activity of at least one of PD-1, PD-L1, BTLA, LAG3, a B7 family member, TIM3, TIGIT or CTLA4.

20. The use of claim **19**, wherein said immune checkpoint inhibitor blocks the activity of PD-1 or PD-L1.

21. The use of claim **20**, wherein said immune checkpoint inhibitor is selected from the group consisting of nivolumab, pembrolizumab, avelumab, atezolizumab, durvalumab, cemiplimab and zimberelimab.

22. The use of claim **19**, wherein said immune checkpoint inhibitor blocks the activity of TIGIT.

23. The use of any one of claims **17** to **22**, wherein said at least one additional therapeutic agent comprises a chemotherapeutic agent, an A2R antagonist, a CD73 inhibitor, and/or radiation.