Supplementary Material

Discovering potential inhibitors of YEATS domain of YEATS2 through virtual screening, molecular optimization and molecular dynamics simulation

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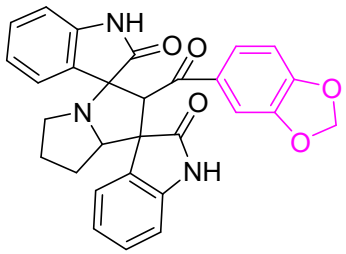
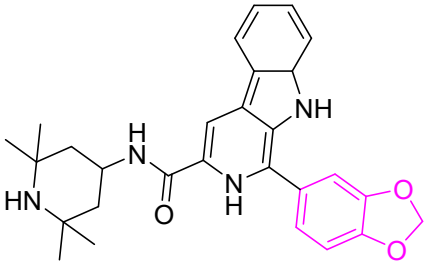
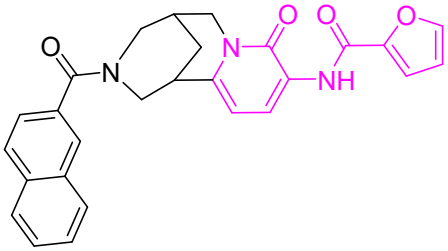
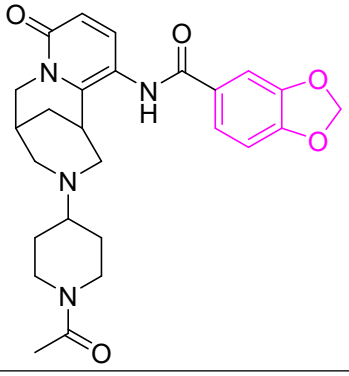
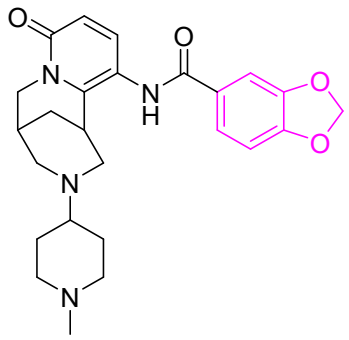
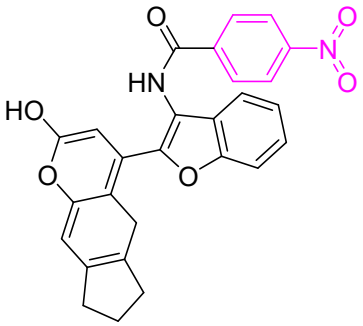
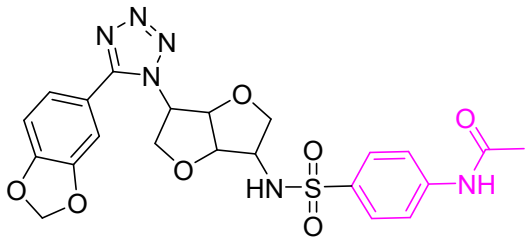
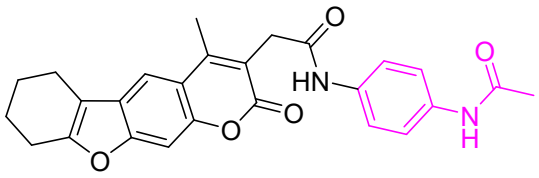
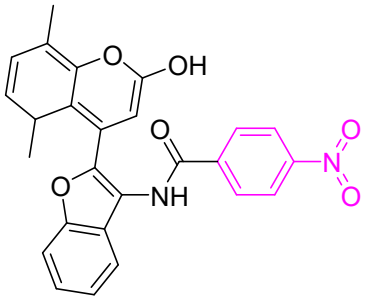
Table S1. Molecules with high affinity and appropriate binding position to the YEATS2 YEATS domain in ZINC Natural Products.

ZINC Natural Products (127695 Compounds, 2016 October 1)			
NO.	Compound	Affinity (kcal/mol)	Structure
1	ZINC35361861	-9.7	
2	ZINC61997740	-9.2	
3	ZINC04258869	-9.1	
4	ZINC08300421	-9.1	

5	ZINC20503705	-9.0	
6	ZINC09183645	-8.9	
7	21799	-8.8	
8	ZINC08791373	-8.8	
9	ZINC09306874	-8.8	

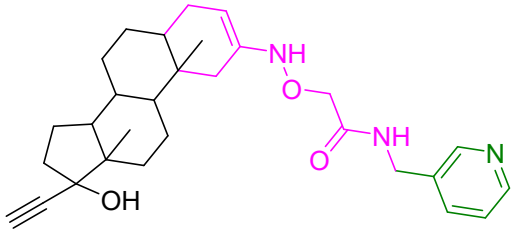
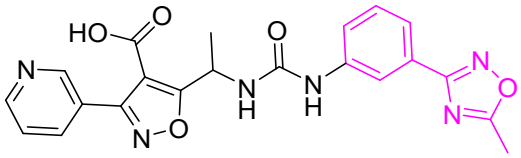
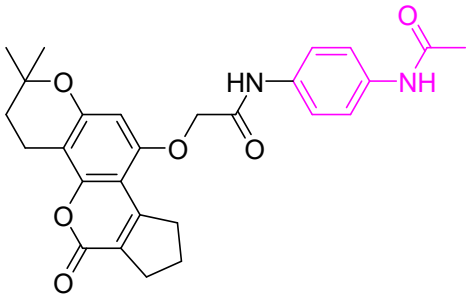
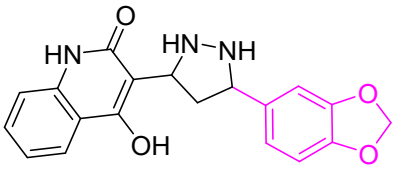
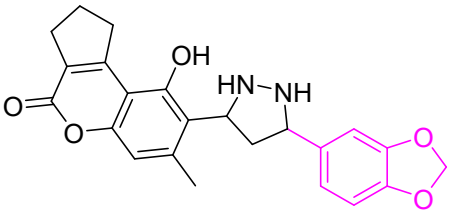
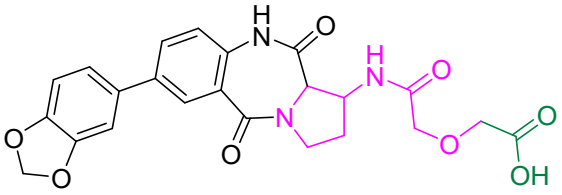
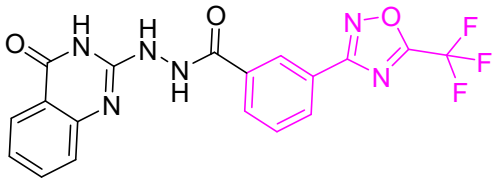
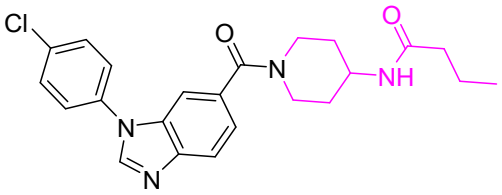
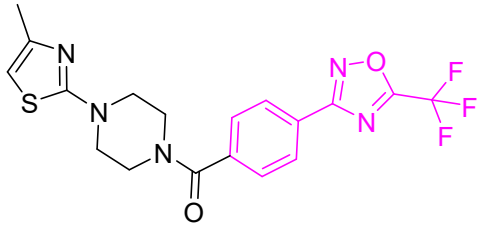
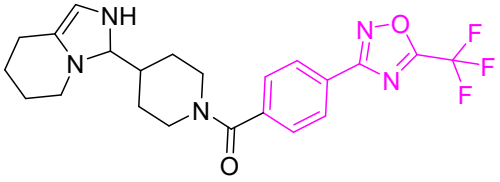
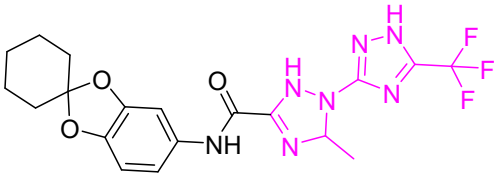
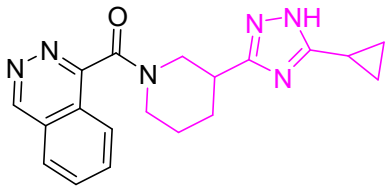
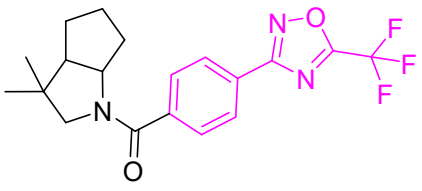
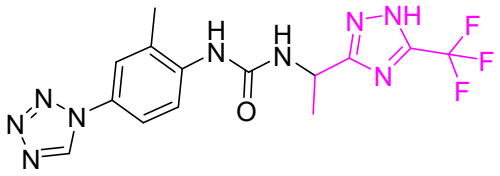
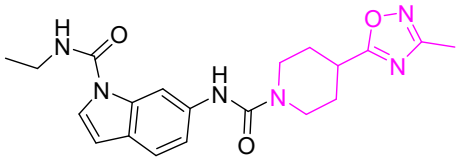
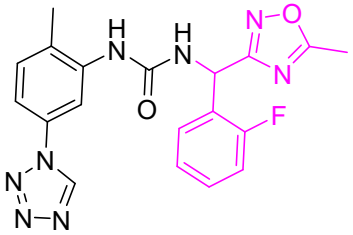
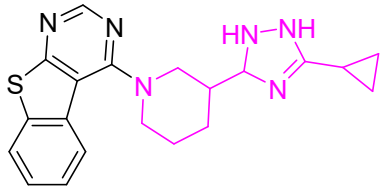
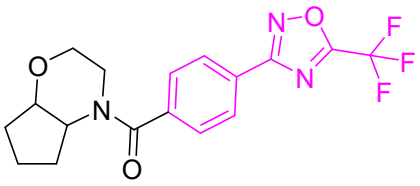
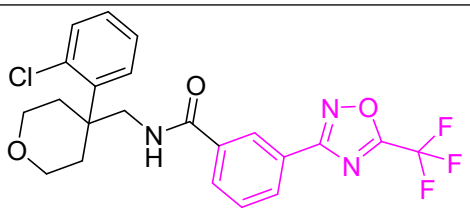
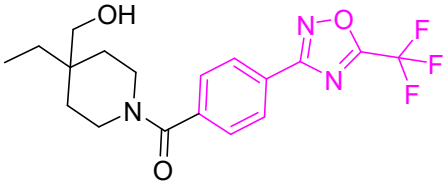
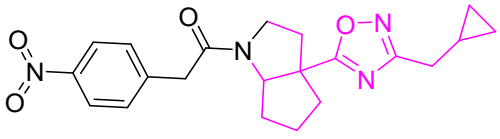
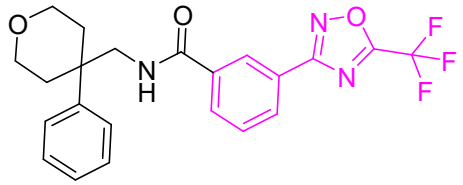
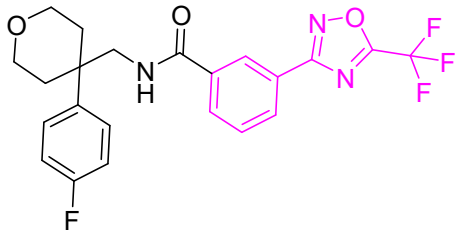
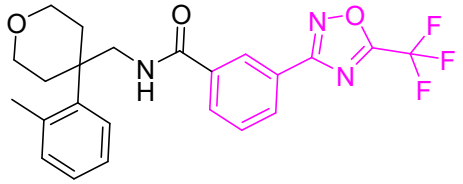
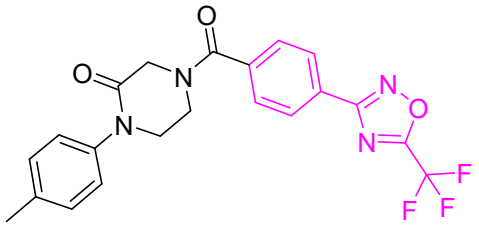
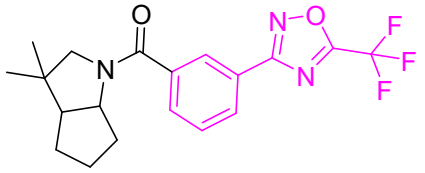
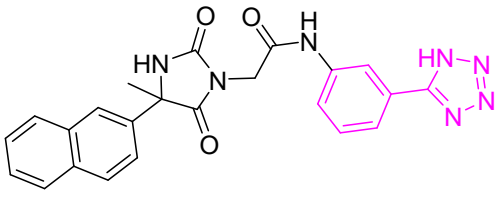
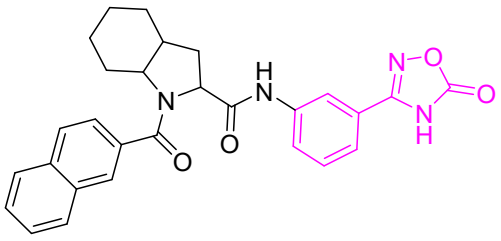
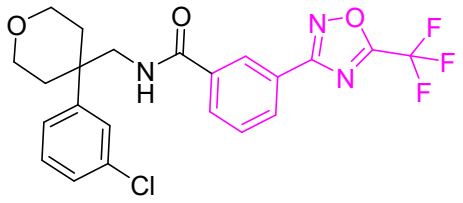
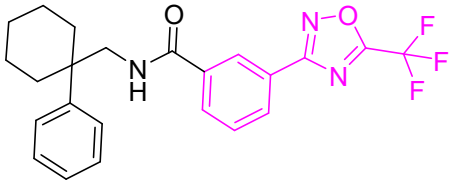
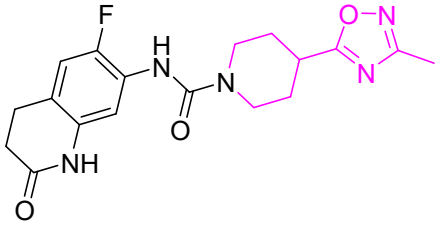
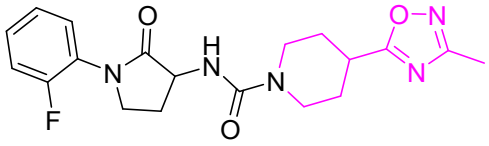
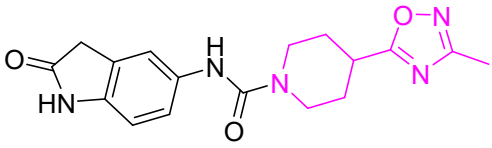
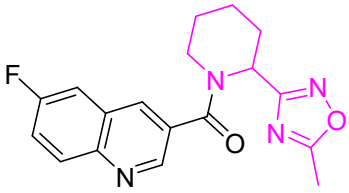
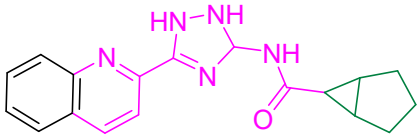
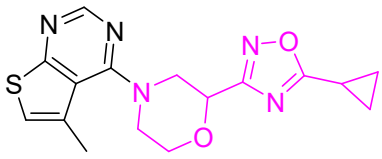
10	ZINC85889186	-8.6	
11	19523	-8.5	
12	ZINC08791689	-8.5	
13	ZINC03846561	-8.5	
14	ZINC12296341	-8.5	
15	ZINC08296611	-8.5	

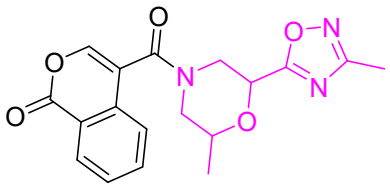
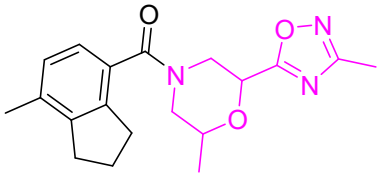
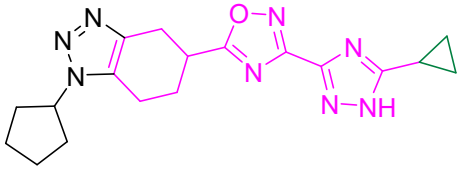
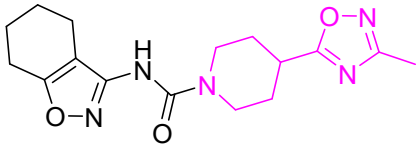
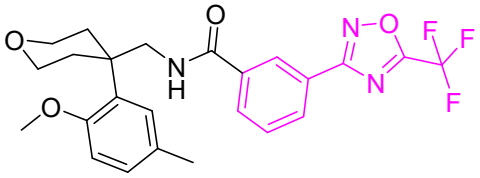
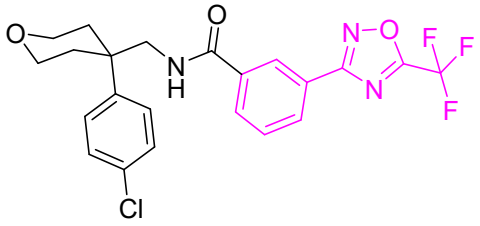
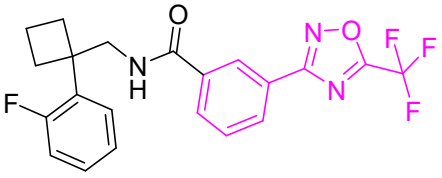
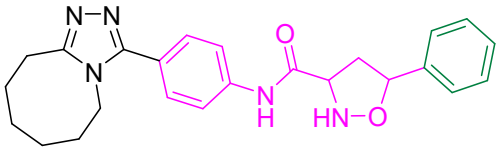
Table S2. Molecules with high affinity and appropriate binding position to the YEATS2 YEATS domain in Enamine Advanced.

Enamine Advanced (448388 compounds, 2020 May)			
NO.	Compound	Affinity (kcal/mol)	Structure
1	Z2118684250	-9.1	
2	Z2098109826	-9.0	
3	Z1148211073	-8.9	
4	Z1919888977	-8.9	
5	Z1323896259	-8.8	
6	Z2958154393	-8.8	
7	Z3021380753	-8.8	

8	Z3711050398	-8.8	
9	Z1258908930	-8.7	
10	Z1385327618	-8.7	
11	Z1452691933	-8.7	
12	Z1967764963	-8.7	
13	Z3905360135	-8.7	
14	Z1551070239	-8.6	
15	Z1849427362	-8.6	

16	Z1873289090	-8.6	
17	Z1873385828	-8.6	
18	Z1873389144	-8.6	
19	Z2085880001	-8.6	
20	Z2232498249	-8.6	
21	Z28082318	-8.6	
22	Z3713600506	-8.6	

23	Z3905360136	-8.6	
24	Z3905360141	-8.6	
25	Z1132217352	-8.5	
26	Z1187372633	-8.5	
27	Z1262386157	-8.5	
28	Z1528581457	-8.5	
29	Z2233592836	-8.5	
30	Z2346955514	-8.5	

31	Z2386291968	-8.5	
32	Z2386293633	-8.5	
33	Z2608066998	-8.5	
34	Z2956873977	-8.5	
35	Z3905360129	-8.5	
36	Z3905360137	-8.5	
37	Z3905360140	-8.5	
38	Z804227812	-8.5	

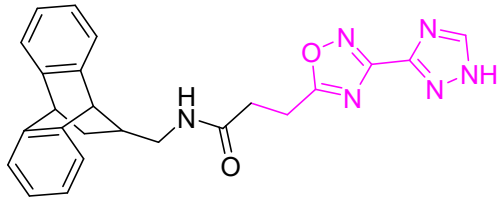
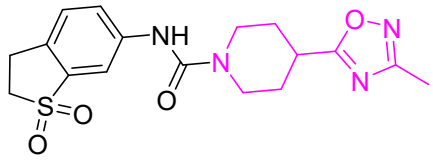
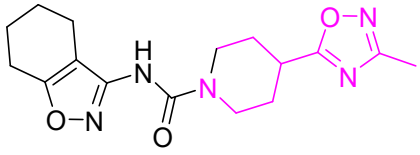
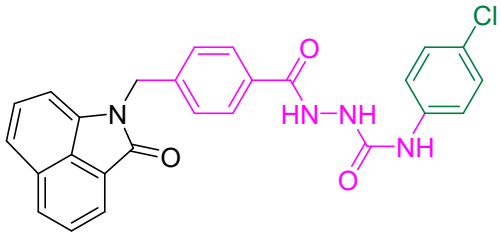
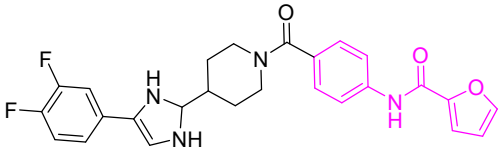
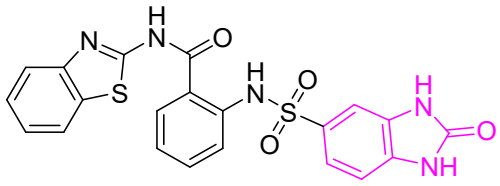
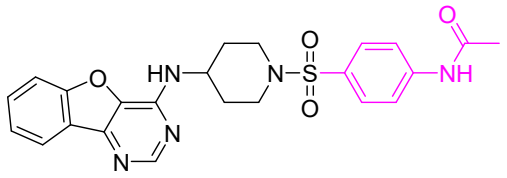
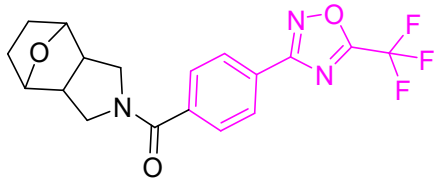
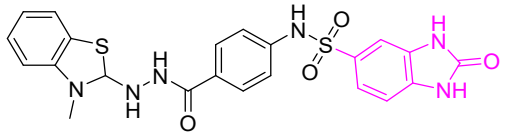
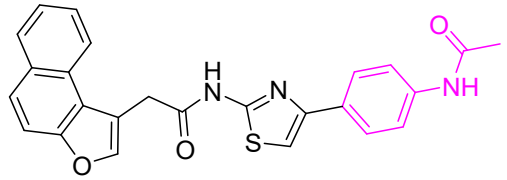
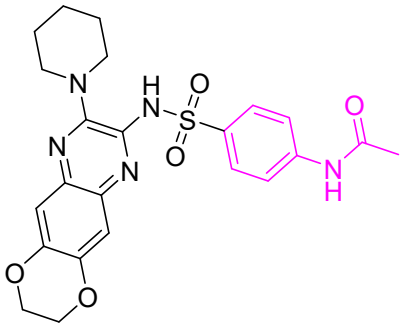
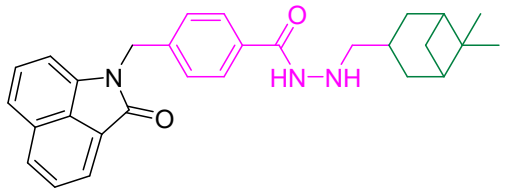
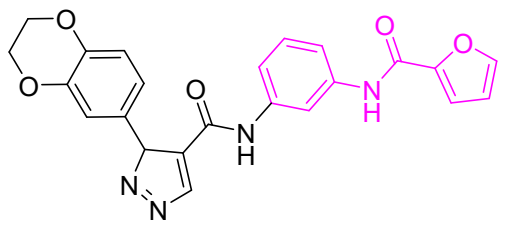
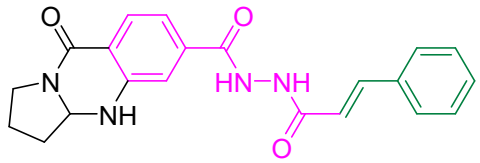
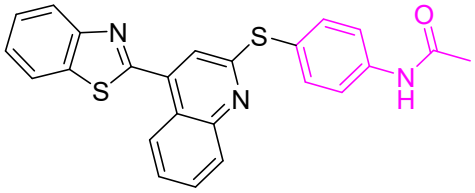
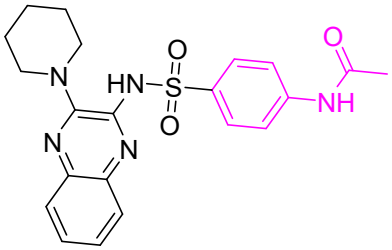
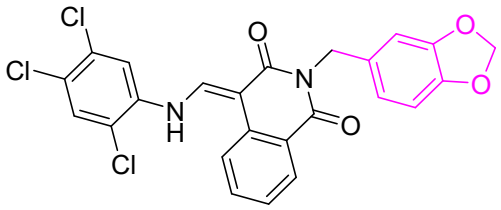
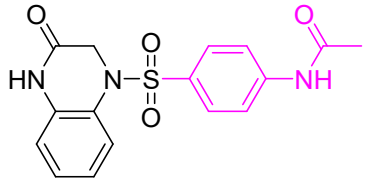
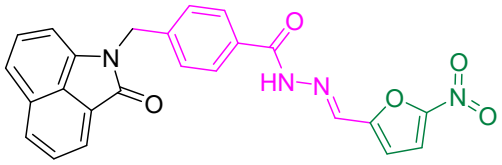
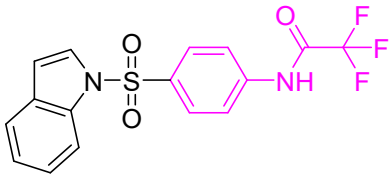
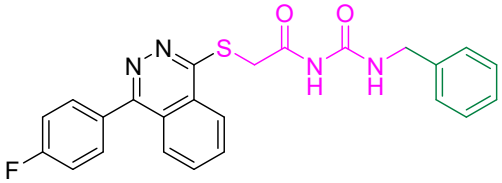
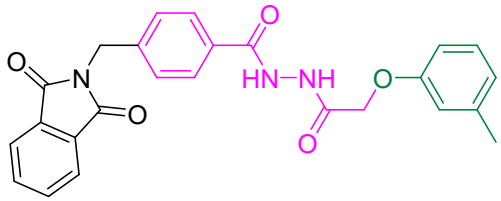
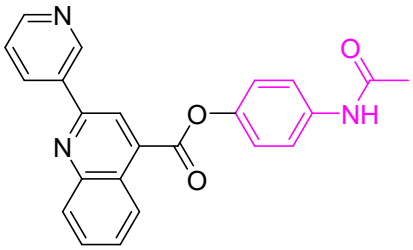
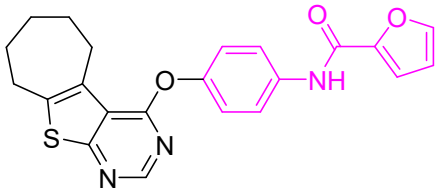
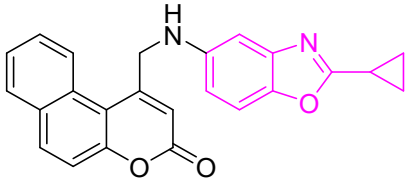
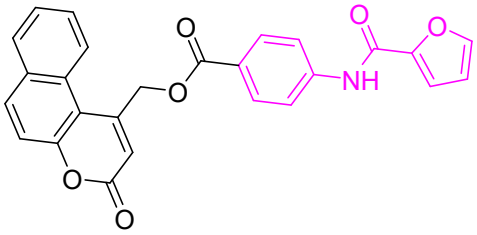
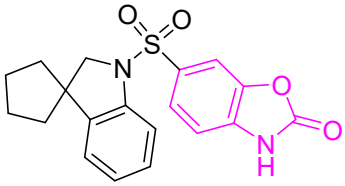
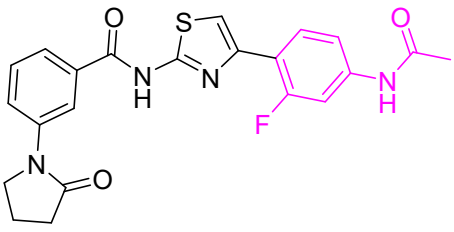
39	Z968681000	-8.5	
40	Z1434124373	-8.5	
41	Z2956873977	-8.5	

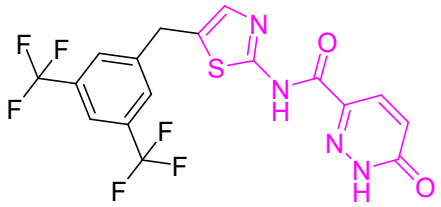
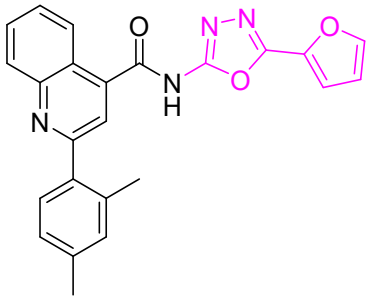
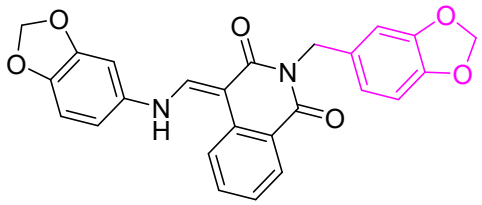
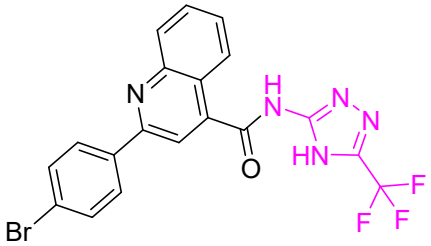
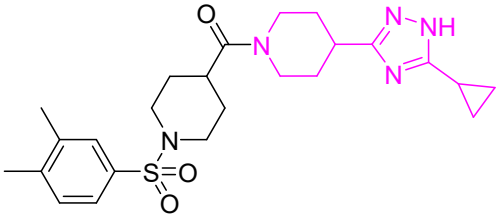
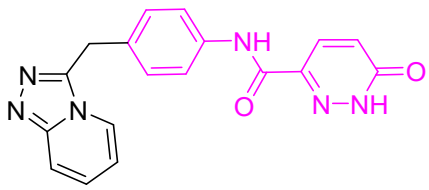
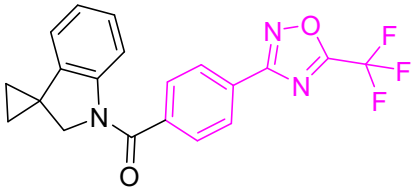
Table S3. Molecules with high affinity and appropriate binding position to the YEATS2 YEATS domain in Enamine HTS.

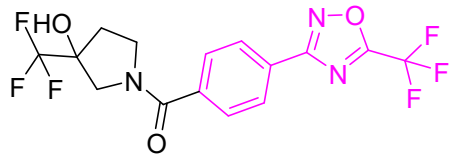
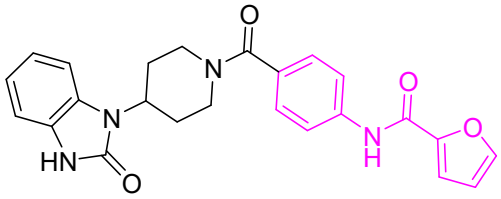
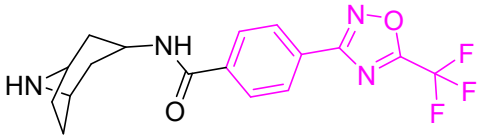
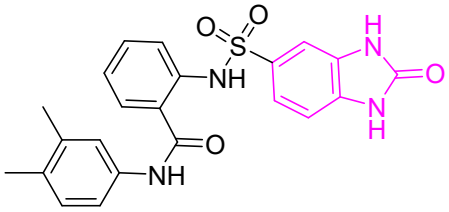
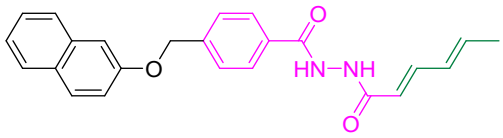
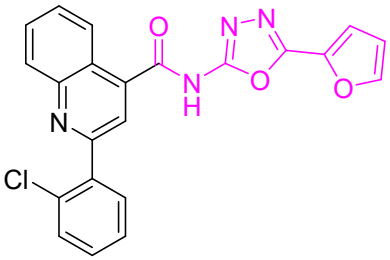
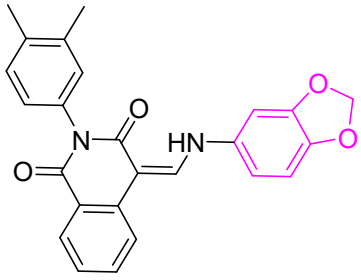
Enamine HTS (1756280 compounds, 2020 May)			
NO.	Compound	Affinity (kcal/mol)	Structure
1	Z44612196	-9.7	
2	Z927561814	-9.5	
3	Z255749124	-9.2	

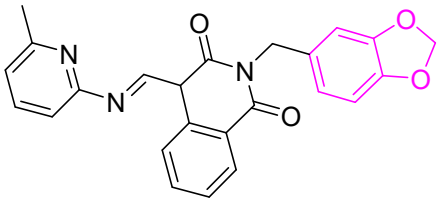
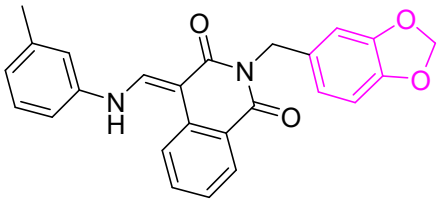
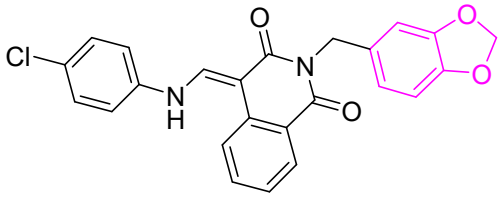
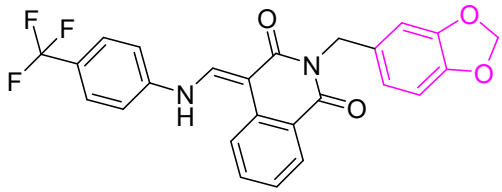
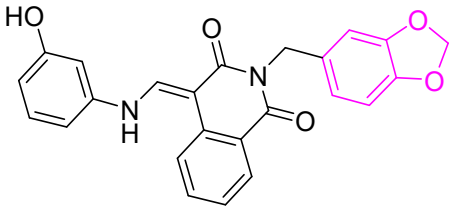
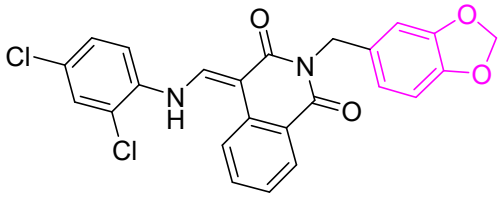
4	Z229478524	-9.1	
5	Z1303141295	-9.0	
6	Z198245876	-9.0	
7	Z27057035	-9.0	
8	Z31192849	-9.0	
9	Z44848962	-9.0	
10	Z236066456	-8.9	

11	Z29902054	-8.9	
12	Z31116504	-8.9	
13	Z31192848	-8.9	
14	Z31285773	-8.9	
15	Z45558953	-8.9	
16	Z54322378	-8.9	
17	Z56851851	-8.9	
18	Z16244153	-8.8	

19	Z286373756	-8.8	
20	Z29109770	-8.8	
21	Z31089631	-8.8	
22	Z369415780	-8.8	
23	Z92503894	-8.8	
24	Z1359473641	-8.7	
25	Z193192822	-8.7	

26	Z280678030	-8.7	
27	Z30470231	-8.7	
28	Z31270549	-8.7	
29	Z86587006	-8.7	
30	Z1014768846	-8.6	
31	Z1175891072	-8.6	
32	Z1246243919	-8.6	

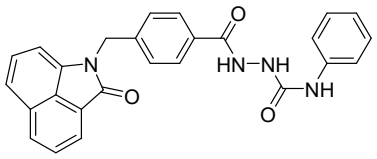
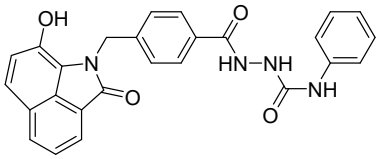
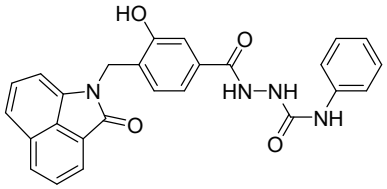
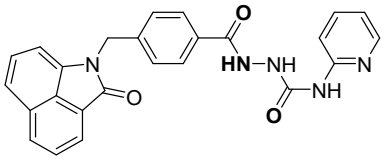
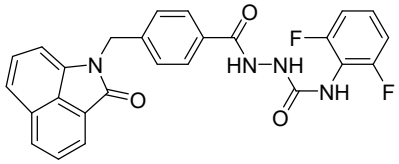
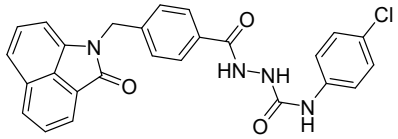
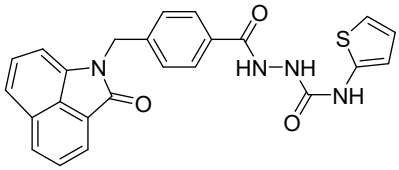
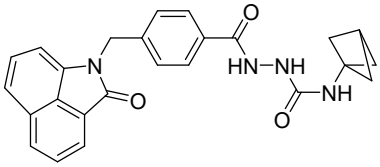
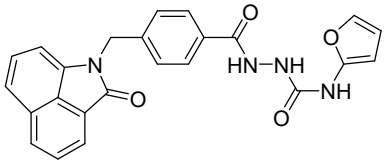
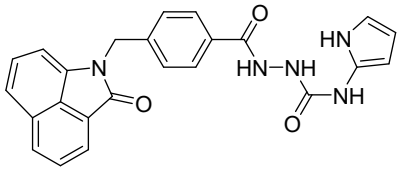
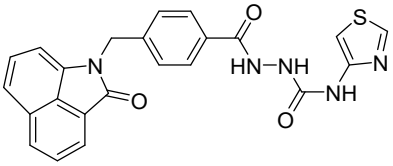
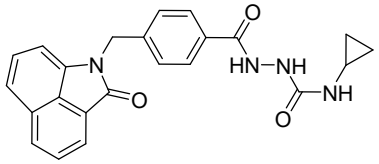
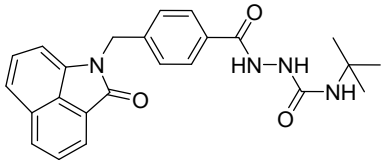
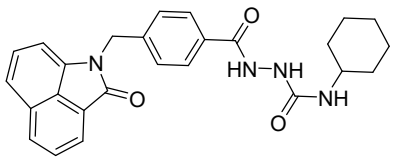
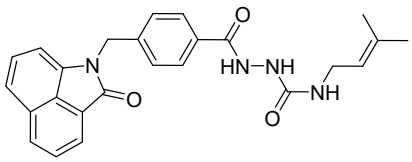
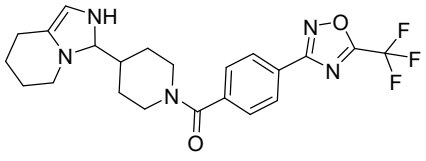
33	Z1257219130	-8.6	
34	Z131403708	-8.6	
35	Z1456429938	-8.6	
36	Z251327578	-8.6	
37	Z283926688	-8.6	
38	Z30471455	-8.6	
39	Z31270545	-8.6	

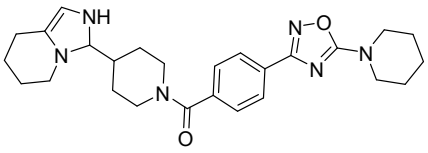
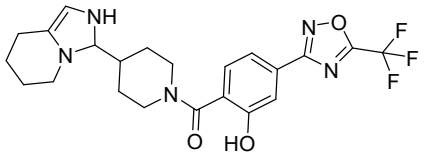
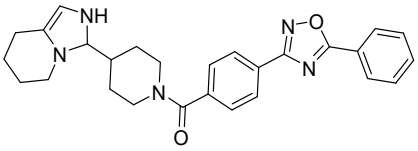
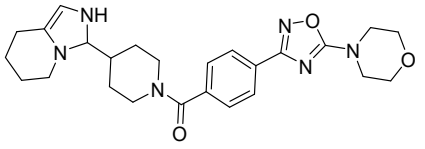
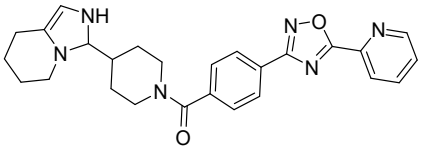
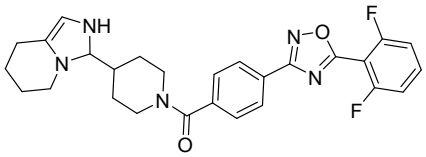
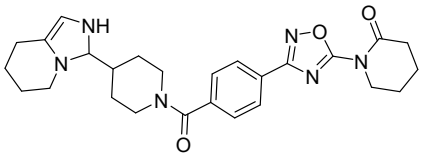
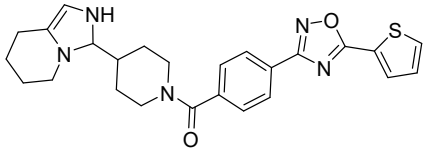
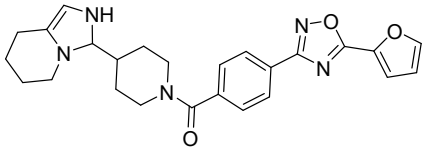
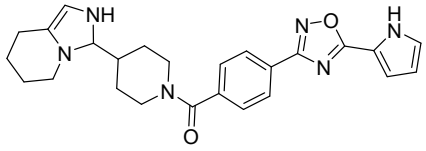
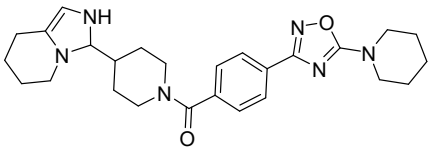
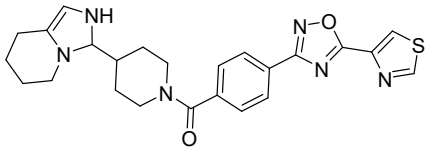
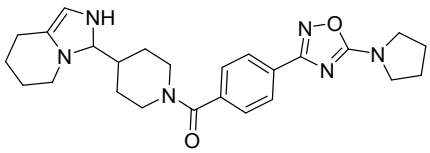
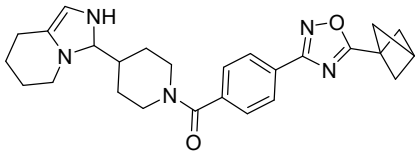
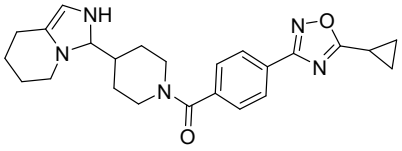
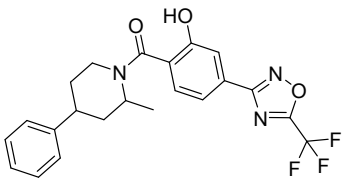
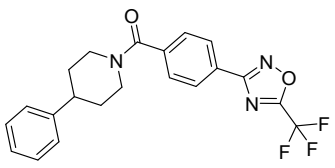
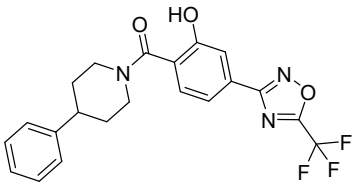
40	Z31272661	-8.6	
41	Z31274597	-8.6	
42	Z31274861	-8.6	
43	Z31274927	-8.6	
44	Z31275103	-8.6	
45	Z31275675	-8.6	

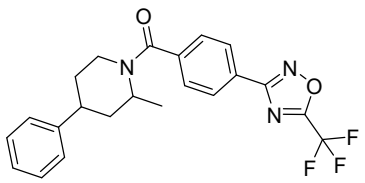
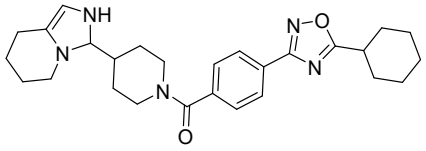
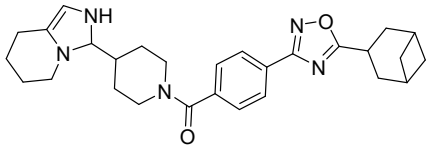
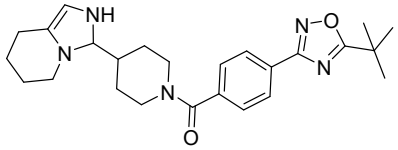
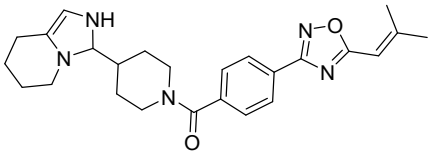
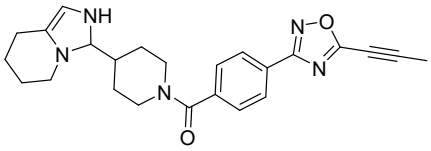
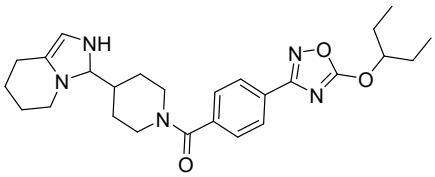
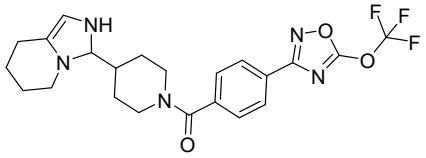
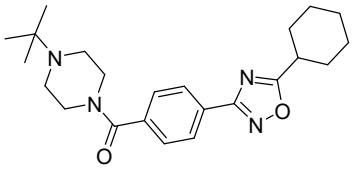
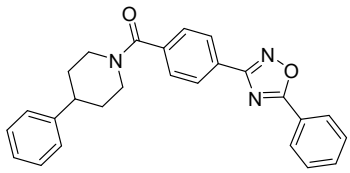
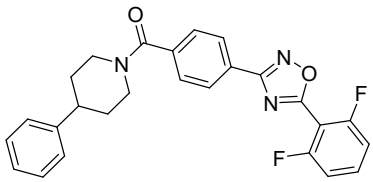
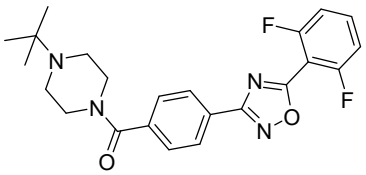
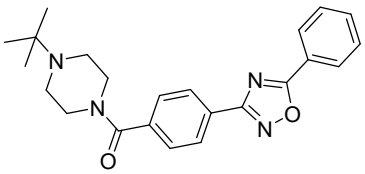
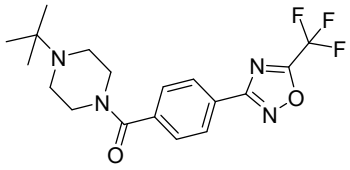
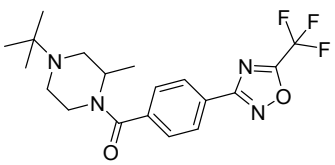
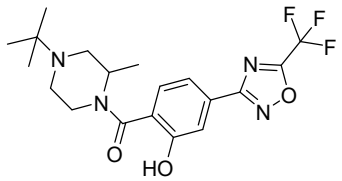
II. All small molecules (657 compounds) obtained by three rounds of molecular optimization.

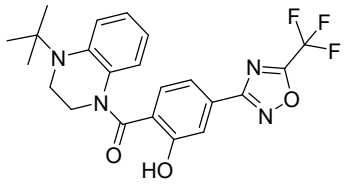
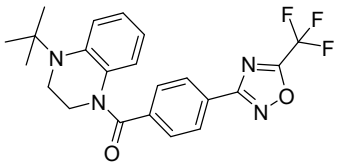
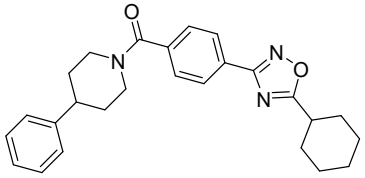
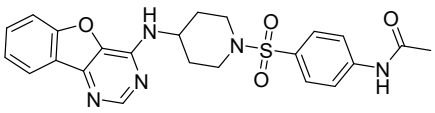
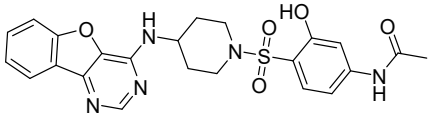
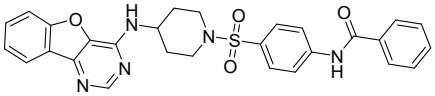
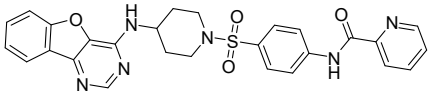
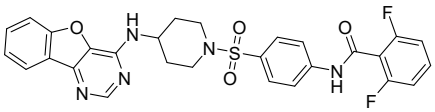
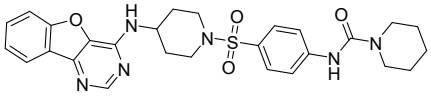
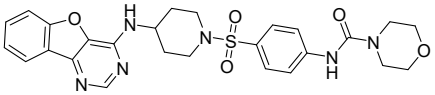
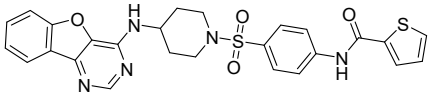
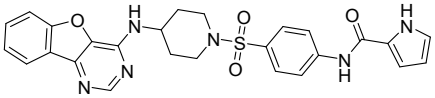
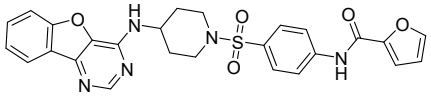
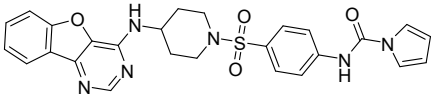
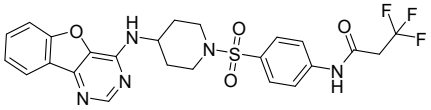
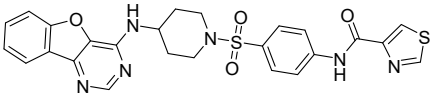
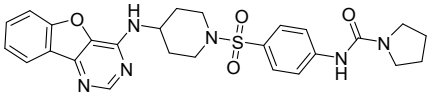
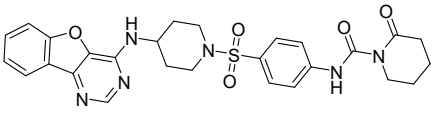
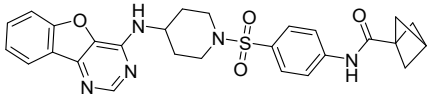
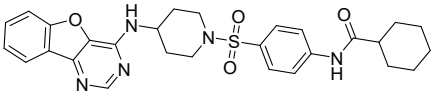
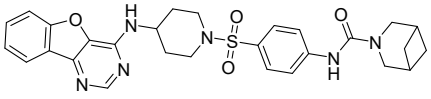
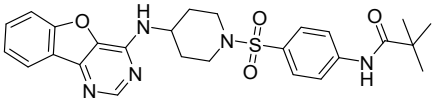
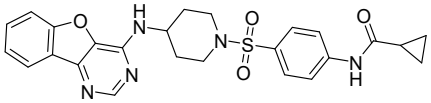
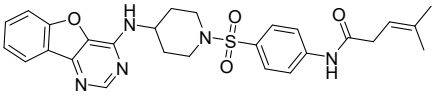
Table S4. The small molecules (288 compounds) obtained by the first round of molecular optimization.

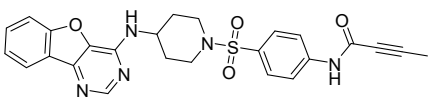
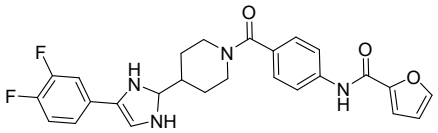
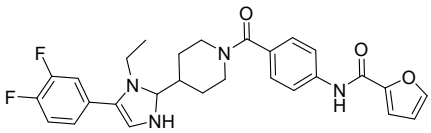
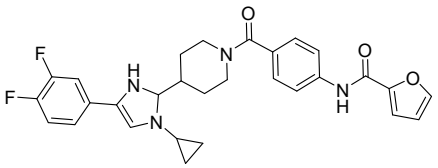
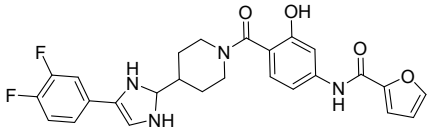
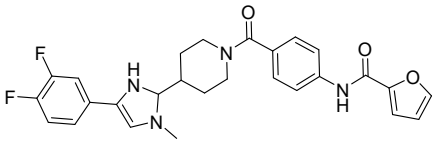
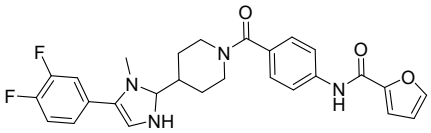
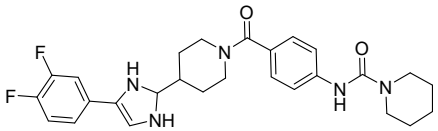
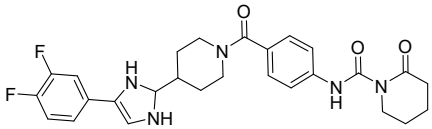
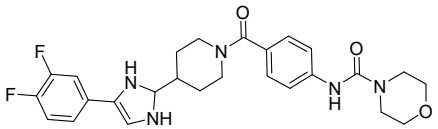
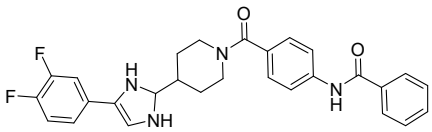
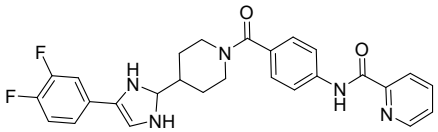
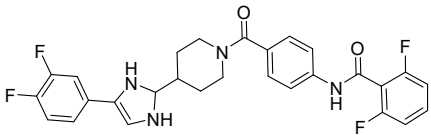
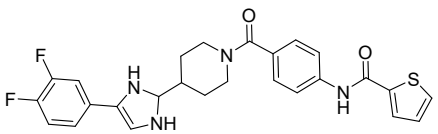
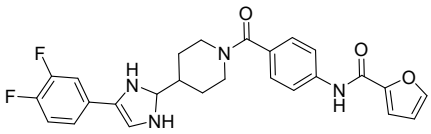
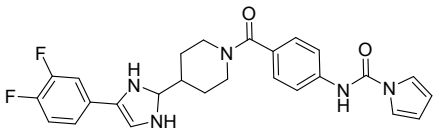
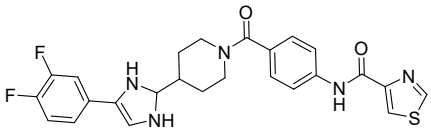
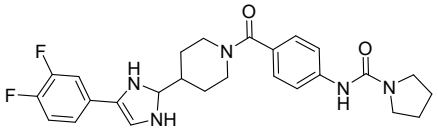
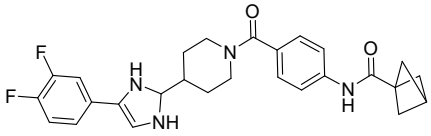
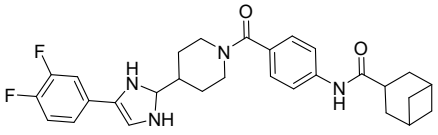
No.	Structure	No.	Structure

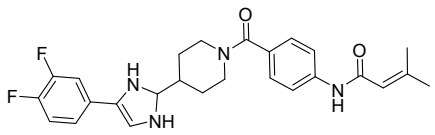
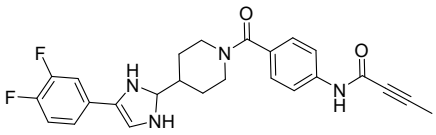
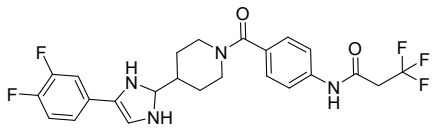
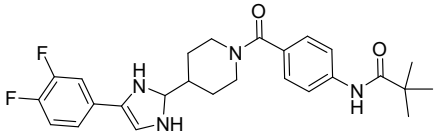
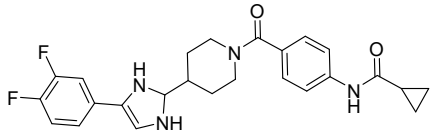
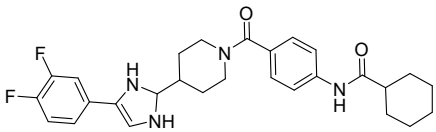
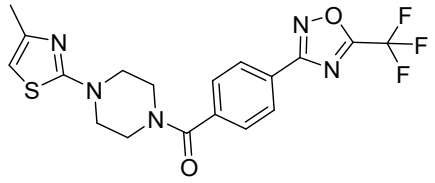
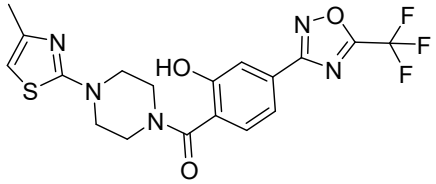
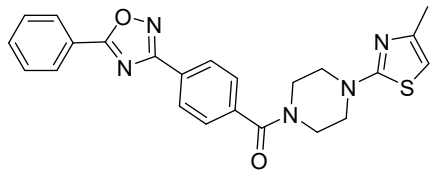
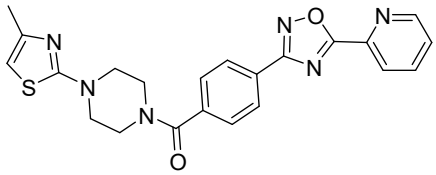
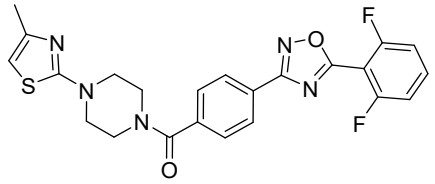
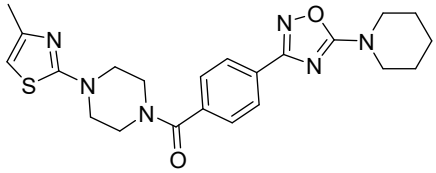
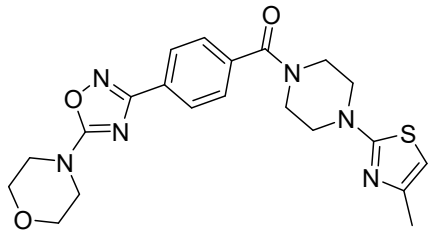
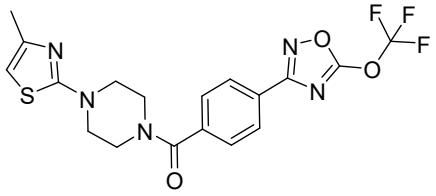
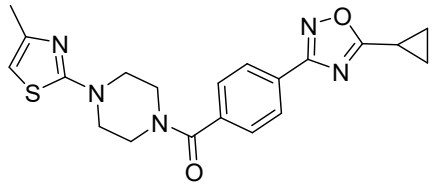
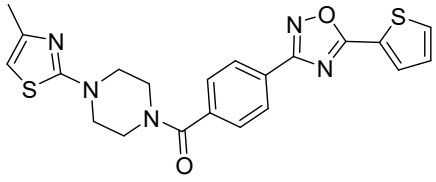
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	
13		14	
15		16	

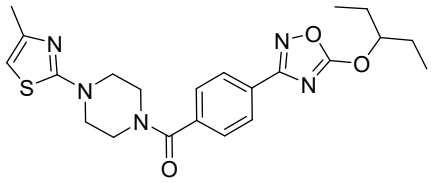
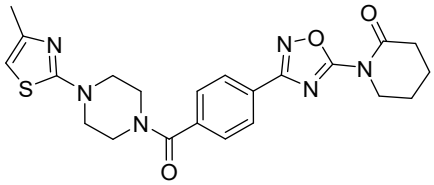
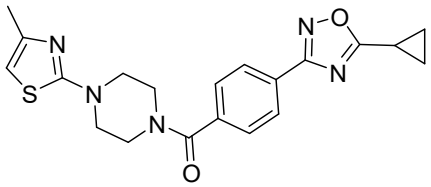
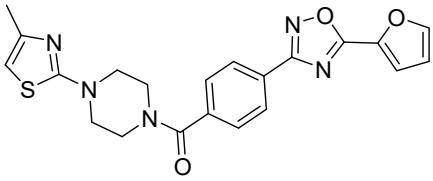
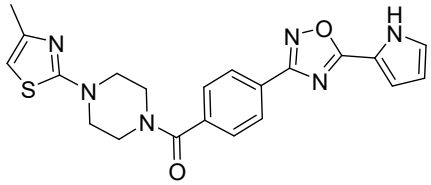
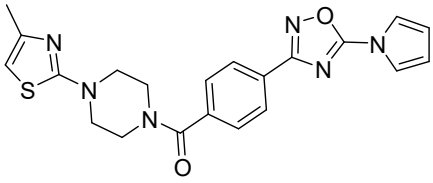
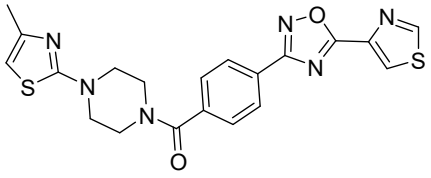
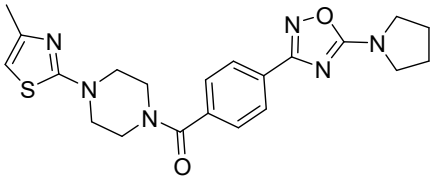
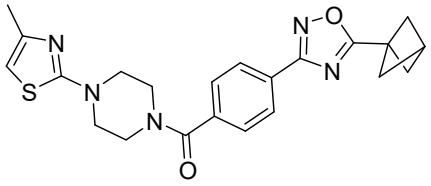
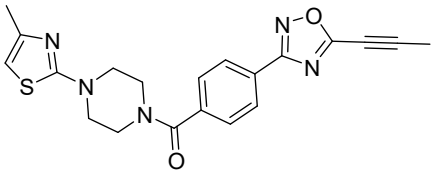
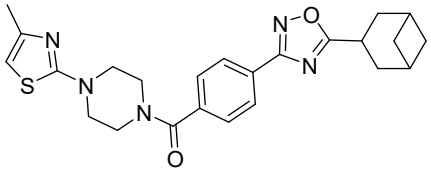
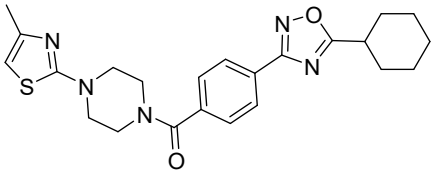
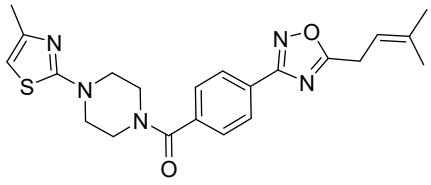
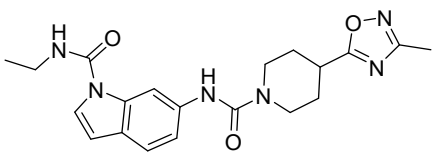
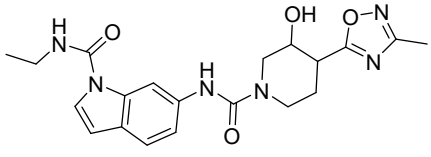
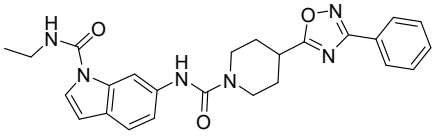
17		18	
19		20	
21		22	
23		24	
25		26	
27		28	
29		30	
31		32	
33		34	

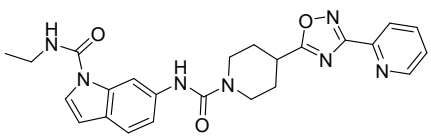
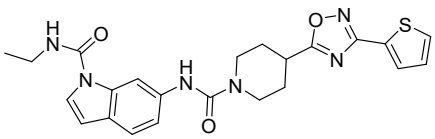
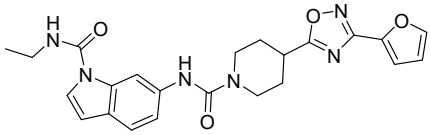
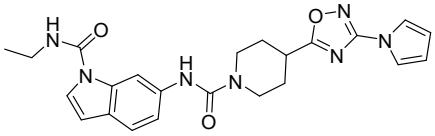
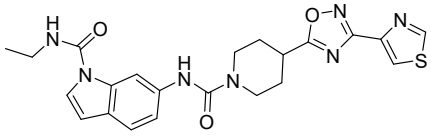
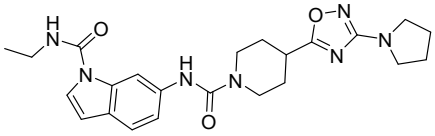
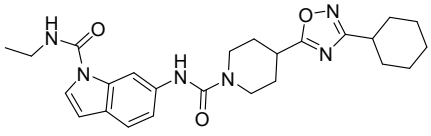
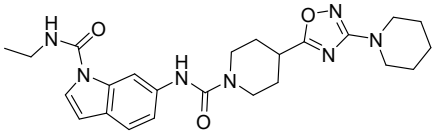
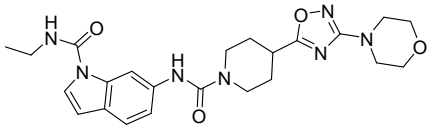
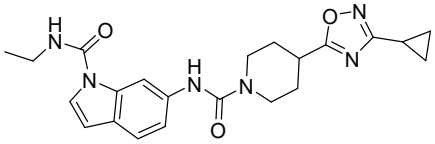
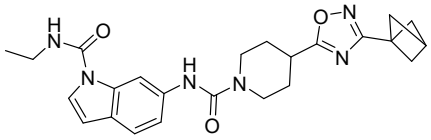
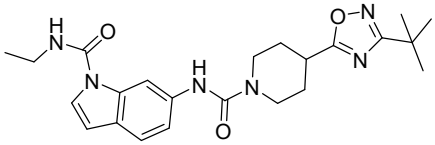
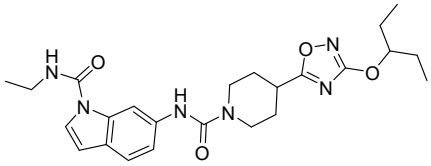
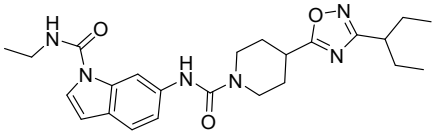
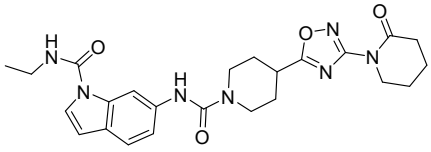
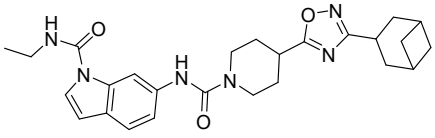
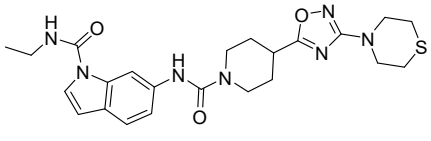
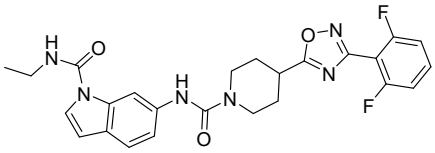
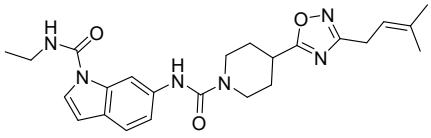
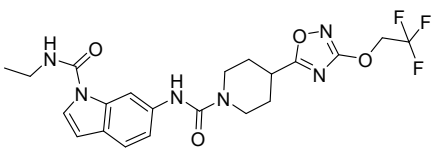
35		36	
37		38	
39		40	
41		42	
43		44	
45		46	
47		48	
49		50	

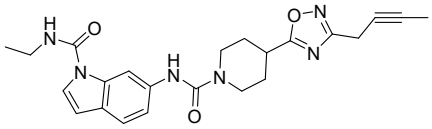
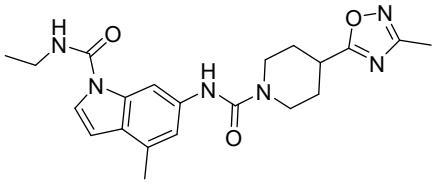
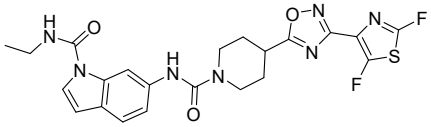
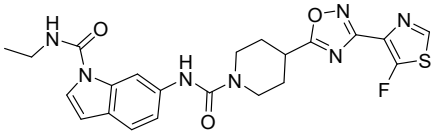
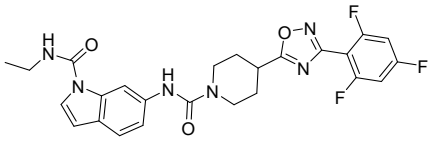
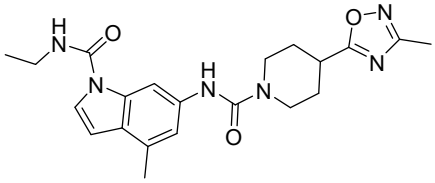
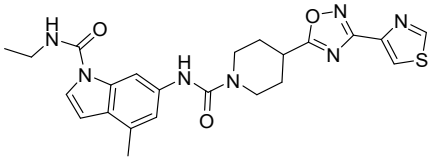
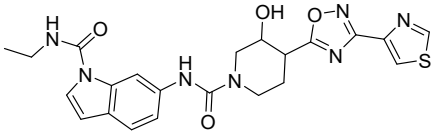
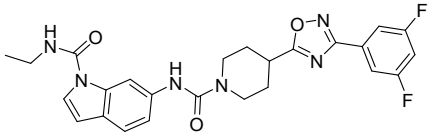
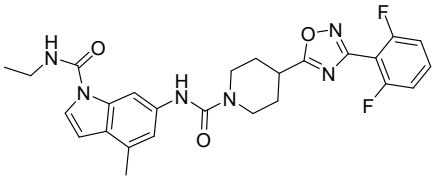
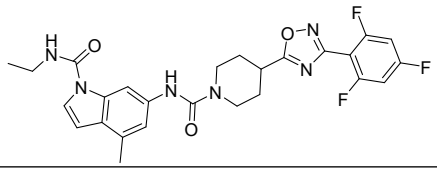
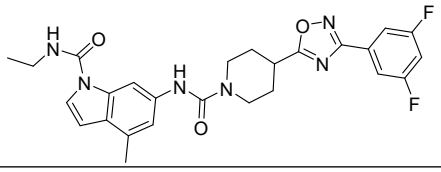
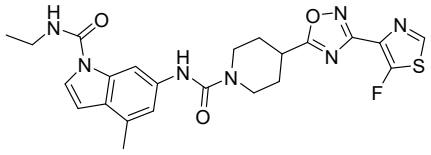
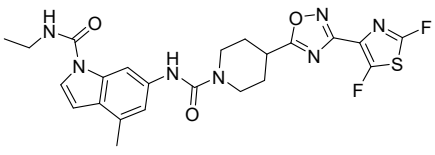
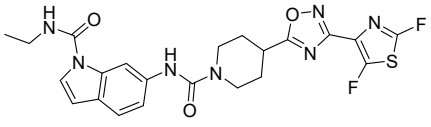
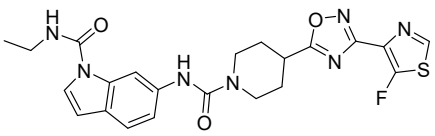
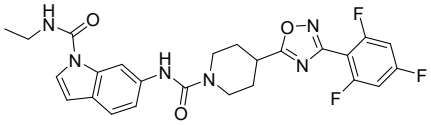
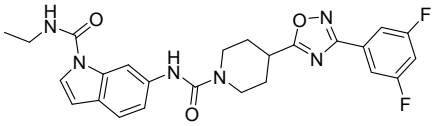
51		52	
53		54	
55		56	
57		58	
59		60	
61		62	
63		64	
65		66	
67		68	
69		70	
71		72	
73		74	

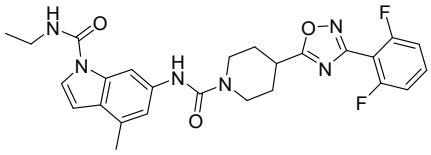
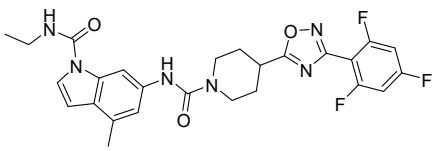
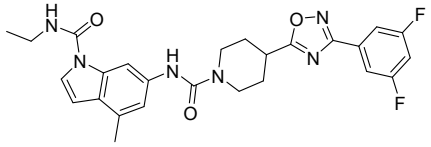
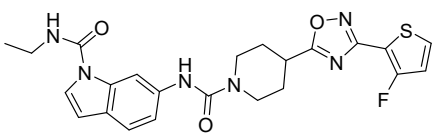
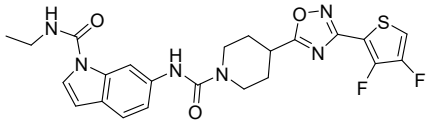
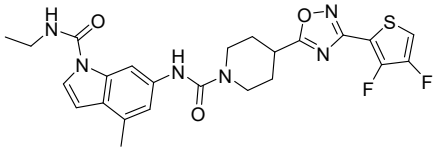
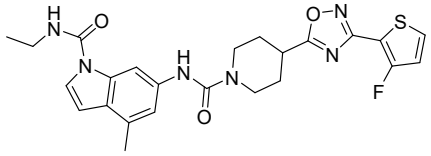
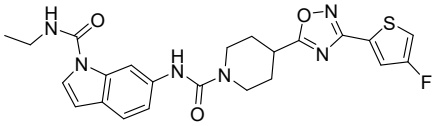
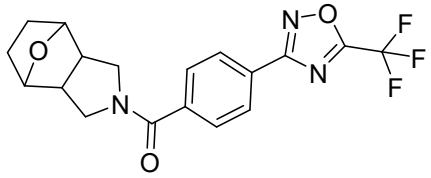
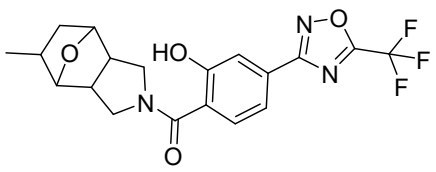
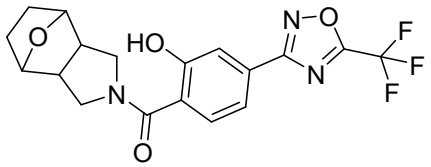
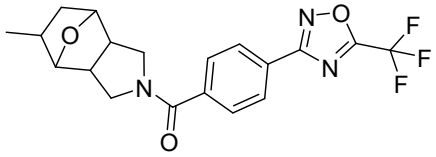
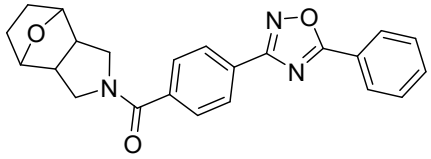
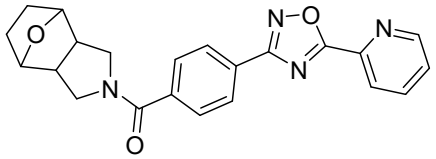
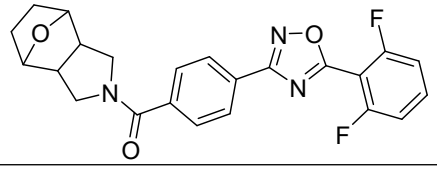
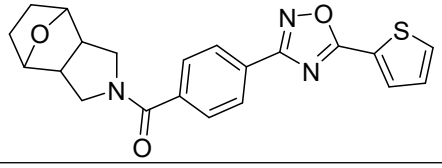
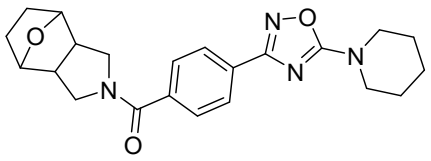
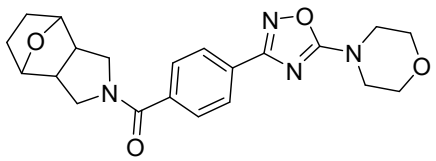
75		76	
77		78	
79		80	
81		82	
83		84	
85		86	
87		88	
89		90	
91		92	
93		94	

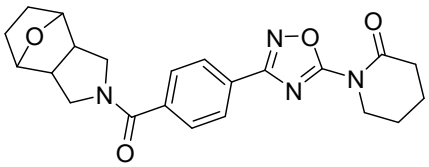
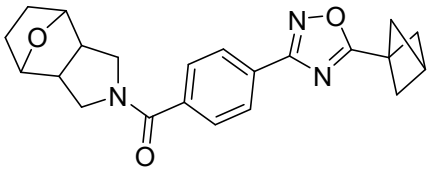
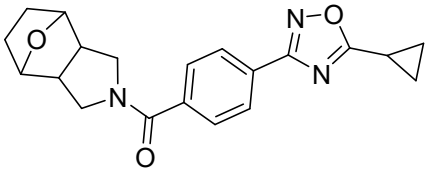
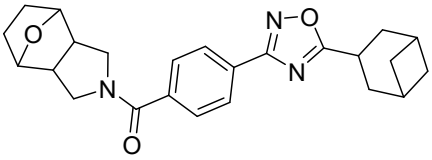
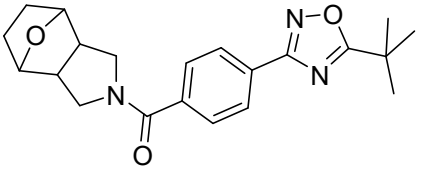
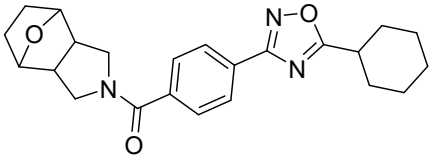
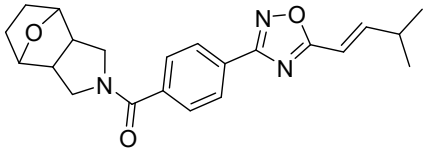
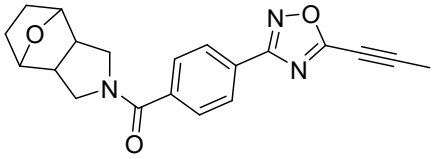
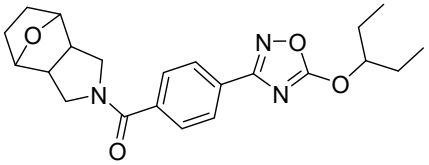
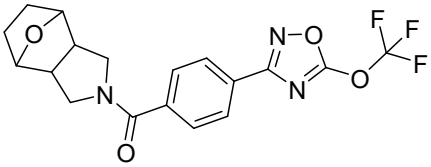
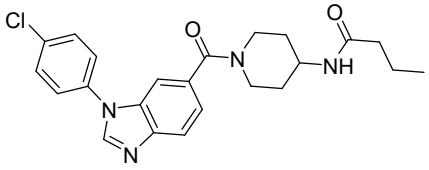
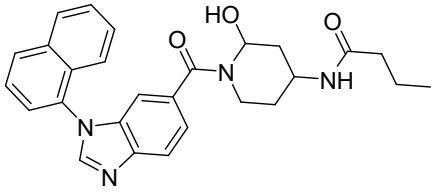
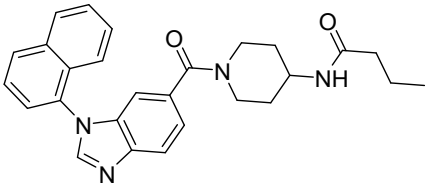
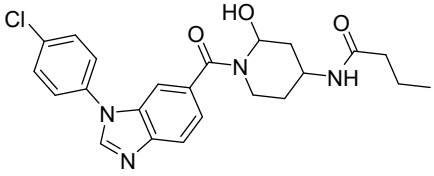
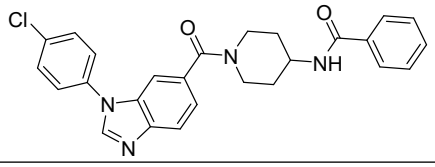
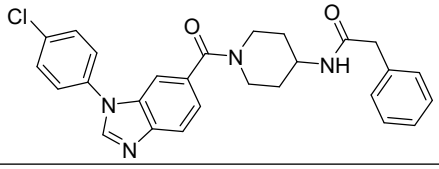
95		96	
97		98	
99		100	
101		102	
103		104	
105		106	
107		108	
109		110	

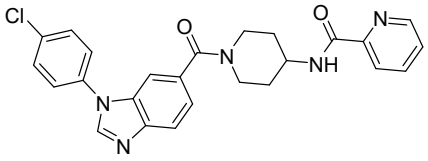
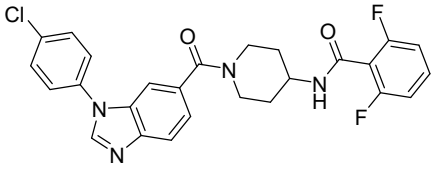
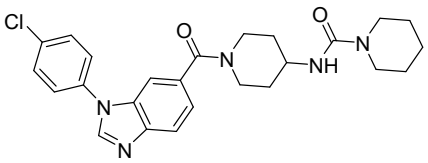
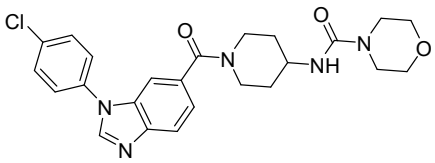
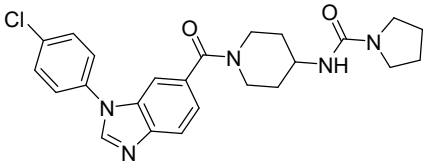
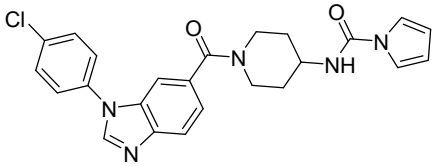
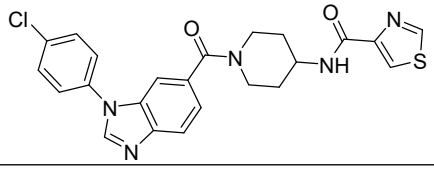
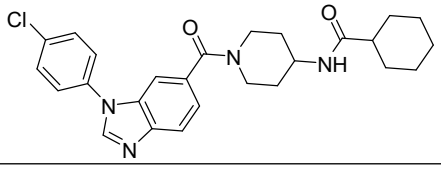
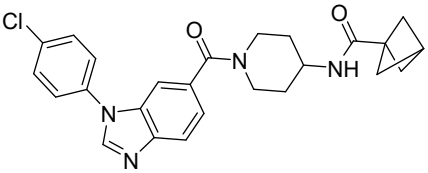
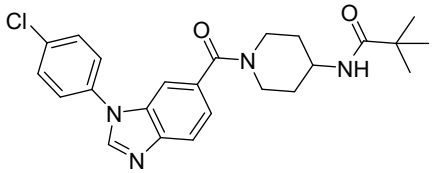
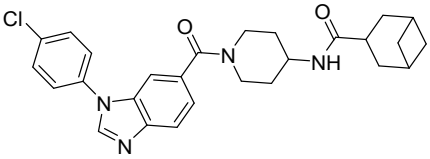
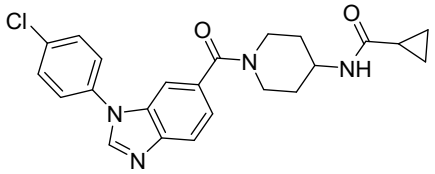
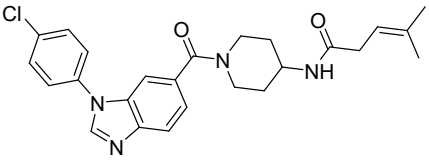
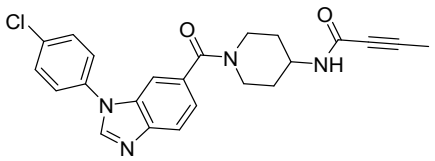
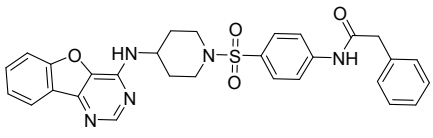
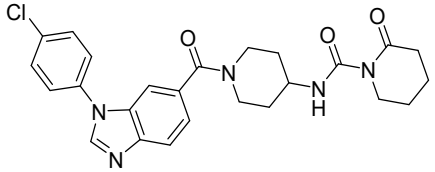
111		112	
113		114	
115		116	
117		118	
119		120	
121		122	
123		124	
125		126	

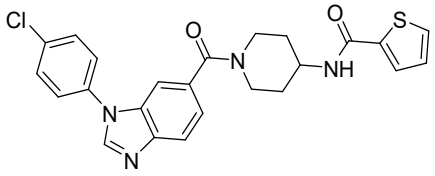
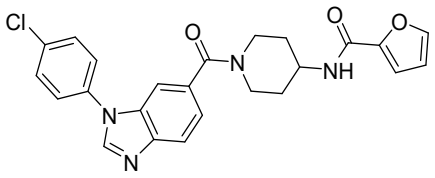
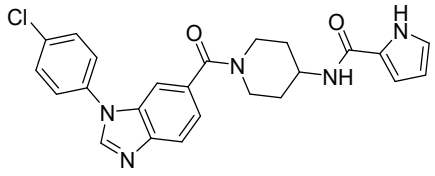
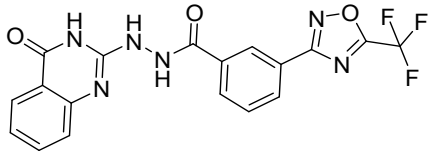
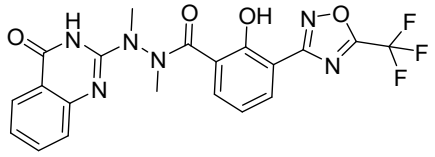
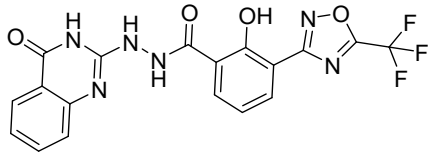
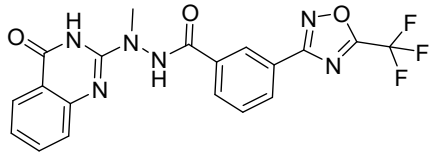
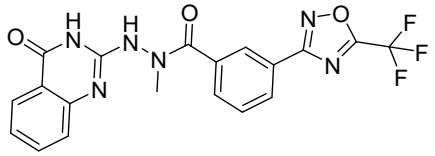
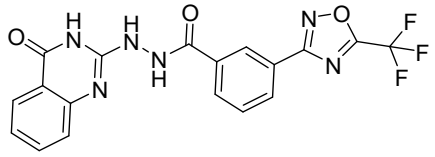
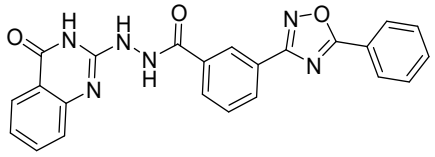
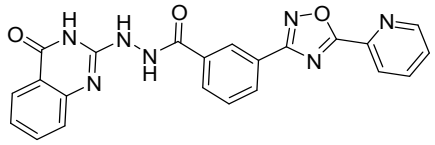
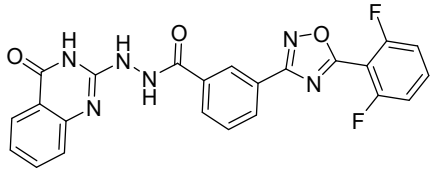
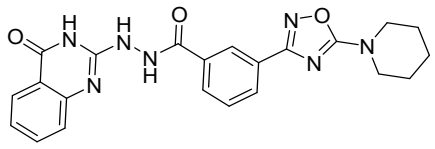
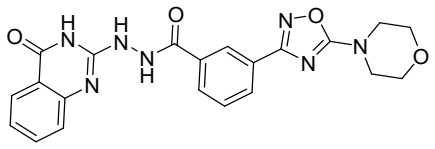
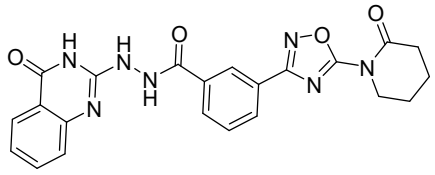
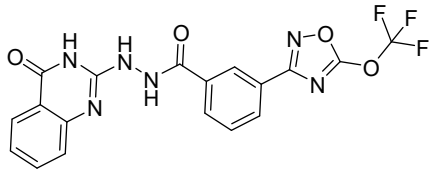
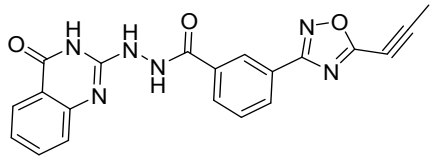
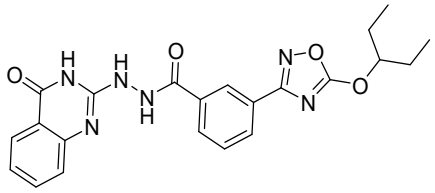
127		128	
129		130	
131		132	
133		134	
135		136	
137		138	
139		140	
141		142	
143		144	
145		146	

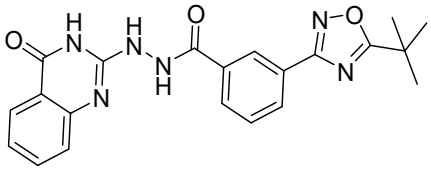
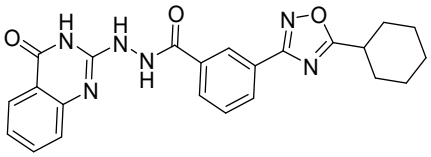
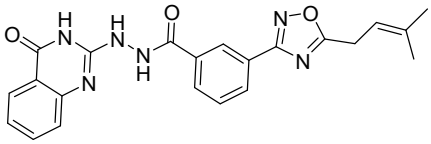
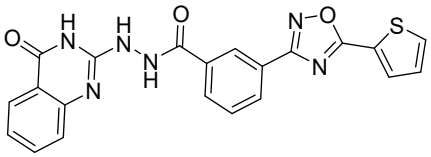
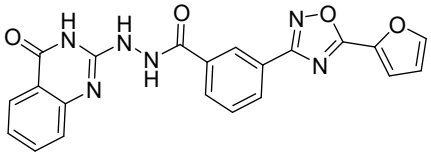
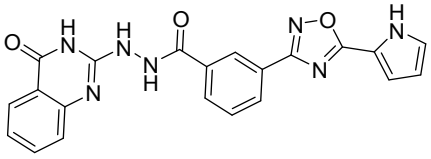
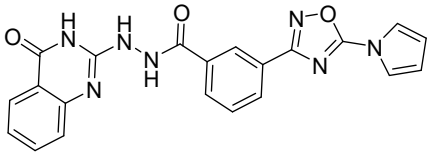
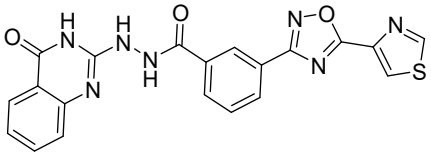
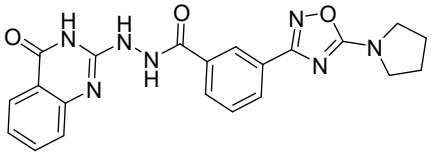
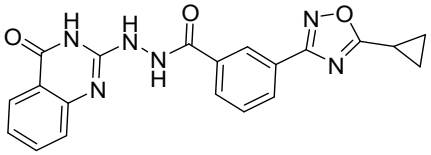
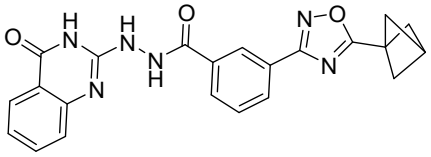
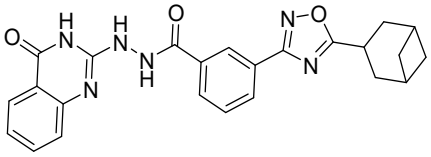
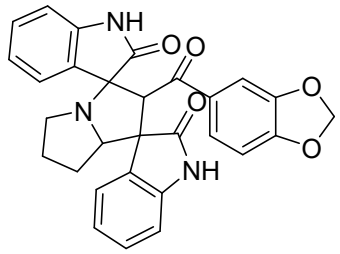
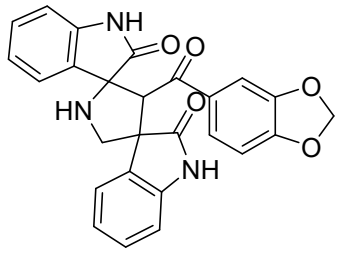
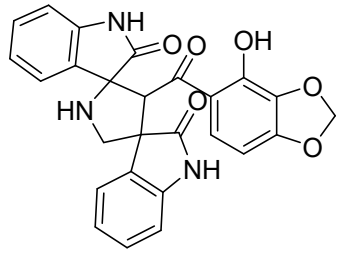
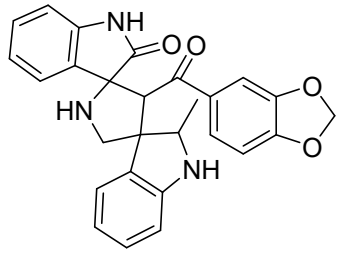
147		148	
149		150	
151		152	
153		154	
155		156	
157		158	
159		160	
161		162	
163		164	

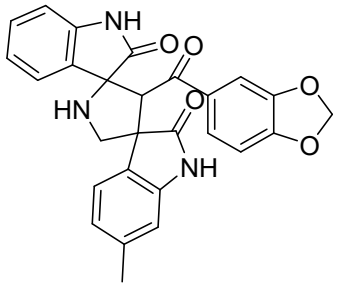
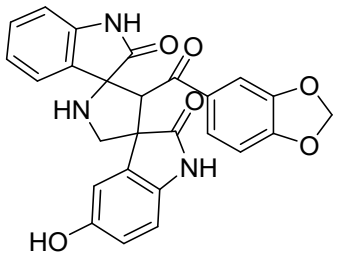
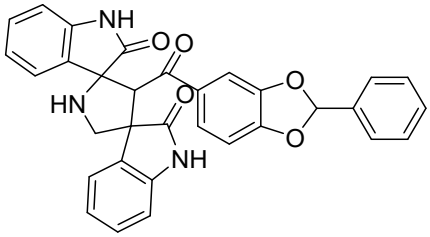
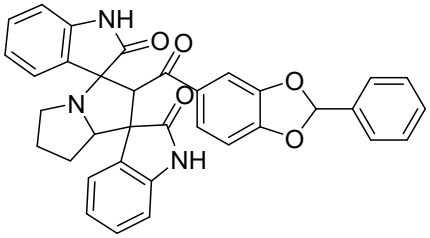
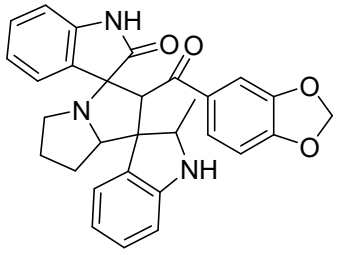
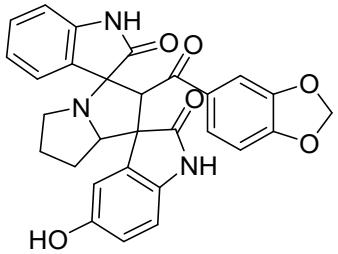
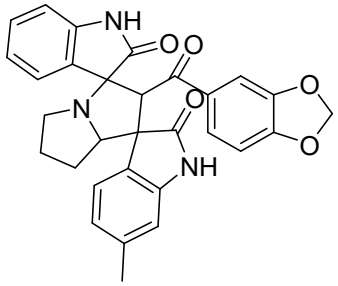
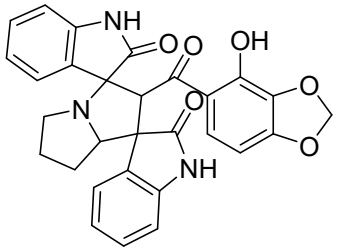
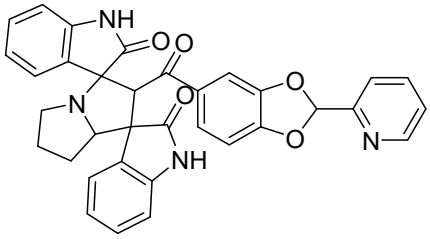
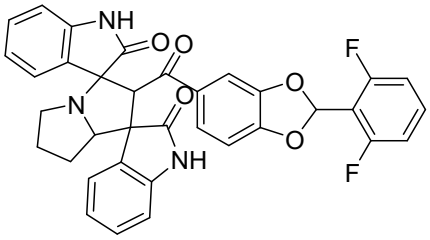
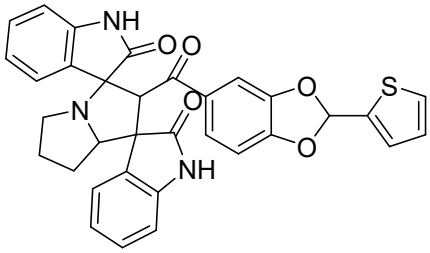
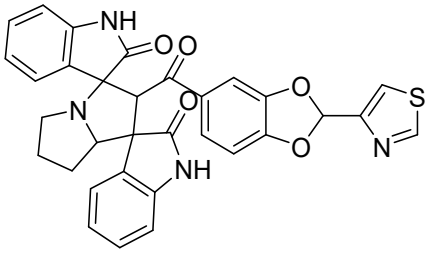
165		166	
167		168	
169		170	
171		172	
173		174	
175		176	
177		178	
179		180	
181		182	

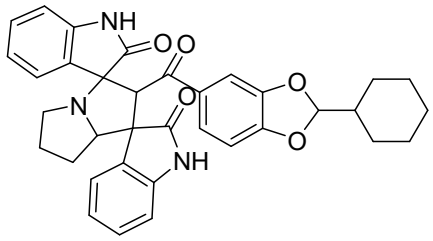
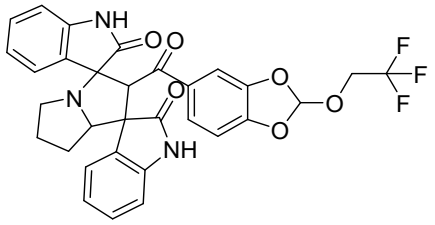
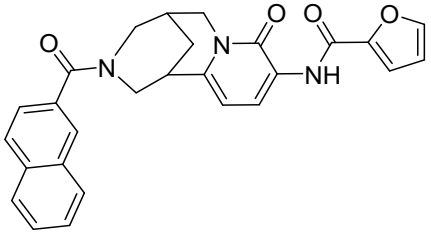
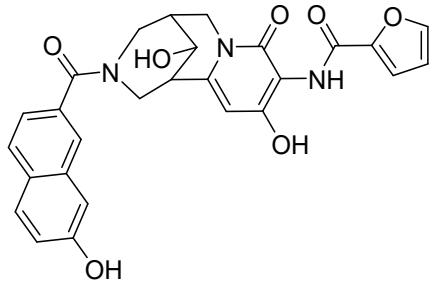
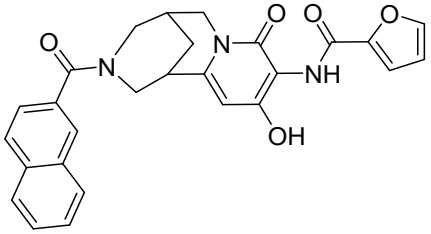
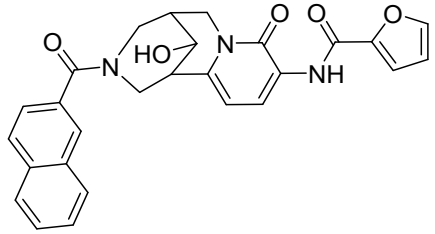
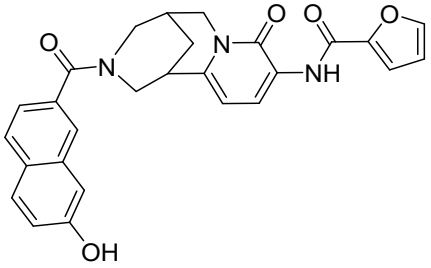
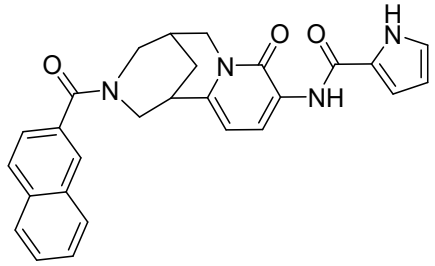
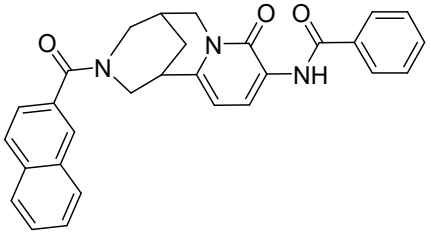
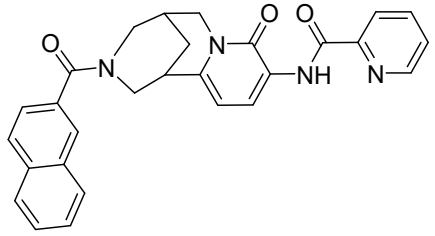
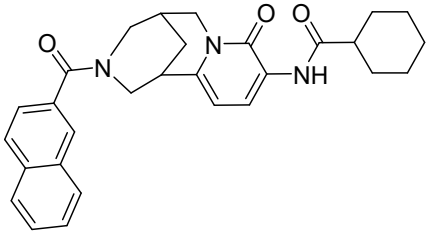
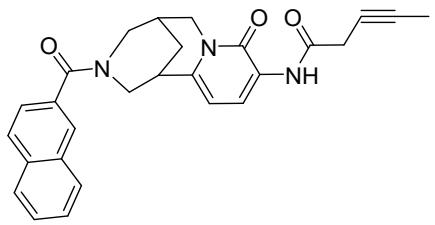
183		184	
185		186	
187		188	
189		190	
191		192	
193		194	
195		196	
197		198	

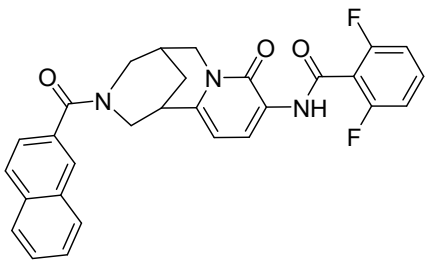
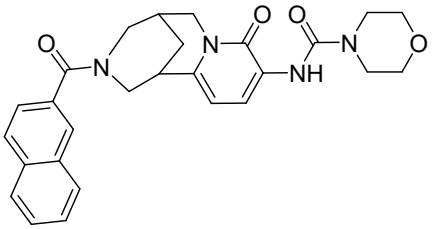
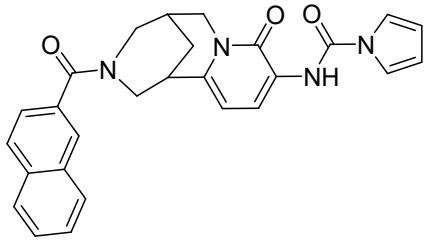
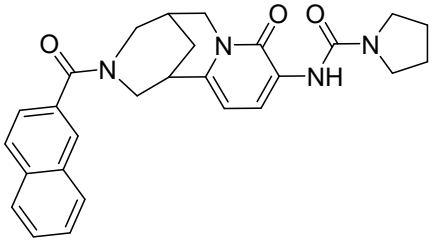
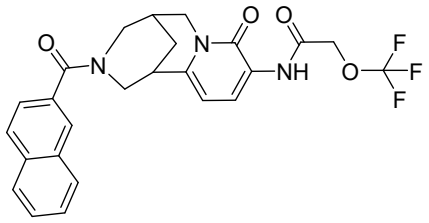
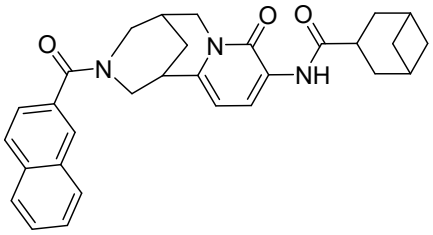
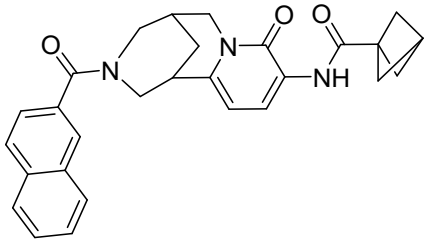
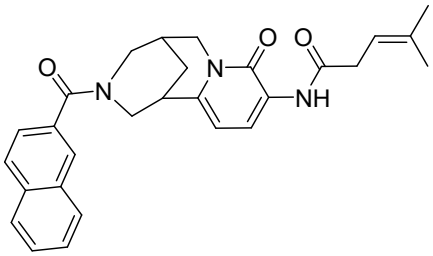
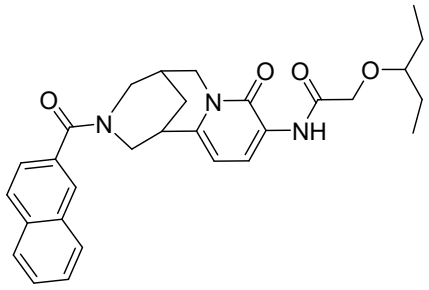
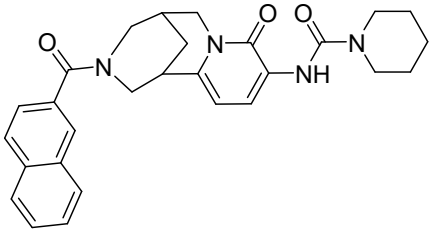
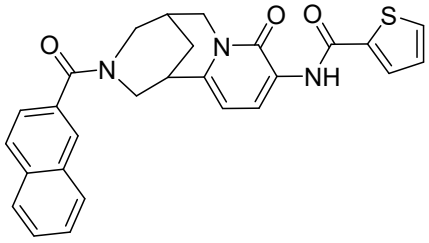
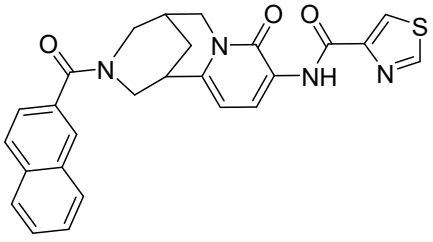
199		200	
201		202	
203		204	
205		206	
207		208	
209		210	
211		212	
213		214	

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		248	

249		250	
251		252	
253		254	
255		256	
257		258	
259		260	

261		262	
263		264	
265		266	
267		268	
269		270	
271		272	

273		274	
275		276	
277		278	
279		280	
281		282	
283		284	

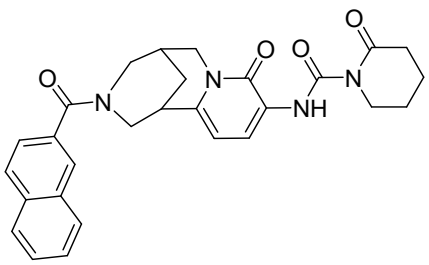
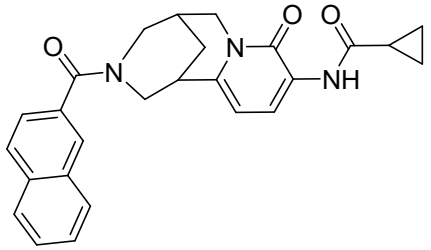
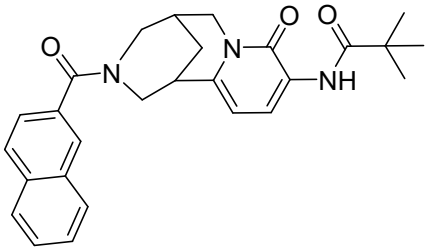
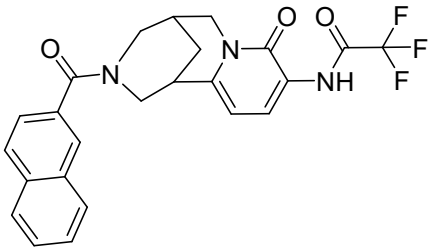
285		286	
287		288	

Table S5. The small molecules (228 compounds) obtained by the second round of molecular optimization.

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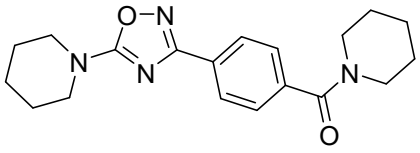
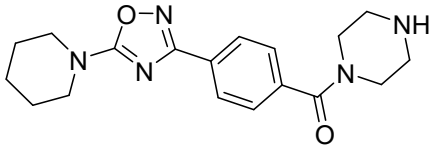
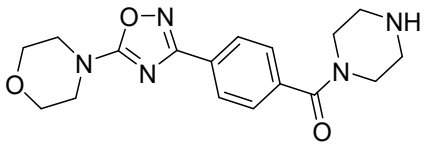
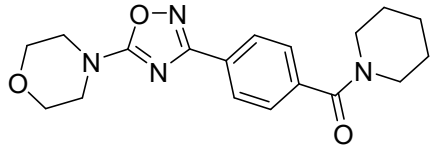
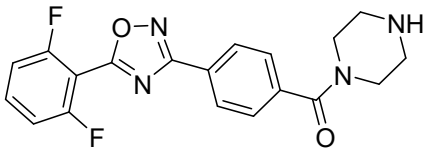
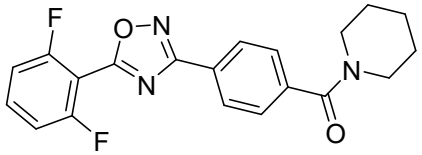
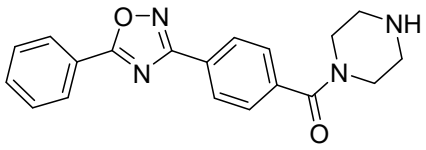
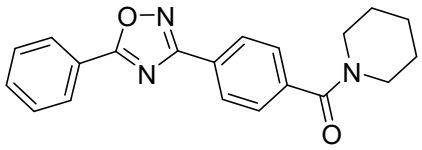
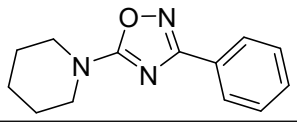
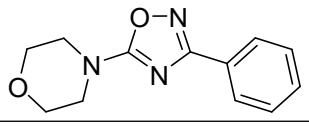
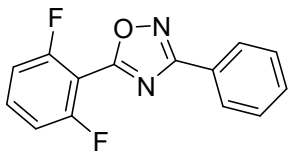
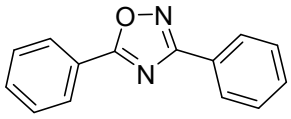
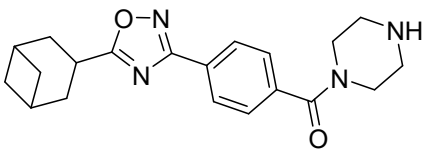
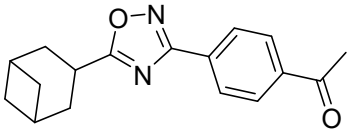
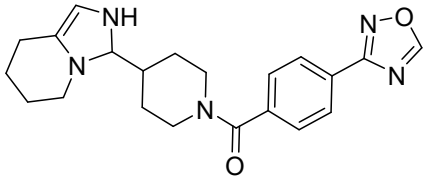
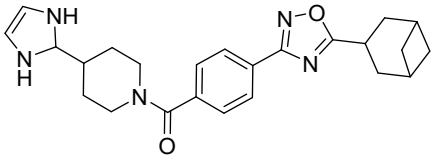
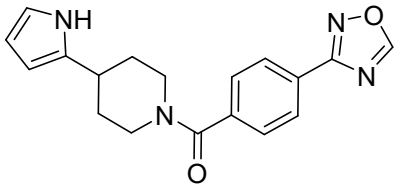
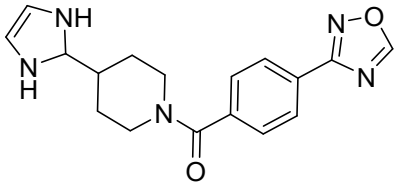
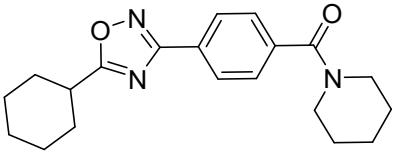
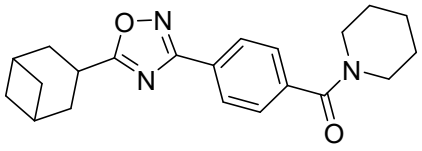
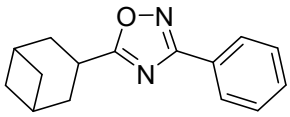
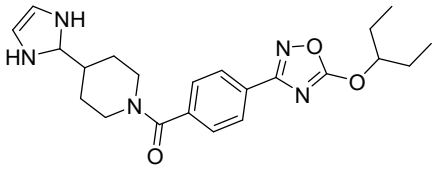
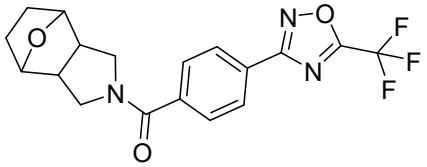
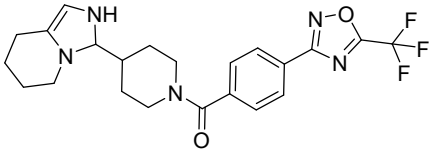
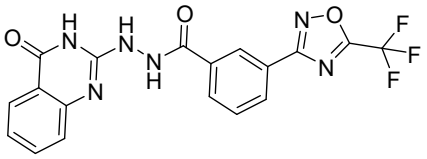
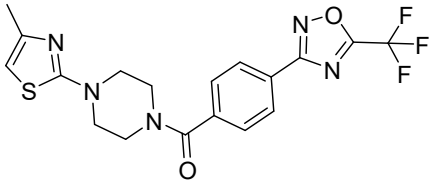
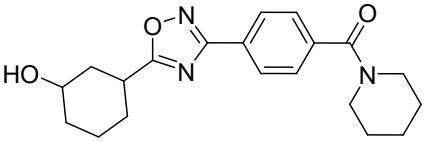
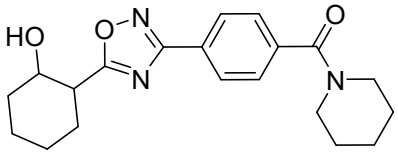
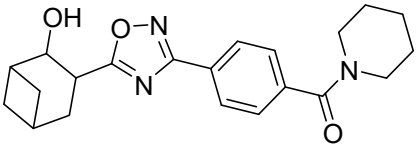
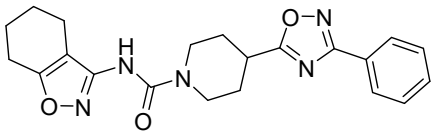
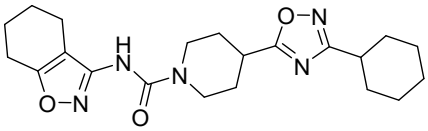
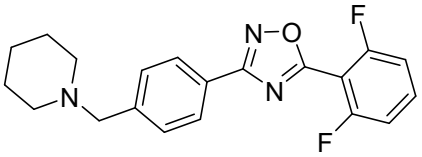
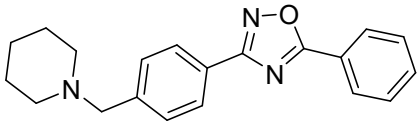
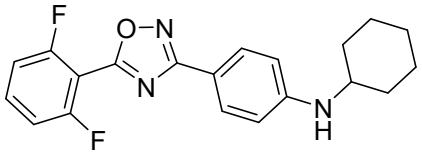
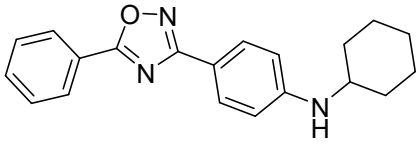
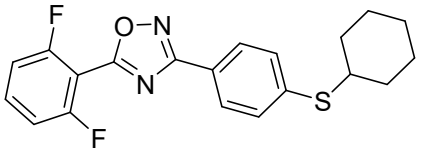
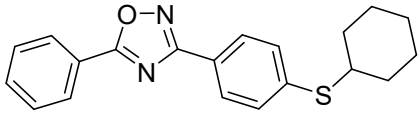
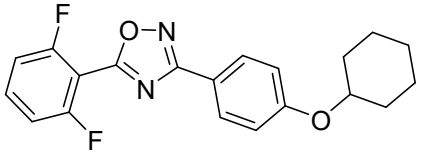
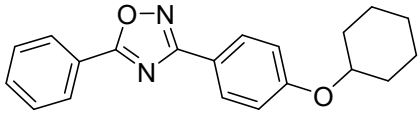
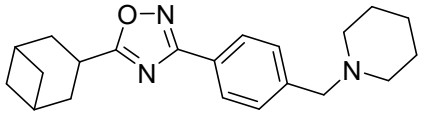
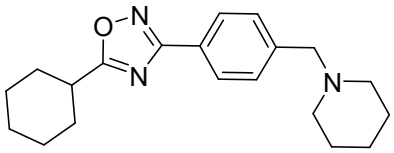
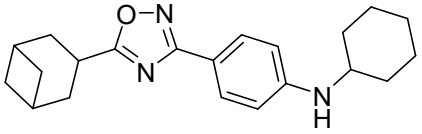
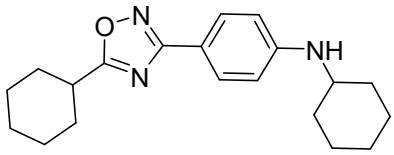
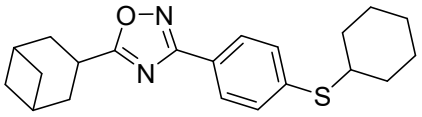
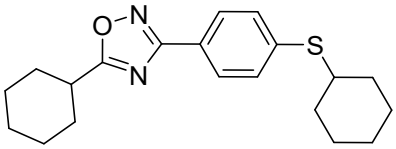
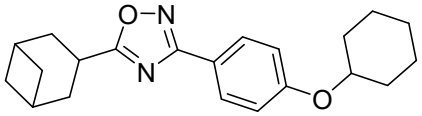
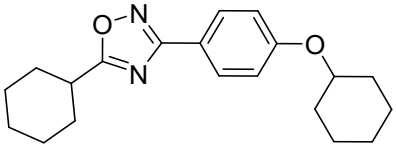
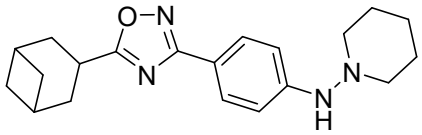
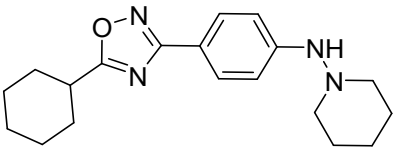
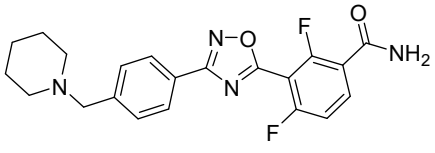
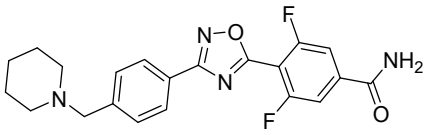
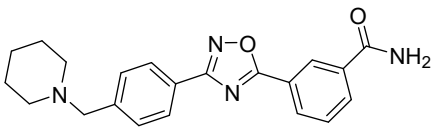
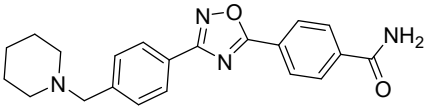
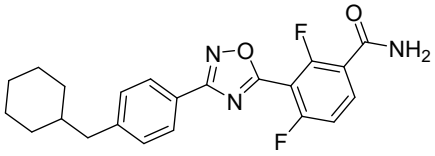
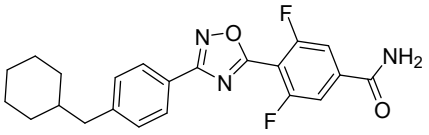
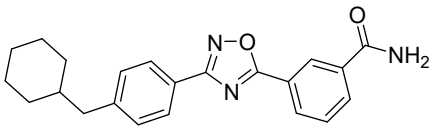
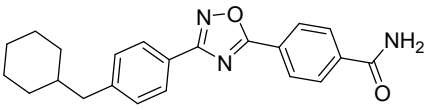
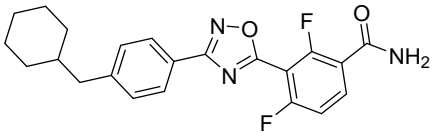
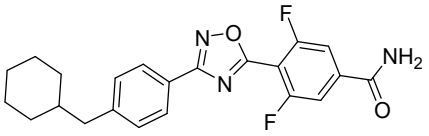
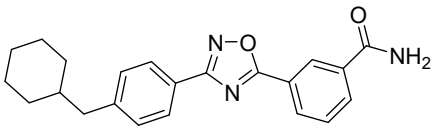
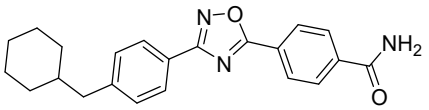
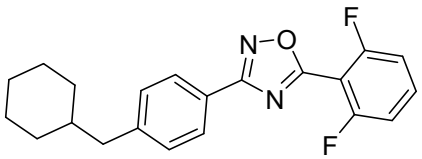
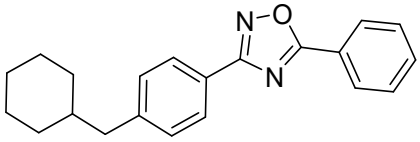
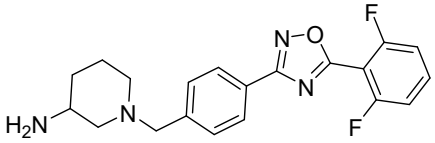
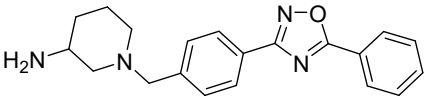
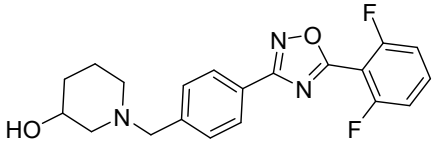
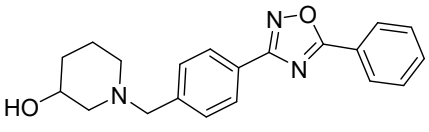
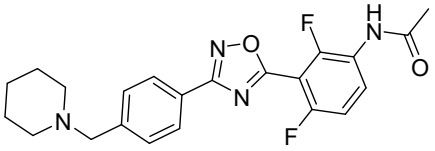
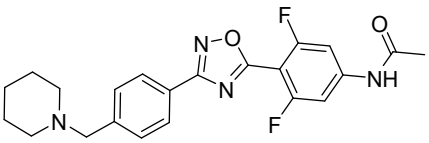
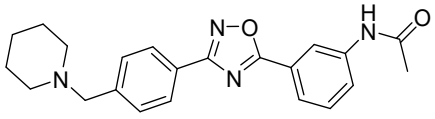
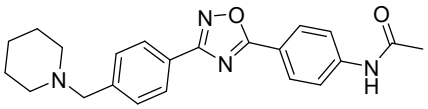
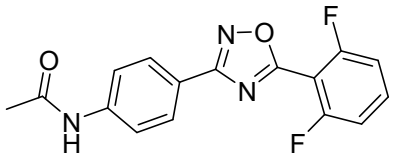
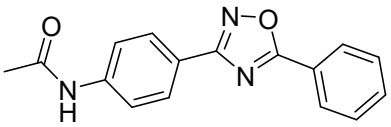
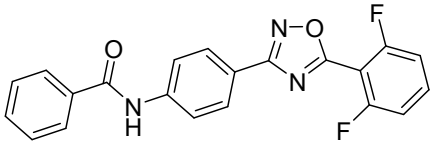
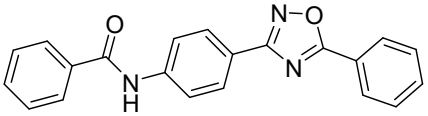
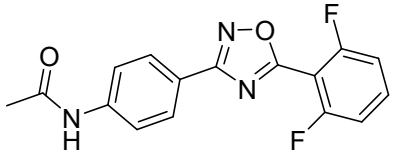
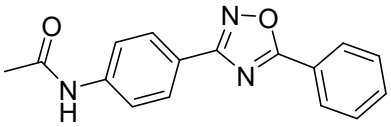
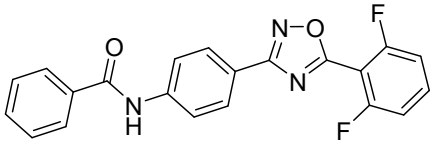
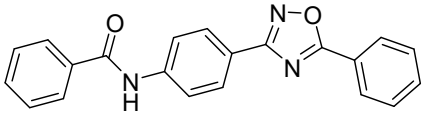
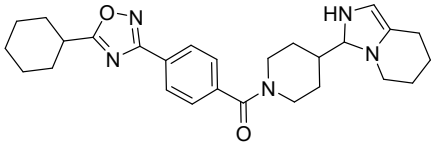
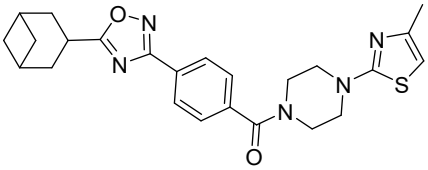
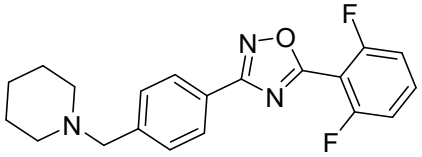
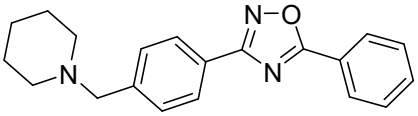
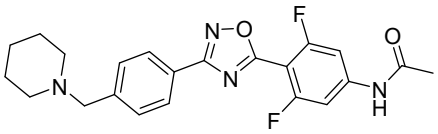
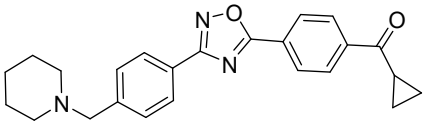
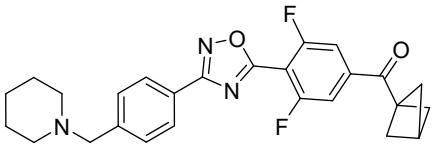
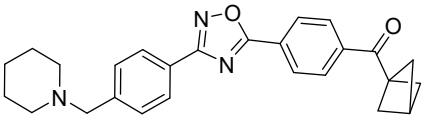
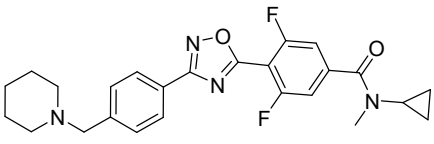
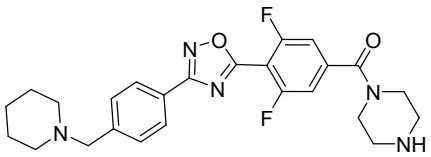
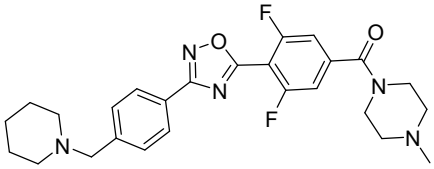
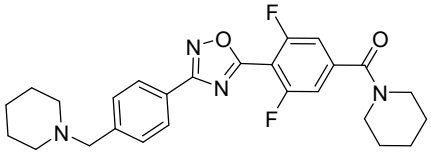
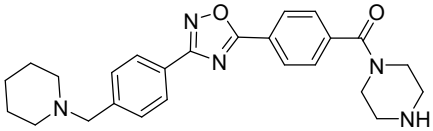
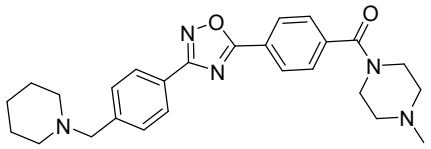
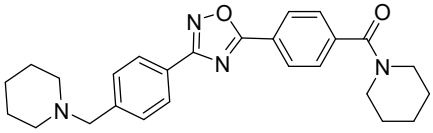
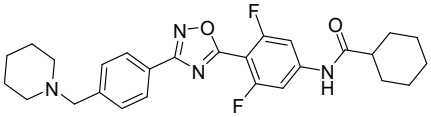
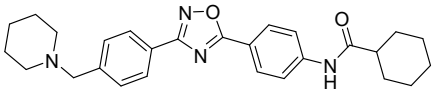
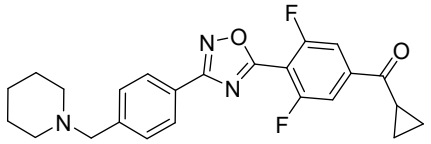
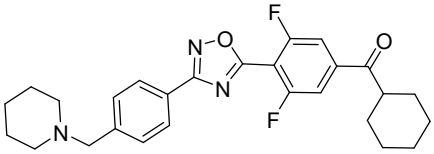
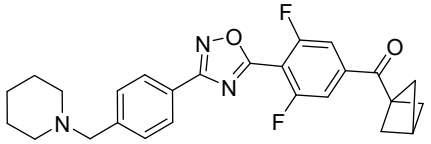
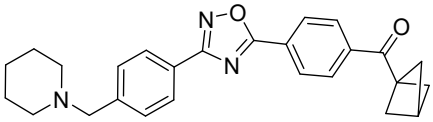
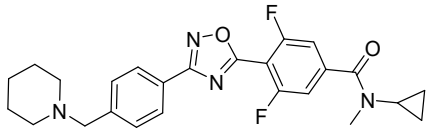
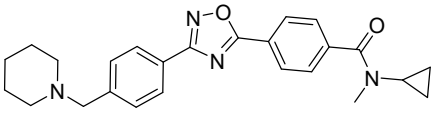
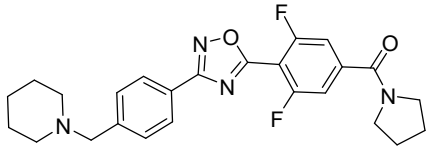
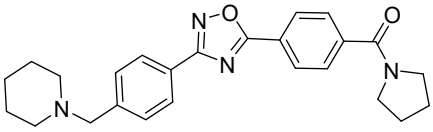
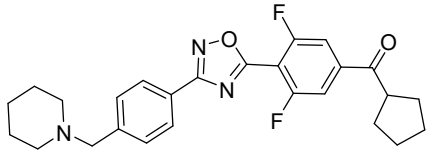
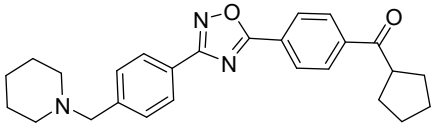
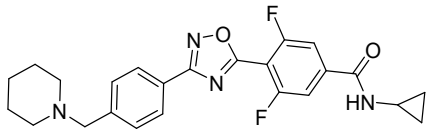
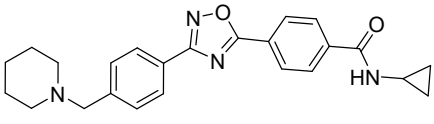
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	

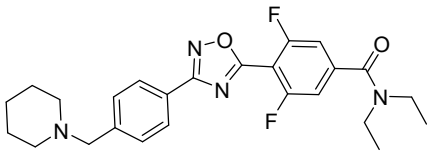
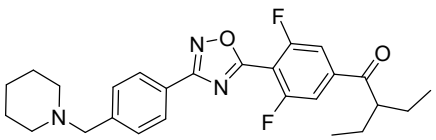
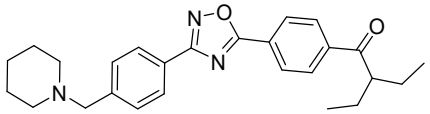
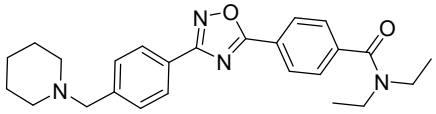
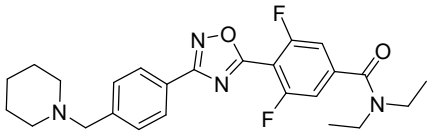
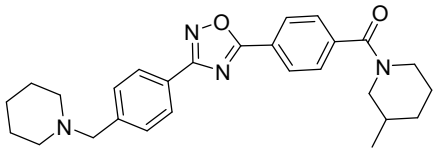
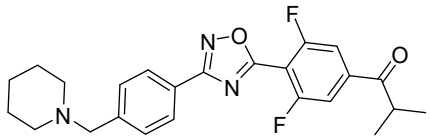
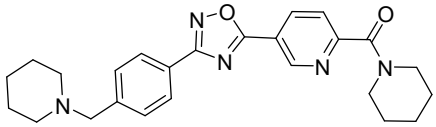
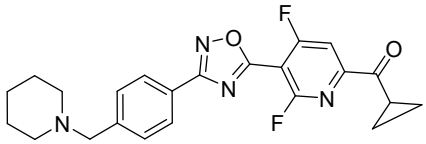
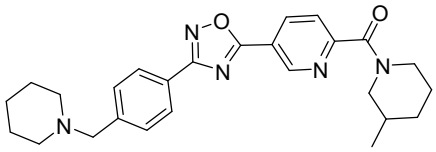
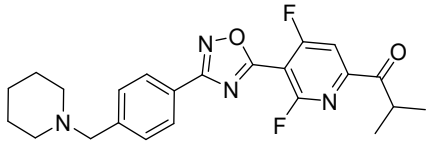
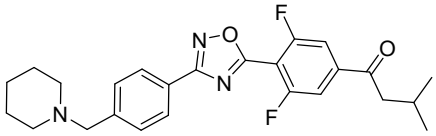
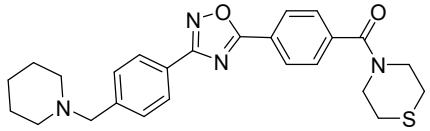
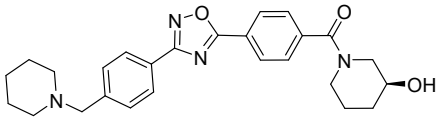
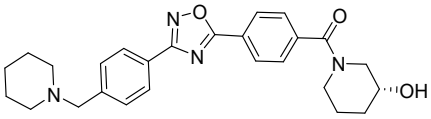
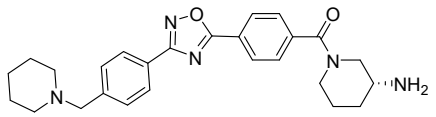
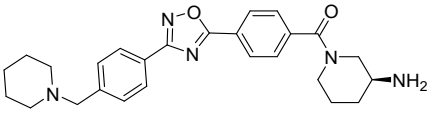
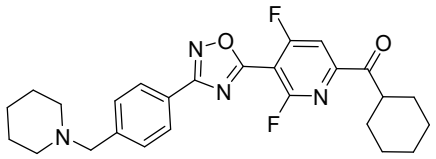
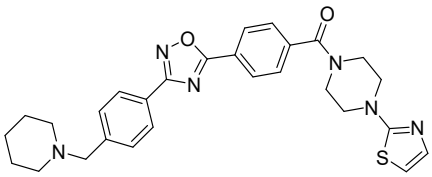
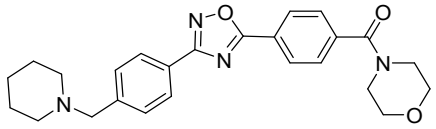
13		14	
15		16	
17		18	
19		20	
21		22	
23		24	
25		26	
27		28	
29		30	

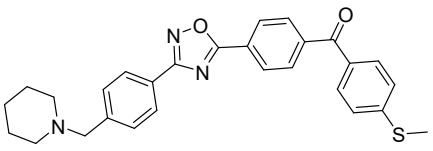
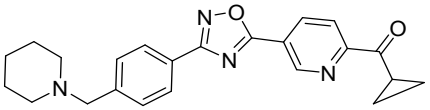
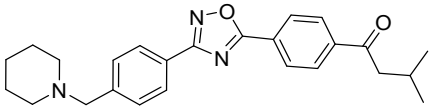
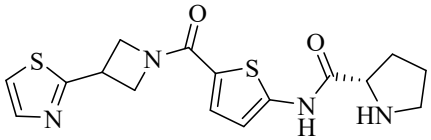
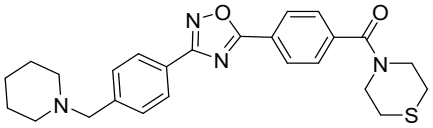
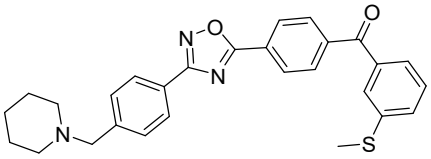
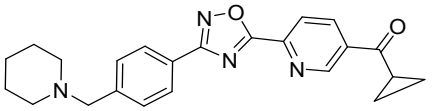
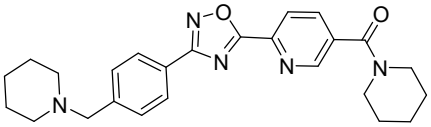
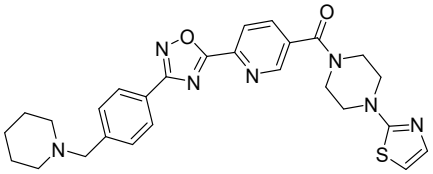
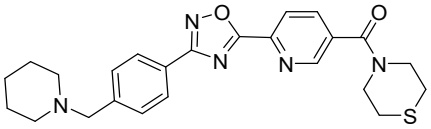
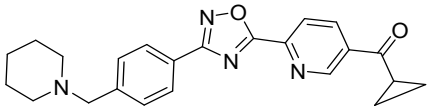
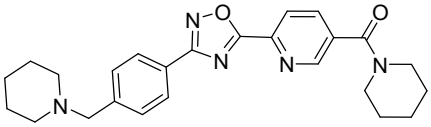
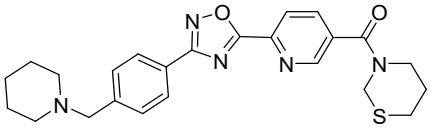
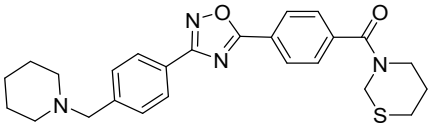
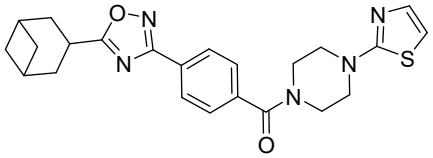
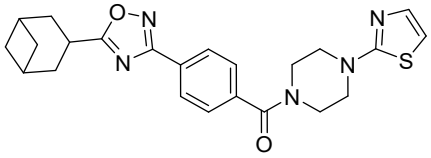
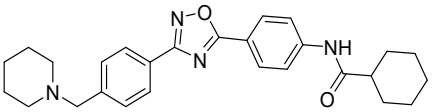
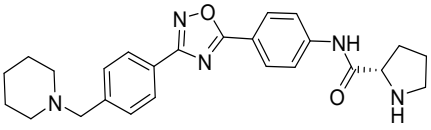
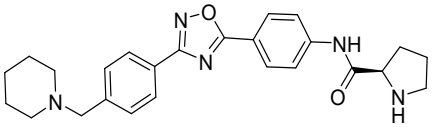
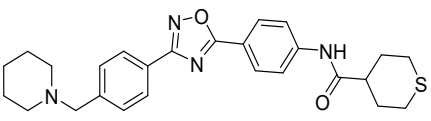
31		32	
33		34	
35		36	
37		38	
39		40	
41		42	
43		44	
45		46	
47		48	
49		50	

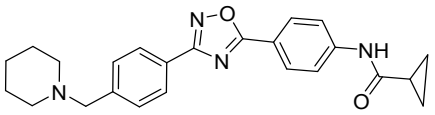
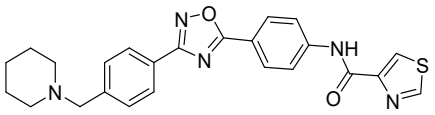
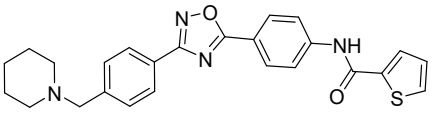
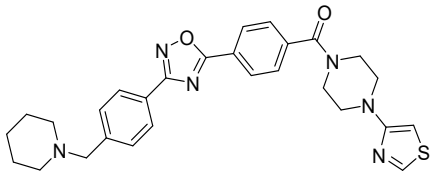
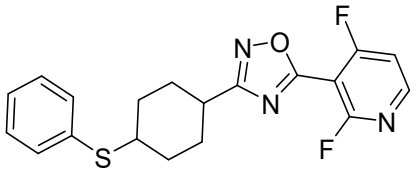
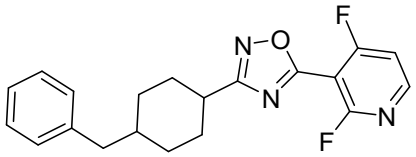
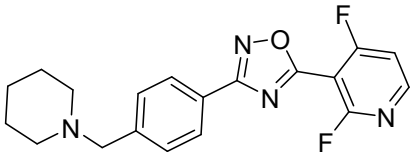
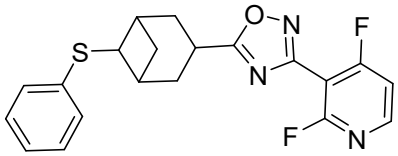
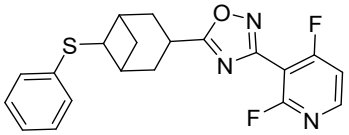
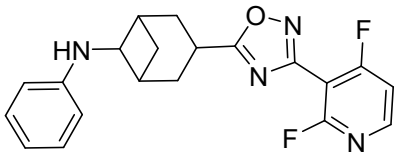
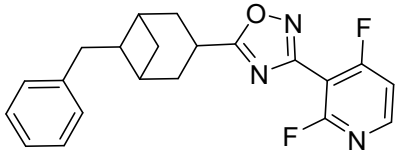
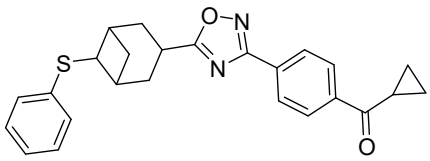
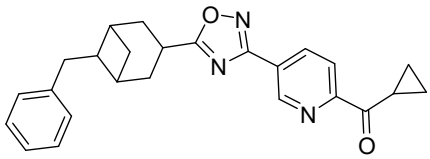
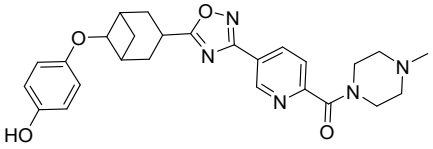
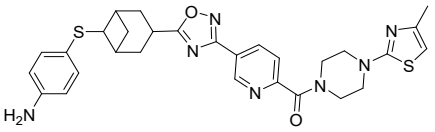
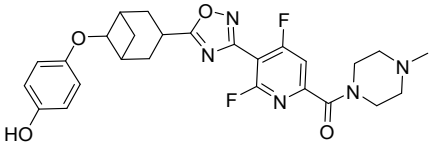
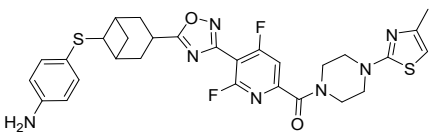
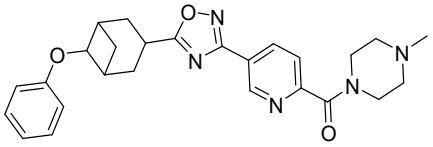
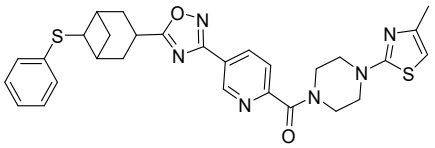
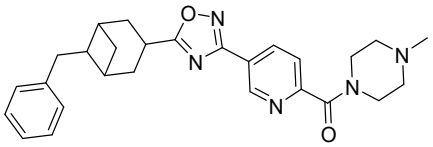
51		52	
53		54	
55		56	
57		58	
59		60	
61		62	
63		64	
65		66	
67		68	
69		70	

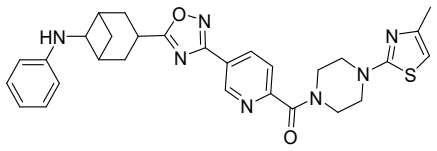
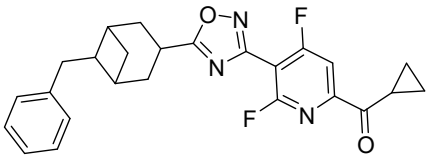
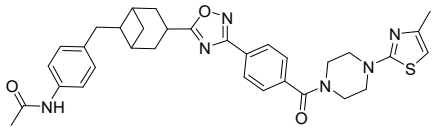
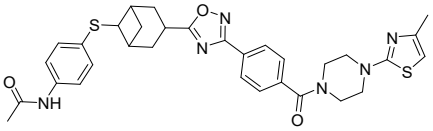
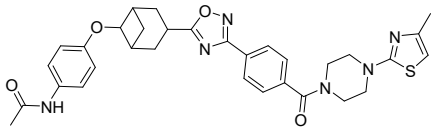
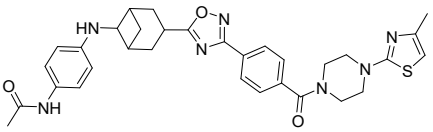
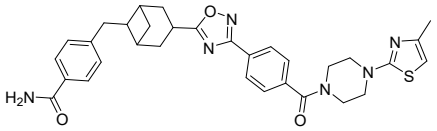
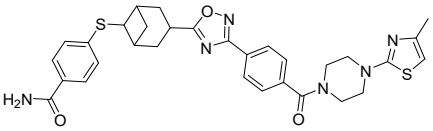
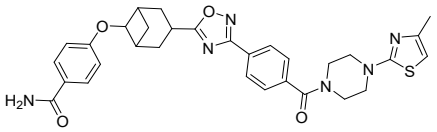
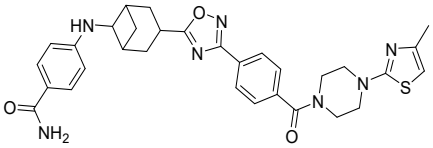
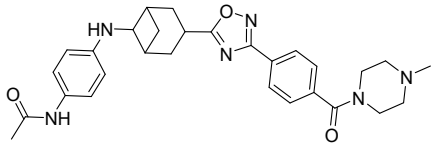
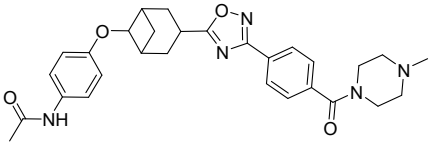
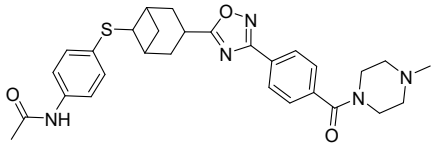
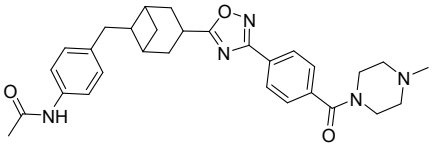
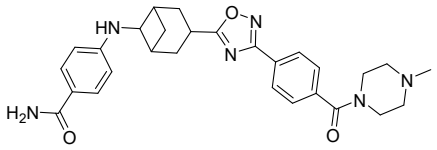
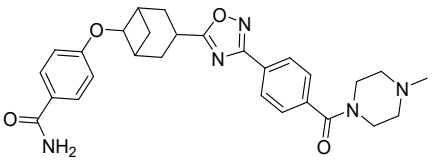
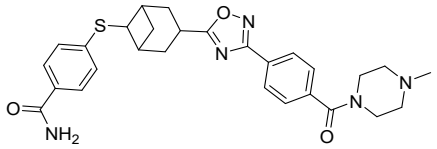
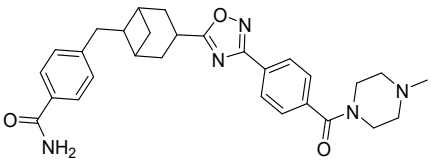
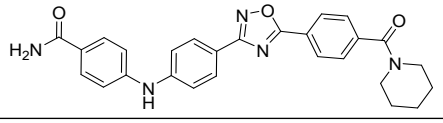
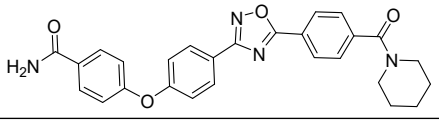
71		72	
73		74	
75		76	
77		78	
79		80	
81		82	
83		84	
85		86	
87		88	

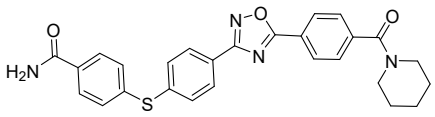
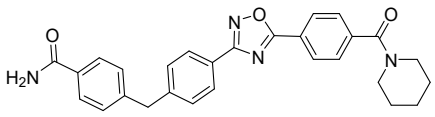
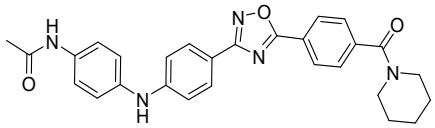
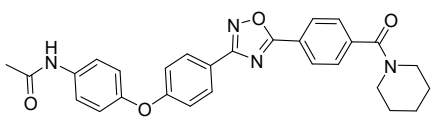
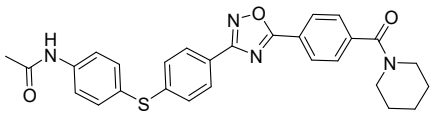
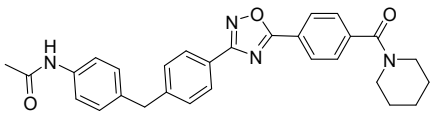
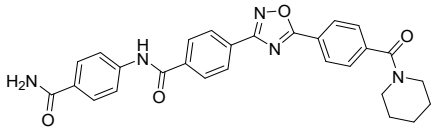
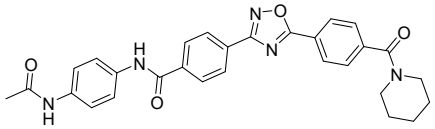
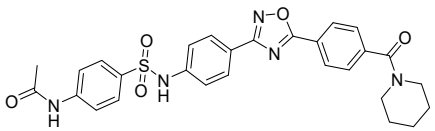
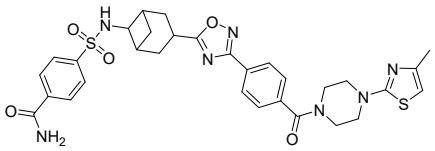
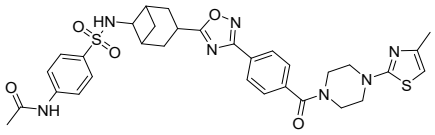
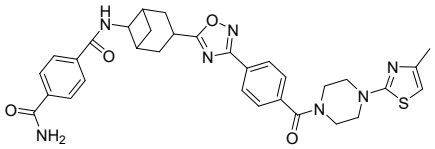
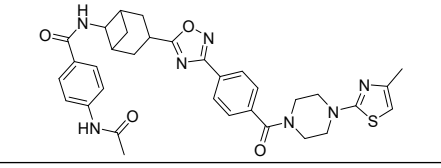
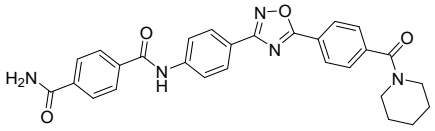
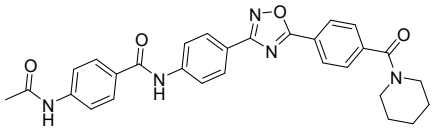
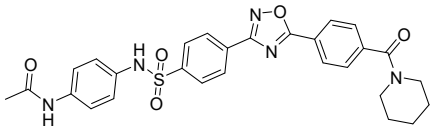
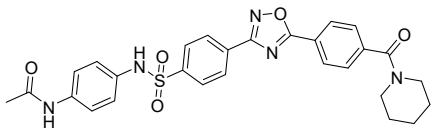
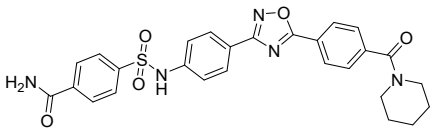
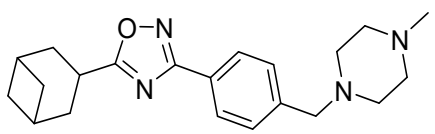
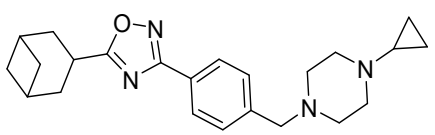
89		90	
91		92	
93		94	
95		96	
97		98	
99		100	
101		102	
103		104	
105		106	
107		108	

109		110	
111		112	
113		114	
115		116	
117		118	
118		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	

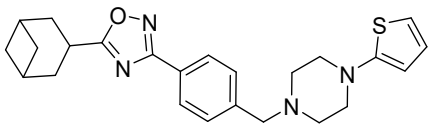
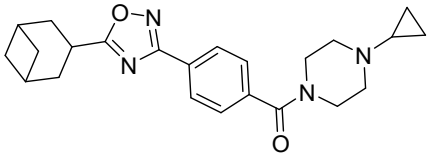
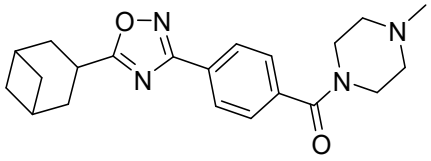
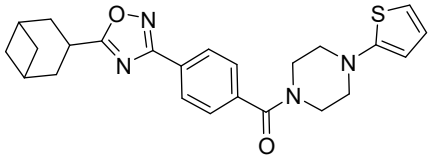
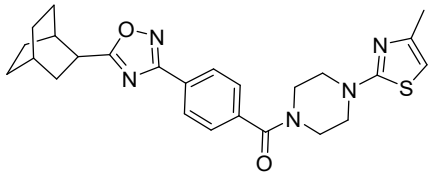
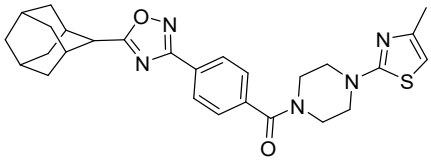
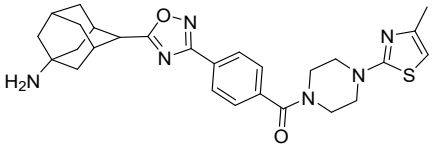
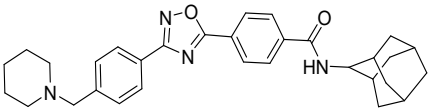
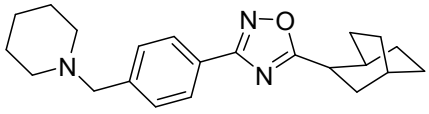
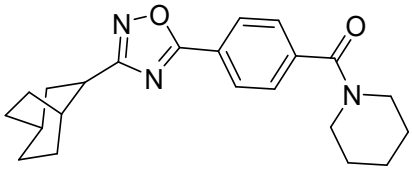
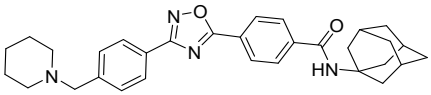
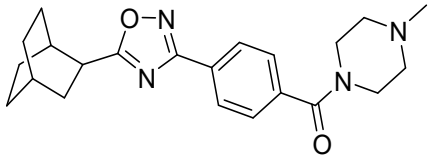
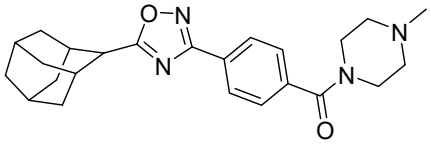
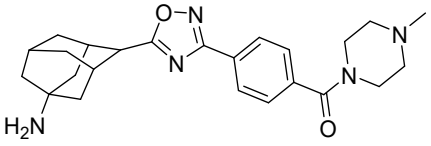
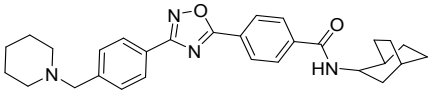
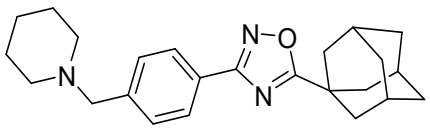
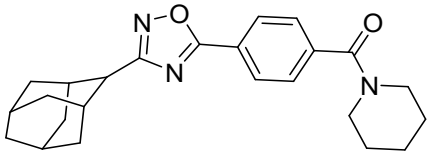
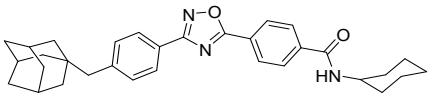
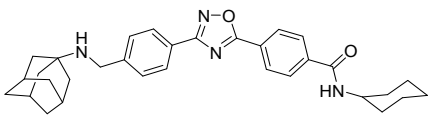
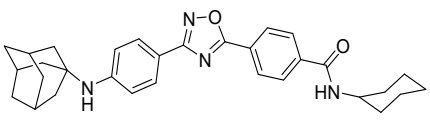
209		210	
211		212	
213		214	
215		216	
217		218	
219		220	
221		222	
223		224	
225		226	
227		228	

Table S6. The small molecules (141 compounds) obtained by the third round of molecular optimization.

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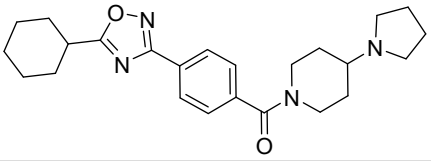
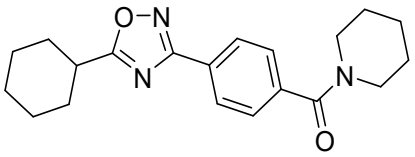
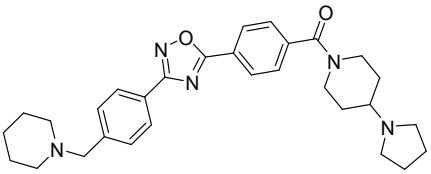
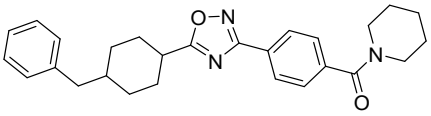
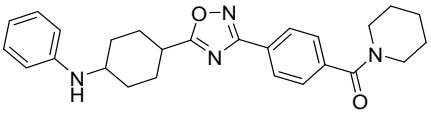
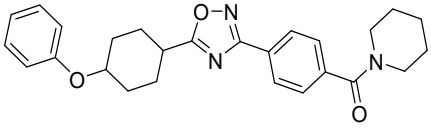
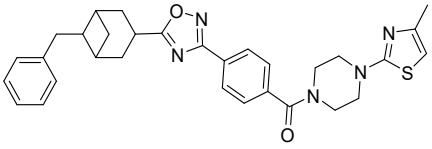
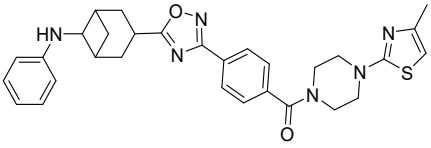
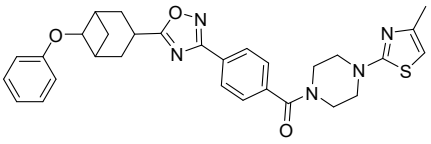
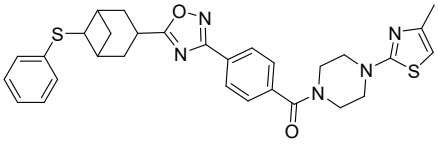
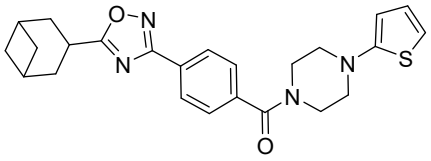
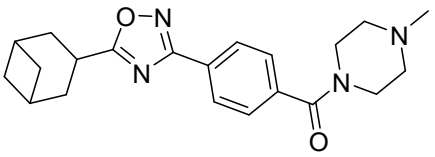
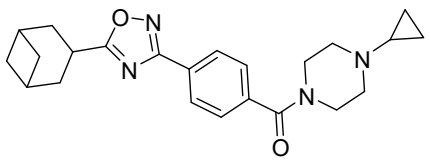
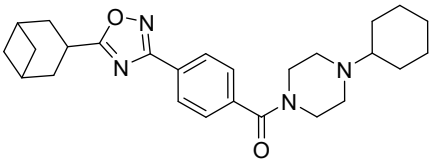
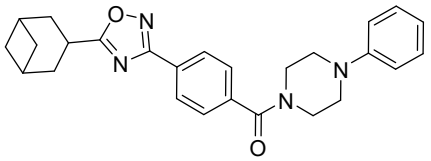
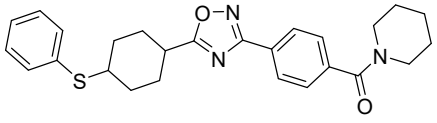
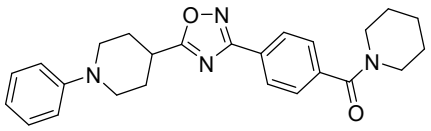
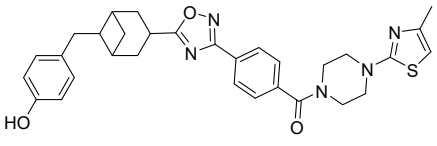
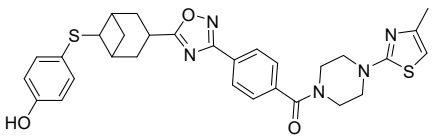
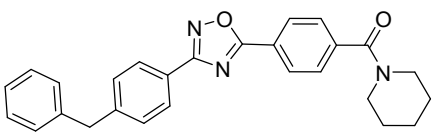
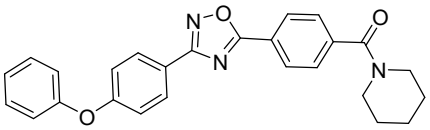
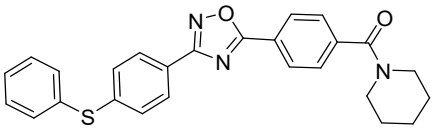
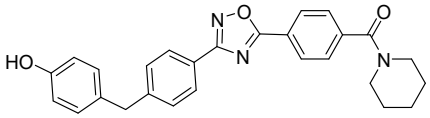
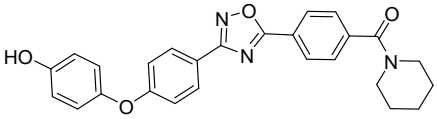
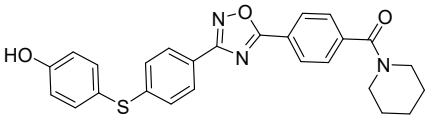
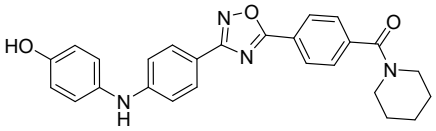
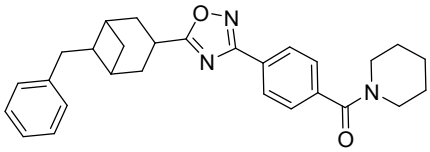
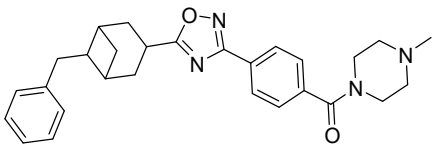
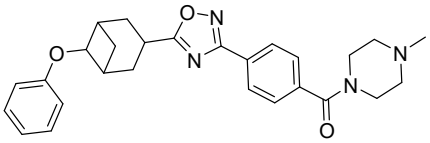
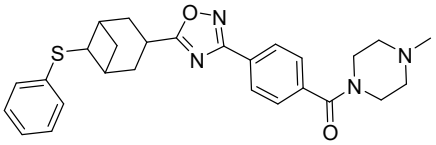
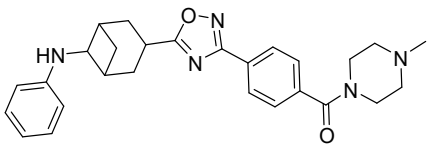
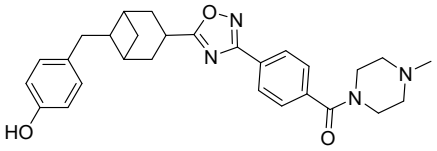
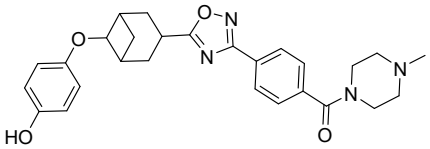
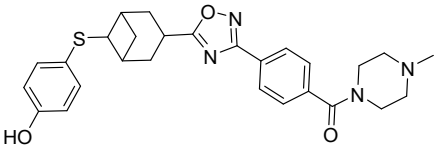
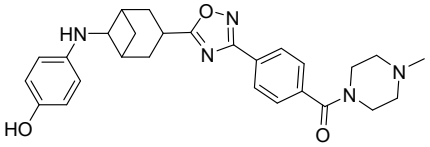
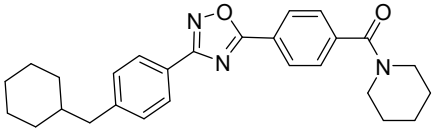
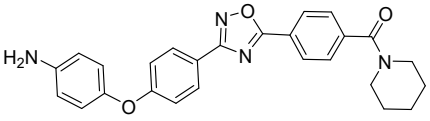
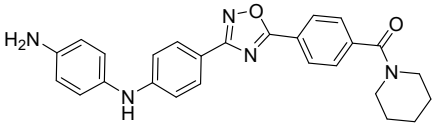
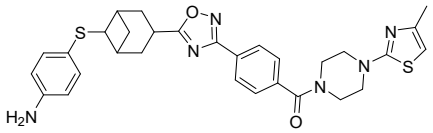
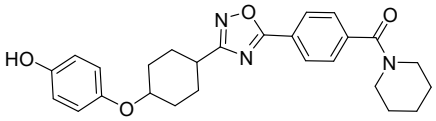
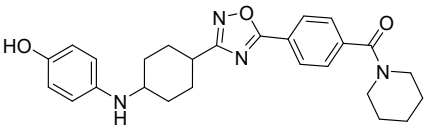
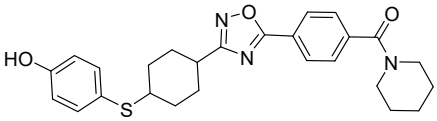
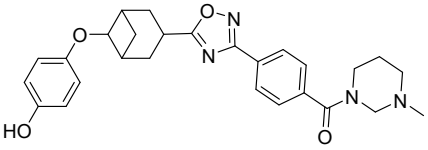
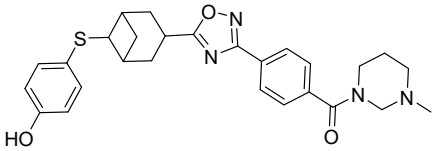
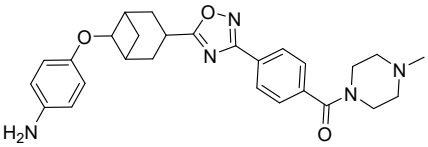
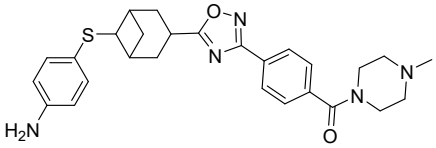
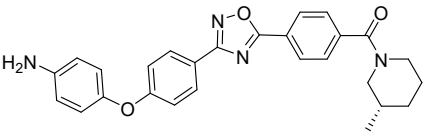
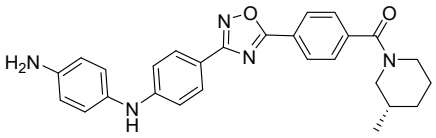
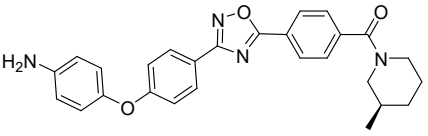
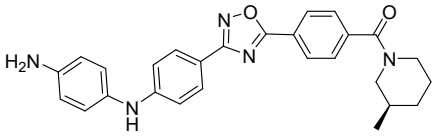
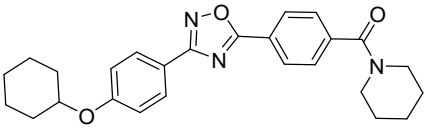
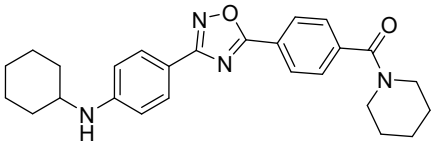
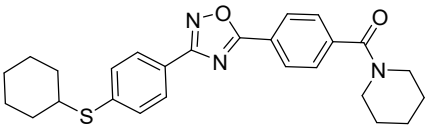
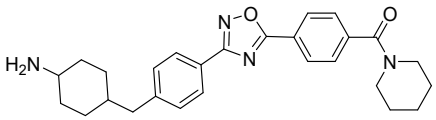
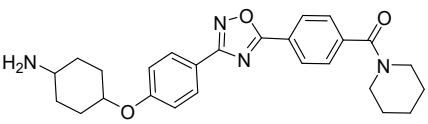
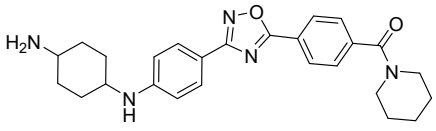
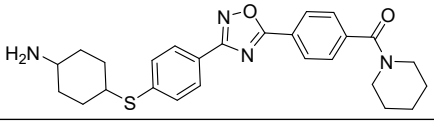
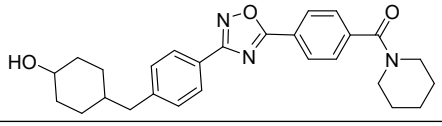
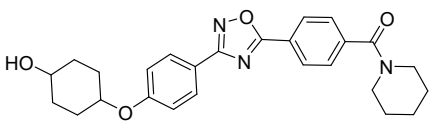
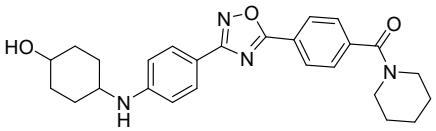
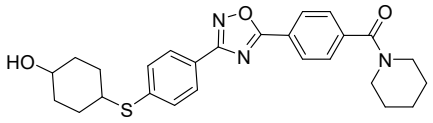
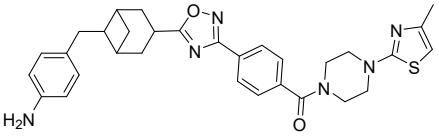
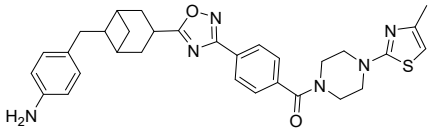
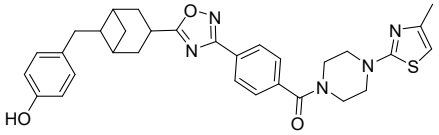
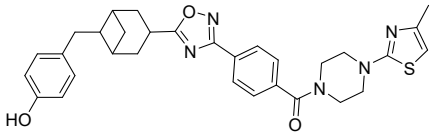
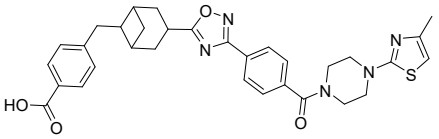
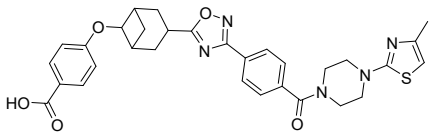
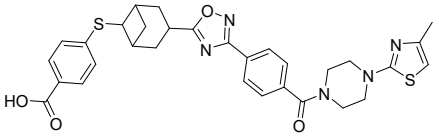
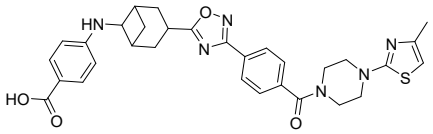
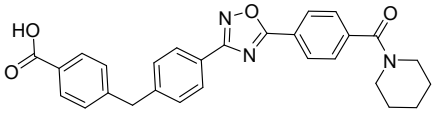
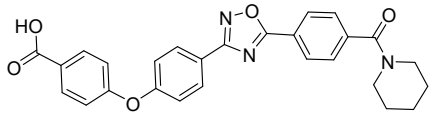
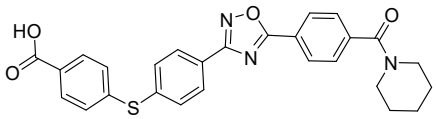
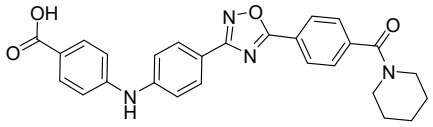
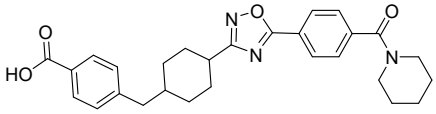
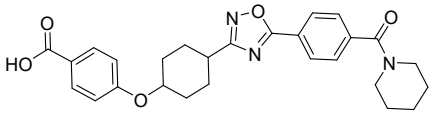
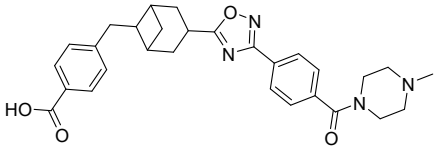
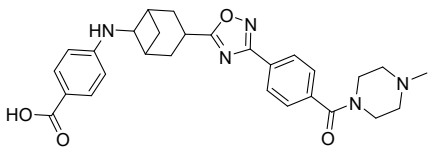
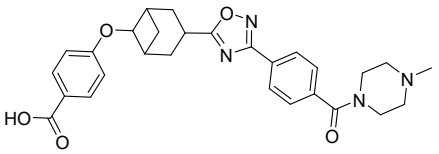
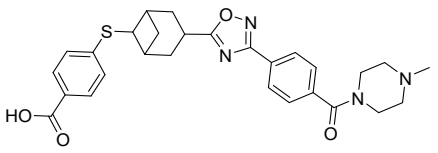
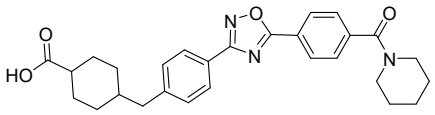
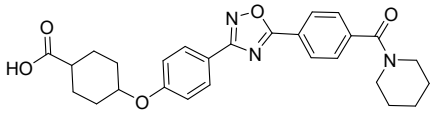
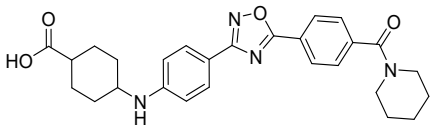
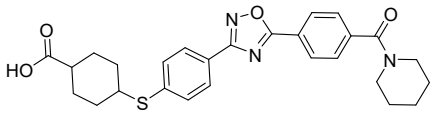
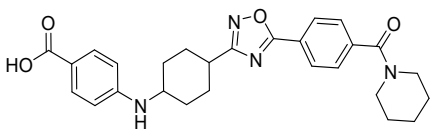
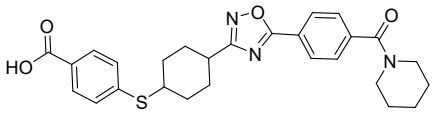
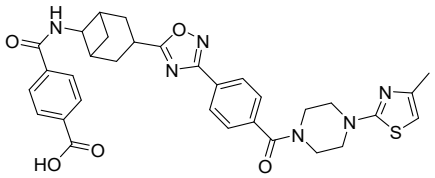
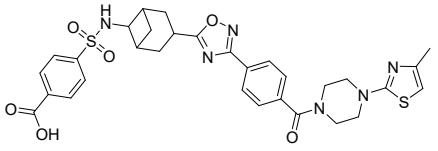
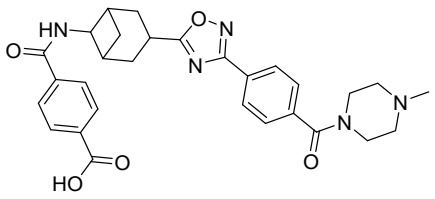
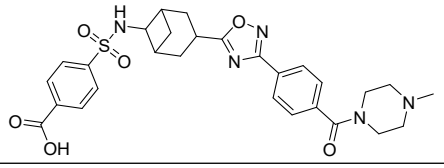
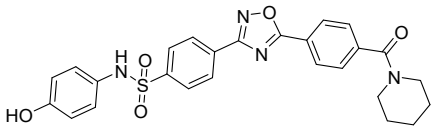
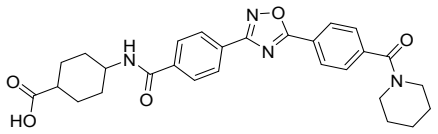
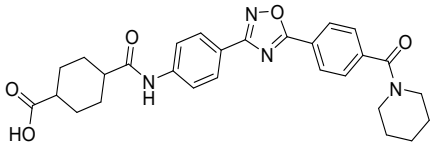
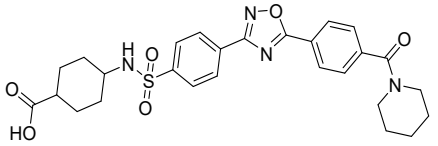
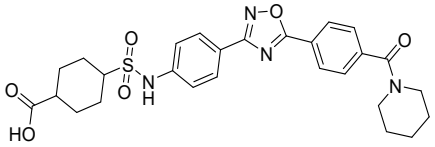
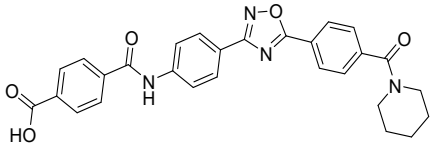
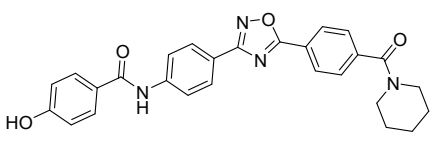
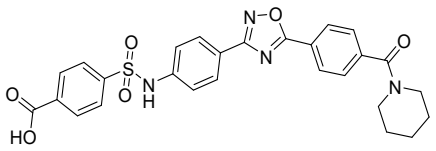
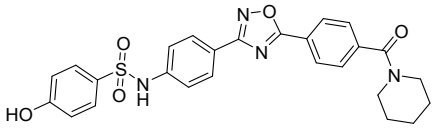
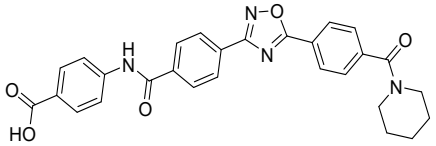
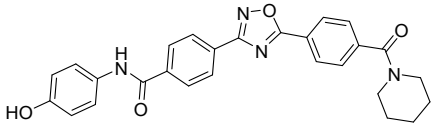
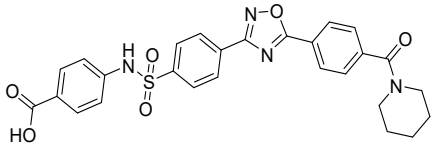
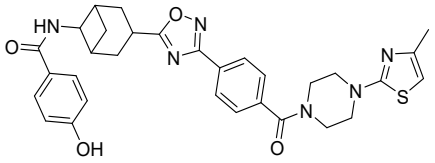
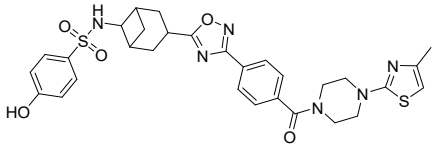
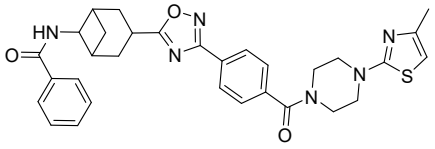
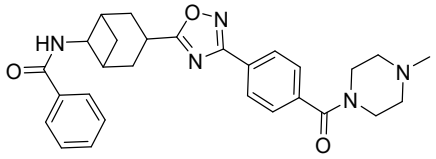
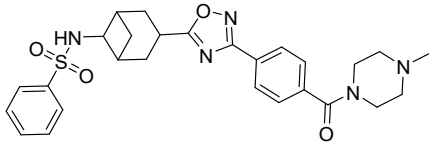
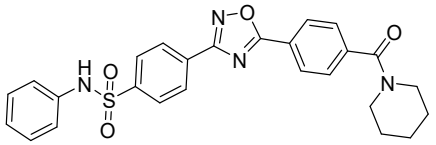
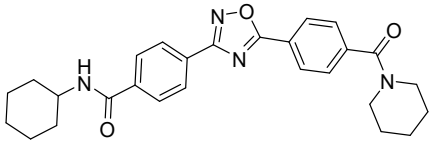
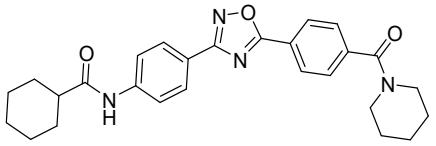
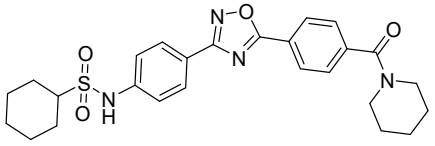
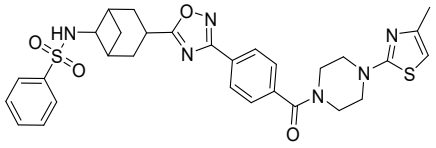
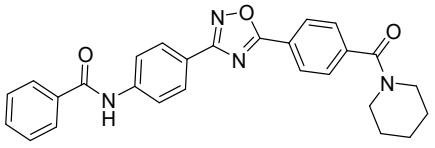
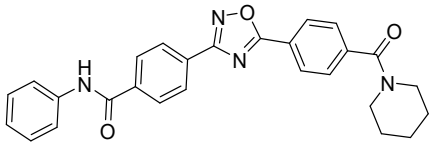
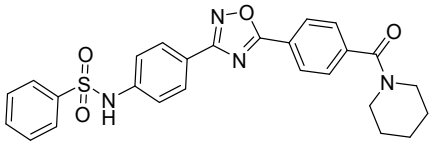
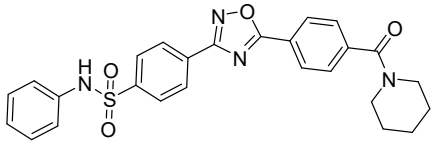
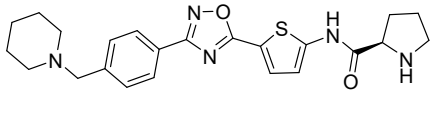
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	
13		14	
15		16	
17		18	

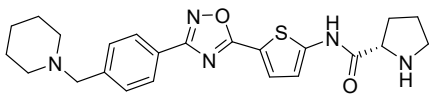
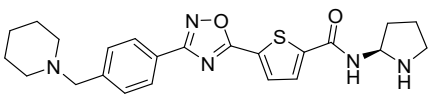
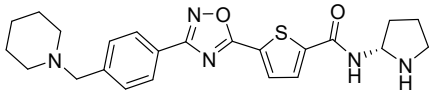
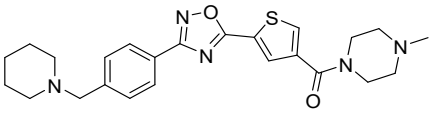
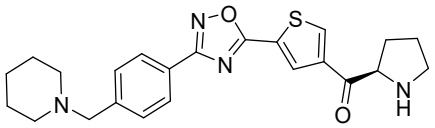
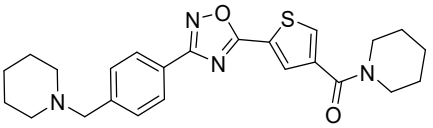
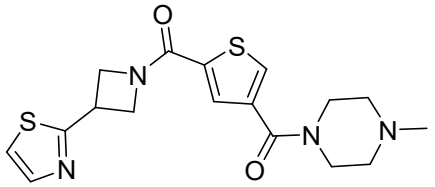
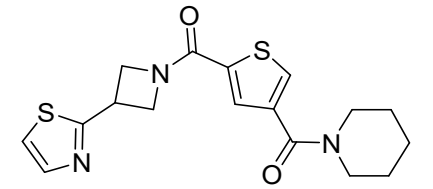
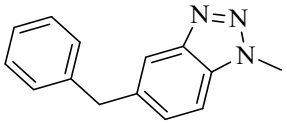
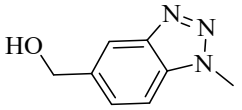
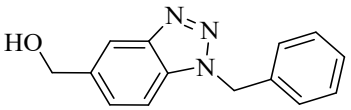
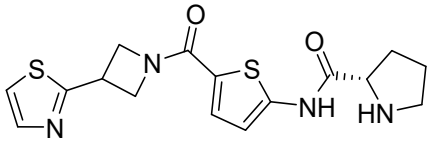
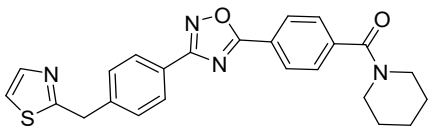
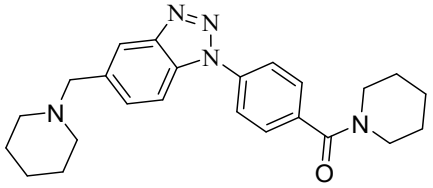
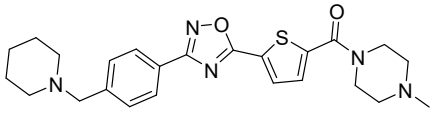
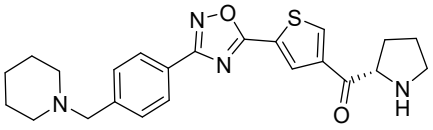
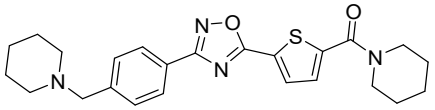
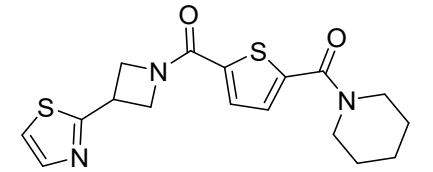
19		20	
21		22	
23		24	
25		26	
27		28	
29		30	
31		32	
33		34	
35		36	
37		38	

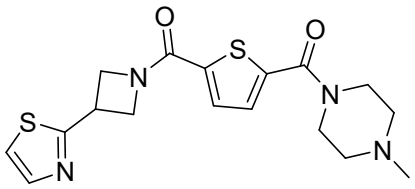
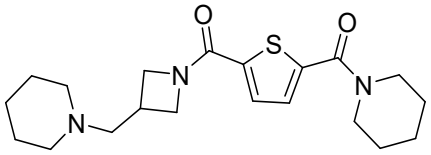
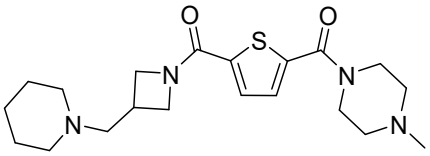
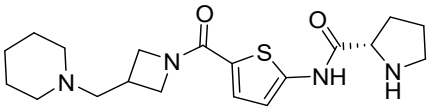
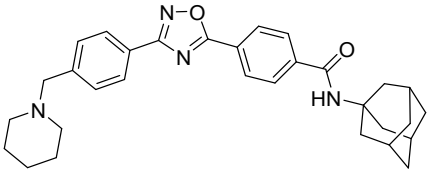
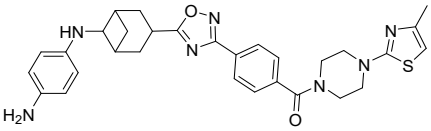
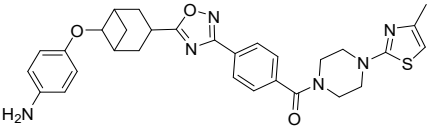
39		40	
41		42	
43		44	
45		46	
47		48	
49		50	
51		52	
53		54	
55		56	
57		58	

59		60	
61		62	
63		64	
65		66	
67		68	
69		70	
71		72	
73		74	
75		76	
77		78	

79		80	
81		82	
83		84	
85		86	
87		88	
89		90	
91		92	
93		94	
95		96	

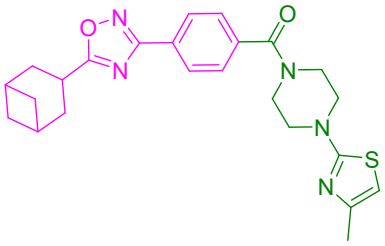
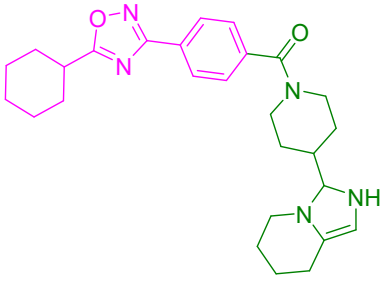
97		98	
99		100	
101		102	
103		104	
105		106	
107		108	
109		110	
111		112	
113		114	
115		116	

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			

III. The structure and docking parameters of selected molecular from molecular optimization

Table S7. The structure and docking parameters of selected molecular from the first round of molecular optimization

No.	Structure	Total score	Crash	Polar
1		23.2464	-2.3488	3.8897
2		22.0997	-3.232	4.258

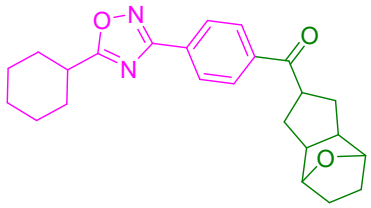
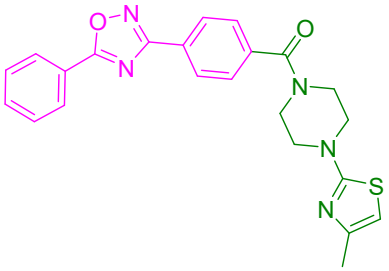
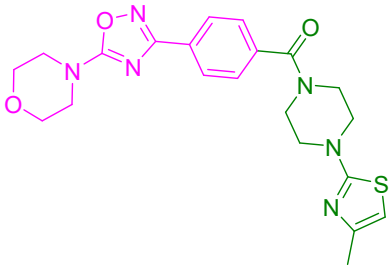
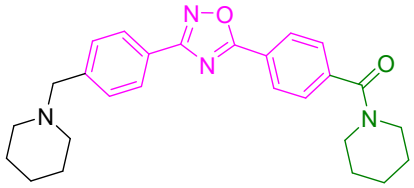
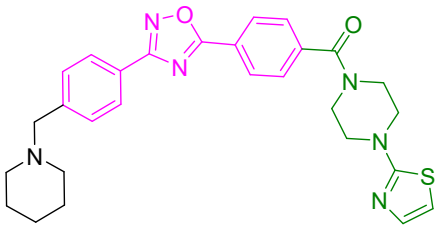
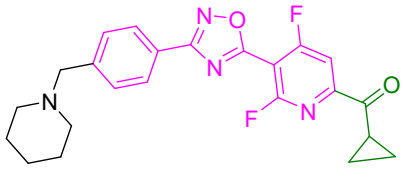
3		19.7138	-2.5142	4.1784
4		20.5698	-2.1063	4.0624
5		20.6115	-2.2196	4.2344

Table S8. The structure and docking parameters of selected molecular from the second round of molecular optimization

No.	Structure	Total score	Crash	Polar
1		22.1532	-2.3824	4.3589
2		22.7328	-3.3721	4.1669
3		22.5528	-2.5012	4.0969

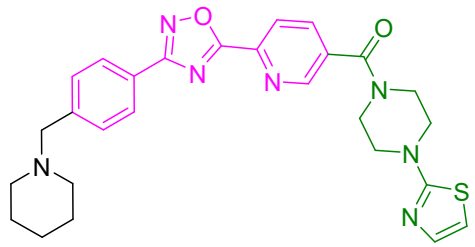
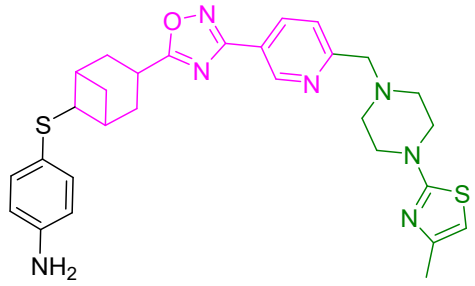
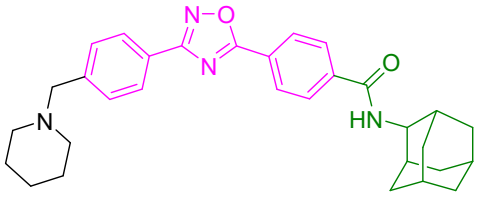
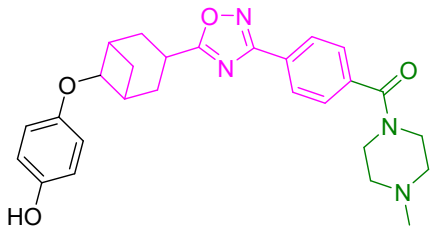
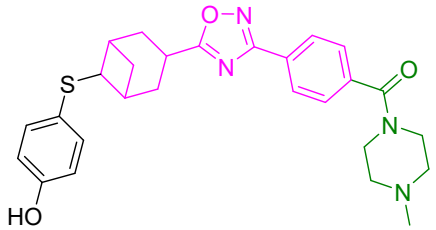
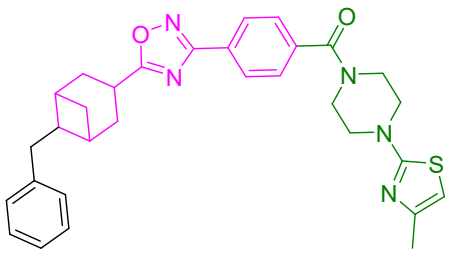
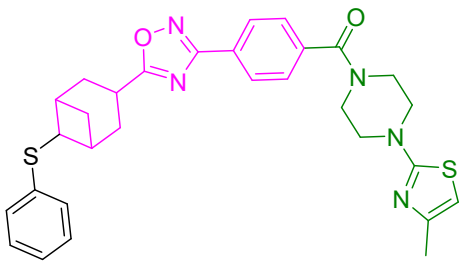
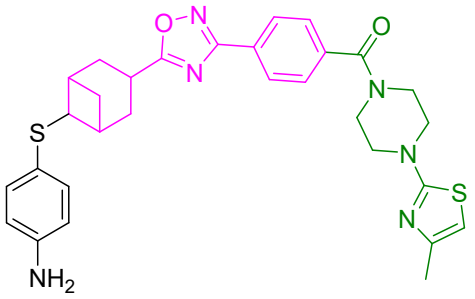
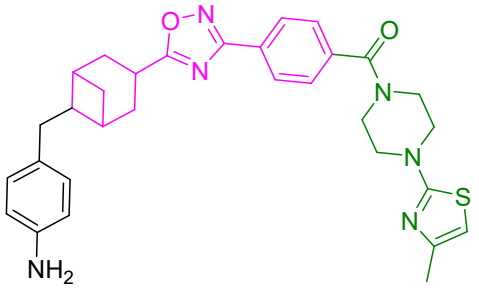
4		22.7051	-2.678	4.3231
5		22.7455	-3.5141	4.4952
6		23.0321	-1.8343	4.3883

Table S9. The structure and docking parameters of selected molecular from the third round of molecular optimization

No.	Structure	Total score	Crash	Polar
1		23.6081	-2.6629	6.7003
2		23.0946	-2.3597	6.0287
3		23.1046	-2.9972	4.0831

4		23.219	-2.6492	3.5733
5		23.6945	-3.0223	4.5986
6		23.0646	-3.2628	4.0801

IV. Figures of Molecular Dynamics Simulation Studies

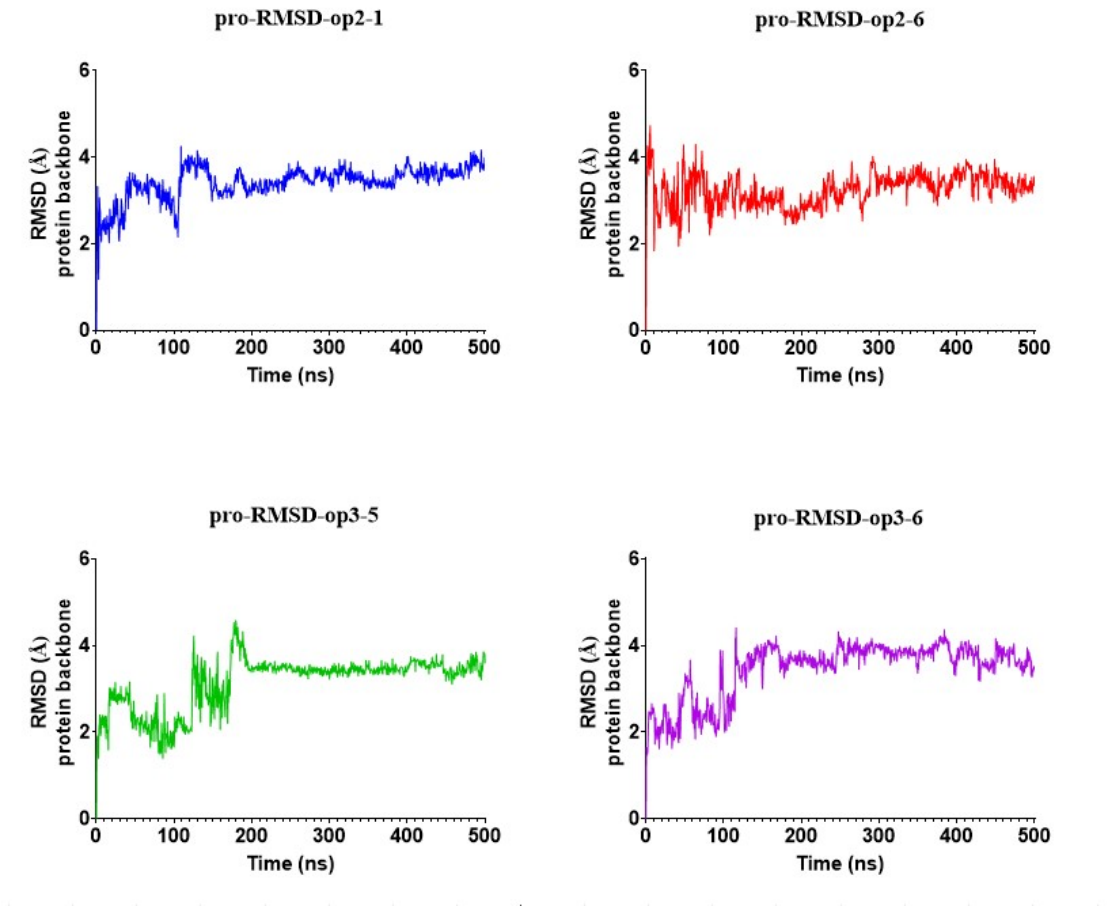


Figure S1. RMSD plot of protein backbone for protein-ligand complexes during 500 ns simulation.

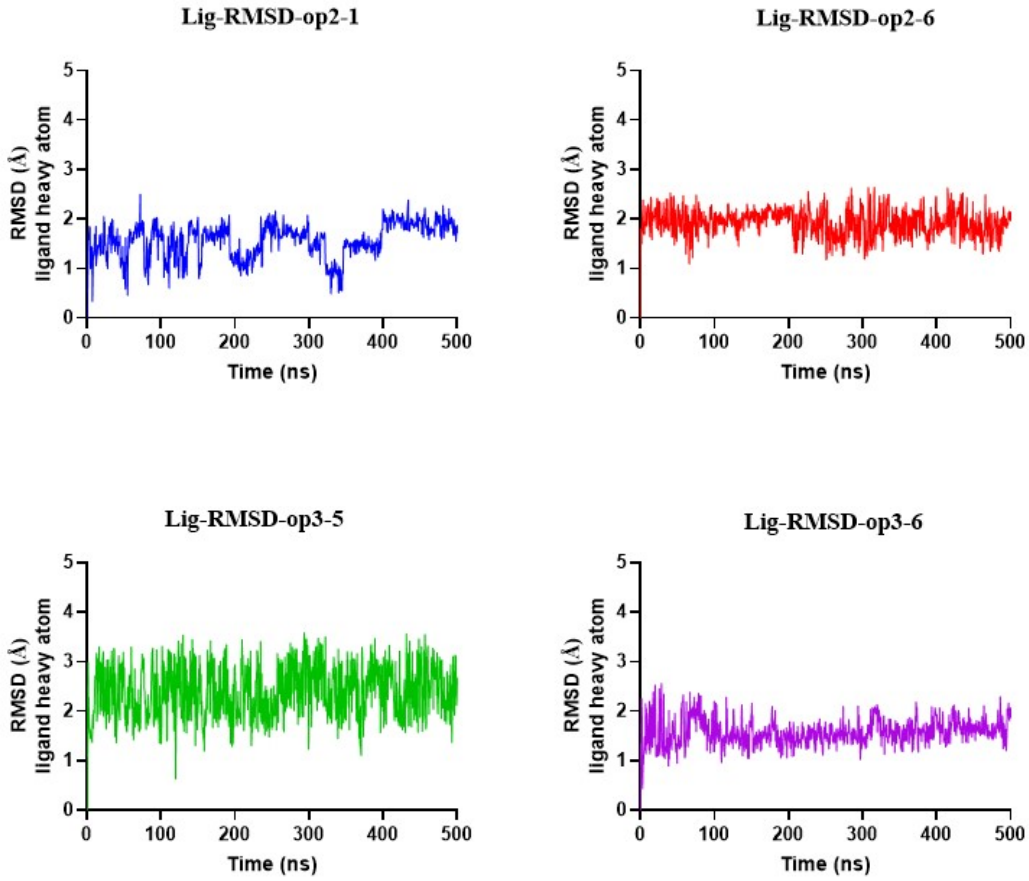


Figure S2. RMSD plot of ligand heavy atoms for protein-ligand complexes during 500 ns simulation.

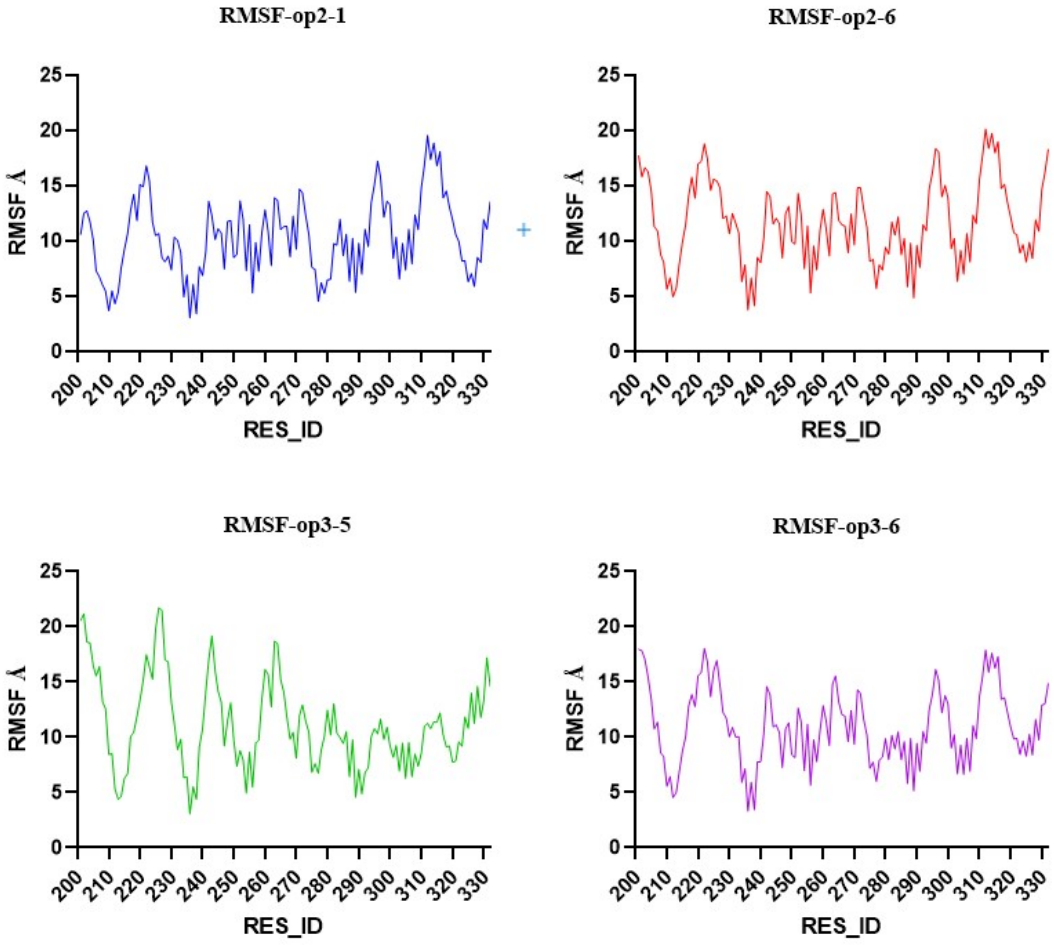


Figure S3. RMSF plot of protein-ligand complexes during 500 ns simulation.

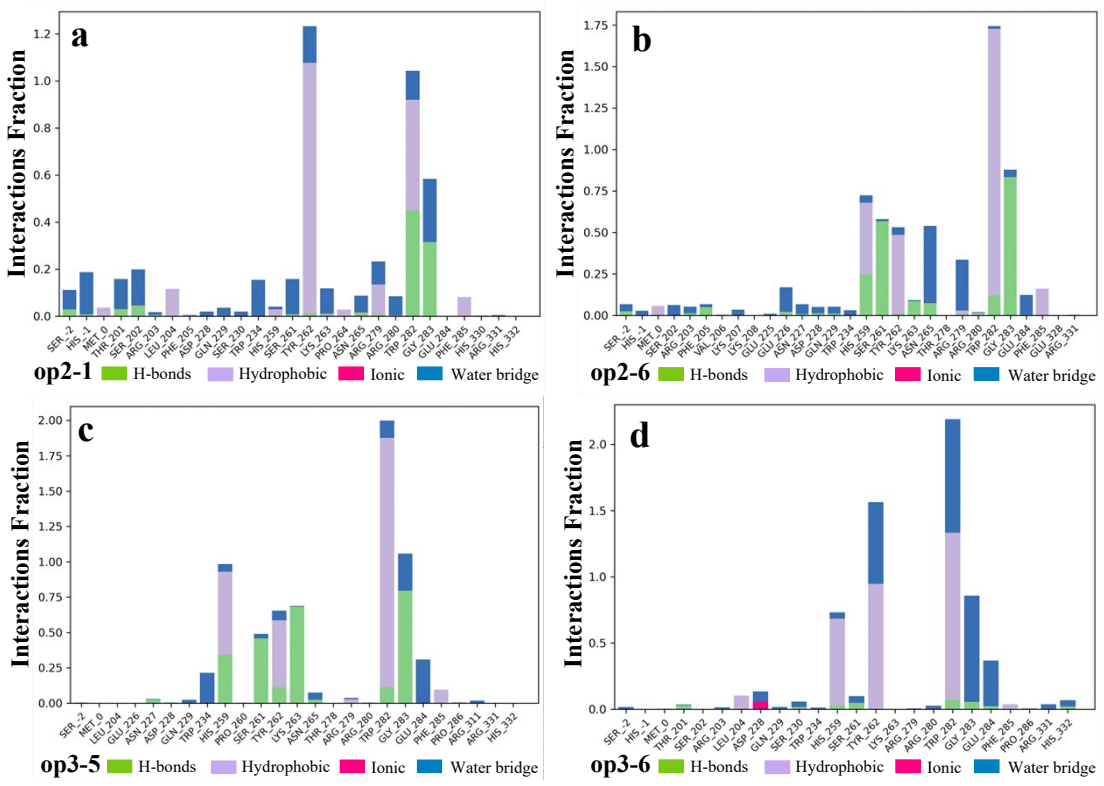


Figure S4. The stacked bar charts showing the protein–ligands interactions found during the 500 ns simulation run. The compounds **op2-1** (a), **op2-6** (b), **op3-5** (c), **and op3-6** (d) form multiple interactions with YEATS2 YEAST domain, mainly including hydrogen bonds, hydrophobic and water bridges. all the complex structures, it has been found to form multiple interactions including hydrogen bonds, hydrophobic, and water bridges. (a)The compound **op2-1** generated multiple interactions at Tyr262, Trp282 and Gly283. (b) The compound **op2-6** formed multiple interactions at His259, Ser261, Tyr262, Asn265, Trp282, and Gly283. (c) The compound **op3-5** formed multiple interactions at His259, Ser261, Tyr262, Lys263, Trp282, and Gly283. (d) The compound **op3-6** generated multiple interactions at His259, Tyr262, Trp282, and Gly283.

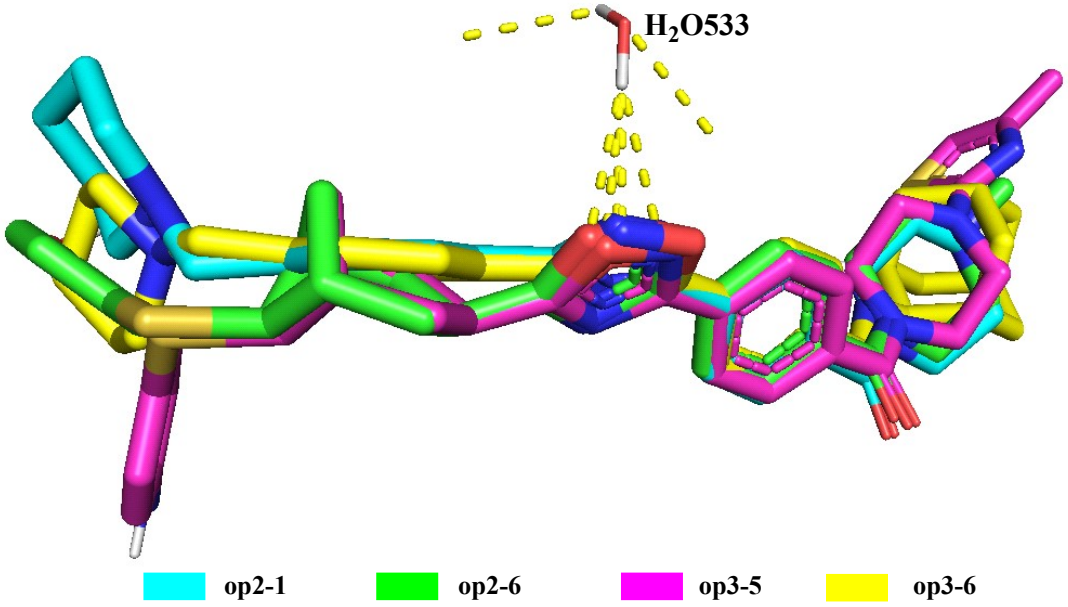


Figure S5. Ligand–H_2O533 contacts during 500 ns simulation.